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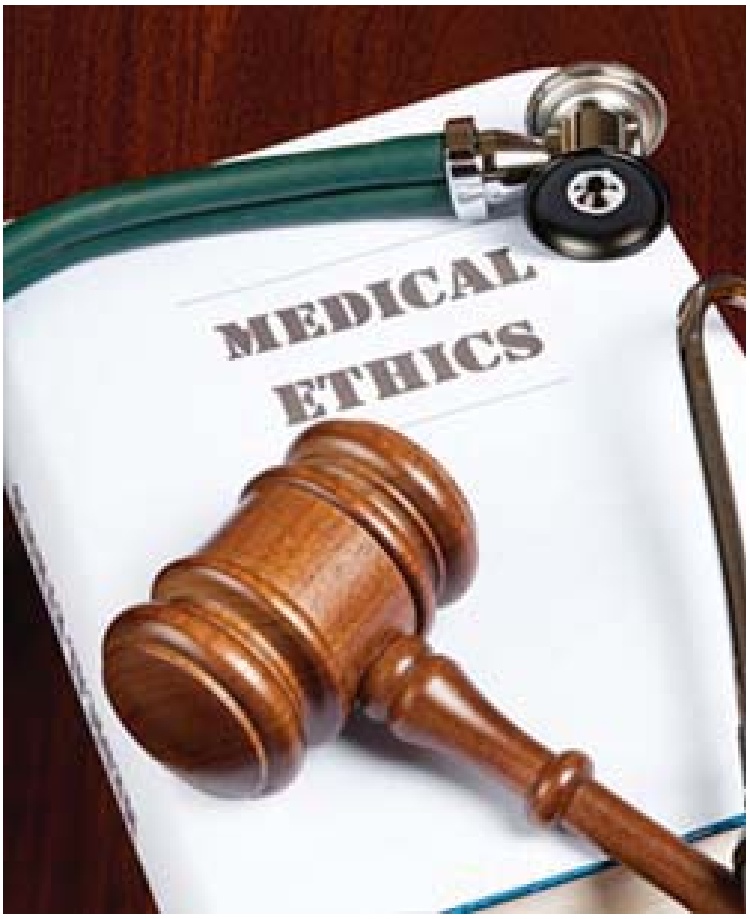

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VOJNOSANITETSKI PREGLED

Prvi broj *Vojnosanitetskog pregleda* izašao je septembra meseca 1944. godine

Časopis nastavlja tradiciju *Vojno-sanitetskog glasnika*, koji je izlazio od 1930. do 1941. godine

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The Journal continues the tradition of *Vojno-sanitetski glasnik* which was published between 1930 and 1941

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CONTENTS / SADRŽAJ

Each profession has its own moral principles, yet those in the field of healthcare have long been attracting public attention because of the importance that healthcare practice bears for human health and life, and thus for the society as a whole. The healthcare worker must comply with all legal norms regulating his/her professional activity, but, in the same time, the ethical principles of their profession. Their deviation can have disastrous consequences both for the patient and for the healthcare professional. These topics are discussed in the section "In Focus" (p. 77–87).

Svaka struka ima svoja moralna načela, ali ona u oblasti zdravstva već duže vreme privlače pažnju javnosti zbog značaja koju zdravstvena delatnost ima za ljudsko zdravlje i život, a time i za društvo u celini. Zdravstveni radnik mora da se pridržava svih zakonskih normi koje regulišu njegovu profesionalnu delatnost, ali, istovremeno, i etičkih načela svoje struke. Odstupanje od njih može da ima nesagledive posledice kako za pacijenta, tako i za samog zdravstvenog radnika. Ove teme obrađene su u rubrici „U fokusu" (str. 77–87).

E D I T O R I A L / U V O D N I K

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Domestic medical journals in the Web of Science – The main route to inclusion of Serbian medicine in the world scientific streams

Domaći medicinski časopisi u *Web of Science* – glavni put za uključenje srpske medicine u svetske naučne tokove

Silva Dobrić

Institute for Scientific Information, Military Medical Academy, Belgrade, Serbia

In late July 2014, almost at the same time when new impact factors (IF) of scientific journals for the previous year 2013 were published, in the journal Scientometrics an article of Ivanovic and Ho [1] was published dealing with the analysis of articles from the Republic of Serbia published in the period 2006–2012 in journals that are indexed in the Science Citation Index Expanded (SCIE) database. As a reminder, the SCIE is the largest bibliographic and citation database of the Institute for Scientific Information (ISI, Philadelphia, USA), now a part of the Thomson Reuters, which together with the other two databases, Social Science Citation Index (SSCI) and the Arts and Humanities Citation Index (AHCI), is the backbone of the so-called world scientific network – the Web of Science (WoS), in which a little more than 12,000 journals with the highest impact in the world of science are included. On the basis of citations of articles published in journals that accompany the WoS, their officially recognized IFs are calculated and published in the Journal Citation Reports (JCR). In the JCR scientific journals are distributed in 232 scientific disciplines and within each discipline are listed according to the value of IF, from the most influential (with the highest IF) to the least influential (with the lowest IF). Indexing of a journal in the WoS databases provides it greater visibility on international scientific scene and potentially a greater impact on the international scientific community. It is therefore the understandable desire of scientists to publish their articles primarily in such journals.

The abovementioned analysis of Ivanovic and Ho [1] showed that the Serbian scientists in the period 2006–2012 published a total of 14,293 articles in journals covered by the SCIE database, out of which the largest number (1,633 or 11%) was published in the category "General and Internal Medicine", which means that the domestic researchers from the medical scientific field in the reporting period were the most productive. It should be noted that this number of articles by domestic authors in the category "General and Internal Medicine" accounts up to 1.5% of all articles that were published in this period in the SCIE covered journals in that category. A significant increase in the number of articles of our scientists in the field of "General and Internal Medicine" was featured after 2008, which coincides with the inclusion in the SCIE

Krajem jula 2014, gotovo istovremeno kada su objavljeni i novi faktori uticaja (impakt faktori – IF) naučnih časopisa za prethodnu 2013. godinu, u časopisu *Scientometrics* objavljen je članak Ivanovića i Ho-a [1] u kome je izvršena analiza radova srpskih naučnika objavljenih u periodu 2006–2012. u časopisima uvrštenim u bazu naučne publicistike *Science Citation Index Expanded* (SCIE). Podsećanja radi, baza SCIE je najveća bibliografsko-citatna baza Instituta za naučne informacije (*Institute for Scientific Information, Philadelphia, USA*), sada u sastavu kompanije *Thomson Reuters*, koja zajedno sa druge dve baze, *Social Science Citation Index* (SSCI) i Arts *and Humanities Citation Index* (AHCI), čini okosnicu tzv. svetske naučne mreže – *Web of Science* (WoS) u koju je trenutno uključeno nešto više od 12 000 časopisa sa najvećim uticajem u svetskoj nauci. Na osnovu citiranosti članaka iz časopisa koje prate baze WoS-a izračunavaju se zvanično priznati IF pojedinih časopisa koji se, potom, objavljuju u publikaciji *Journal Citation Reports* (JCR). U JCR-u časopisi su raspoređeni u 232 naučne discipline, a unutar svake discipline navedeni su prema vrednosti IF, od najuticajnijeg (s najvišim IF) prema najmanje uticajnom (s najnižim IF). Ulazak nekog časopisa u sistem praćenja baza WoS-a obezbeđuje mu veću vidljivost na međunarodnooj sceni i potencijalno veći uticaj na međunarodne naučne tokove. Stoga, razumljiva je i želja naučnika da svoje radove prvenstveno objavljuju u takvim časopisima [2].

Napred pomenuta analiza Ivanovića i Ho [1] pokazala je da su srpski naučnici u periodu 2006–2012. godine u časopisima koje prati baza SCIE objavili ukupno 14 293 članka, od kojih je najveći broj (1 633 ili 11%) objavljen u kategoriji „Opšta i interna medicina", što znači da su domaći istraživači iz medicinskog naučnog polja u posmatranom periodu bili najproduktivniji. Treba istaći da ovaj broj članaka domaćih autora u kategoriji „Opšta i interna medicina" predstavlja čak 1,5% svih članaka koji su u tom periodu objavljeni u časopisima iz te kategorije. Značajan porast broja objavljenih članaka naših naučnika u oblasti „Opšte i interne medicine" bio je najizraziti posle 2008. godine, što koincidira sa uključenjem u bazu SCIE dva domaća medicinska časopisa: Vojno-

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two domestic medical journals: the *Vojnosanitetski Pregled* (VSP) and the *Srpski Arhiv za Celokuupno Lekarstvo*. In these journals (particularly in the VSP) the most articles in the category "General and Internal Medicine" were published by domestic authors. Although the VSP and *Srpski Arhiv za Celokupno Lekarstvo* have at the moment very low IF (0.269 and 0.169, respectively), which calls into question the actual impact of Serbian scientists from medical scientific fields to the world scientific streams, it is obvious that these two journals represent the main route to access international scientific scene for most domestic medical experts and thanks to them they and their articles, have a chance to be recognized and cited by international scientific community.

This is probably why already a few previous years, especially after inclusion of the VSP in the SCIE database in 2008, we recorded a constant influx of a large number of manuscript in the Editorial Office of the Journal. In the past year, namely from December 15, 2013 to December 15, 2014 the Editorial Office of the VSP received a total of 314 manuscripts: 74 (23.6%) from the military medical facilities, 194 (61.8%) from the civilian medical and academic institutions, and 46 (14.6%) from abroad. This number is about 28% higher than in 2013, or about 12% higher than in 2012, and is an indicator of continously high interest of both domestic authors and those from abroad to publish their articles in our journal. We are particularly pleased with the fact that more and more authors from abroad want to publish their articles in the VSP making it to be a "real" international scintific journal.

As in previous years, the largest number of manuscripts received during 2014 belongs to the category of Original articles (202 or 64.3%), followed by those from the category Case reports (76 or 24.2%), and those from the category Current topics and General review (19 or 6%). From these papers 43 (13.7%) were archived as inappropriate without sending to reviewers, so the remaining 271 (86.3%) of the received papers came in the reviewing process. Out of these papers, 146 (53.9%) have been already evaluated by reviewers (of that number 70.5% after revisions were accepted for publication, and 29.5% were rejected), while the remaining 125 (46.1%) papers are still under review.

In the past year, a total of 185 articles from different categories were published in the VSP (Table 1). As in previous years, the largest number of articles belonged to the categories of Original articles (54.6%) and Case reports (22.7%), which corresponds to the structure of received papers in earlier years. As in the earlier few years, during 2014, each month, along with the printed issue of the Journal, 4–6 articles were electronically published as OnLine-First, with the corresponding DOI numbers, so that these articles were available to readers at the website of the Journal and *via* doiSerbia service before publication in the printed version of the Journal.

When analyzing the published articles in the VSP in 2014 by the authors' affiliations, once again, as in previous years, the largest number of them (including book reviews) was by the authors from the so-called 'civilian institutions', domestic and foreign civilian and Military medical institutions (69.2 %), followed by the articles co-written by authors from both civilian and military medical institutions (16.7%), while the lowest number of articles was by the authors from the Military Medical Academy and other military medical centers (14.1%). Analysis of the published

sanitetskog pregleda (VSP) i Srpskog arhiva za celokupno lekarstva. Upravo u njima, pogotovo u VSP-u, objavljen je i najveći broj članaka domaćih autora. Iako i VSP i Srpski arhiv za celokupno lekarstvo imaju trenutno skroman IF (0,269, odnosno 0,169), što dovodi u pitanje stvarni uticaj srpskih naučnika iz medicinskog naučnog polja na svetske naučne tokove, očito je da su ova dva časopisa za većinu domaćih medicinskih stručnjaka glavni izlaz na međunarodnu naučnu scenu i da zahvaljujući njima oni, odnosno njihovi radovi, imaju šansu da budu prepoznati i citirani u međunarodnim naučnim krugovima.

Ovo je verovatno razlog što već nekoliko prethodnih godina, pogotovo posle uključenja VSP u bazu SCIE 2008. godine, beležimo konstantno veliki priliv radova u Redakciju našeg časopisa.

U protekloj godini, tačnije od 15.12. 2013. do 15.12. 2014. godini u Redakciju VSP-a stiglo je ukupno 314 radova: 74 (23,6%) iz vojnozdravstvenih ustanova, 194 (61,8%) iz civilnih zdravstvenih i akademskih institucija i 46 (14,6%) iz inostranstva. Ovaj broj je za oko 28% viši nego u 2013. godini, odnosno oko 12% viši nego u 2012, i pokazatelj je nesmanjenog interesovanja kako domaćih autora, tako i onih iz inostranstva da objave rad u našem časopisu. Posebno raduje podatak o 14,6% pristiglih radova čiji su autori iz inostranstva, što pokazuje zainteresovanost i međunarodne naučne javnosti da objavljuje radove u VSP-u, što ga sve više čini „pravim" međunarodnim časopisom.

Kao i prethodnih godina, najveći broj pristiglih radova tokom 2014. godine pripada kategoriji Originalnih članaka (202 ili 64,3%), zatim slede Prikazi slučajeva (76 ili 24,2%), pa radovi iz kategorije Aktuelne teme i Opšti pregledi (19 ili 6%). Od ovih radova 43 (13,7%) su arhivirana kao neodgovarajuća bez prethodnog slanja recenzentima, tako da je u postupak recenzije ušao 271 (86,3%) rad. Od tog broja recenzentski je obrađeno 146 (53,9%) radova (od njih je 70,5%, nakon učinjenih korekcija prihvaćeno za publikovanje, a 29,5% je odbijeno), dok se preostalih 125 (46,1%) još nalazi u postupku recenzije.

U protekloj godini, na stranicama VSP-a objavljeno je ukupno 185 članaka iz različitih kategorija (Tabela 1). Kao i do sada, najveći broj objavljenih članaka pripadao je kategoriji Originalni članci (54,6%) i onima iz kategorije Prikaz bolesnika (22,7%), što odgovara i strukturi primljenih radova u ranijim godinama. I tokom 2014, svaki mesec, uz štampani broj časopisa, 4–6 članaka bilo je objavljeno elektronski kao *OnLine-First*, sa pripadajućim DOI brojem, tako da su ti radovi bili dostupni čitaocima preko sajta časopisa i servisa DOI*Serbia* i pre objave u štampanoj verziji.

S obzirom na institucije autora čiji su radovi objavljeni u VSP-u u toku protekle godine, ponovo je, kao i prethodnih godina, najveći broj objavljenih radova (uključujući i prikaze knjiga) bio od autora iz civilnih institucija, domaćih i stranih (69,2%), zatim slede zajednički radovi autora iz civilnih i vojnozdravstvenih institucija, uglavnom iz VMA (16,7%), dok je najmanje radova bilo od autora iz VMA i drugih vojnozdravstvenih centara (14,1%). Ako se posebno analiziraju radovi čiji su autori, odnosno koautori iz inostranstva, njih je među objavljenim radovima u 2014. godini bilo 28 (15,1%).

Table 1

Categories and the number of articles published in the Vojnosanitetski Pregled in 2014/ Kategorije i broj članaka objavljenih u Vojnosanitetskom pregledu u 2014.

Category / Kategorija	Articles/ Članci	
	n	%
Editorial/ Uvodnik	6	3.2
Original Article/ Originalni članak	101	54.6
General Review/ Opšti pregled	6	3.2
Current Topic/ Aktuelna tema	10	5.4
Practical Advice for Physicians/ Seminar praktičnog lekara	1	0.5
Case Report/ Prikaz slučaja	42	22.7
Preliminary Report/ Prethodno saopštenje	1	0.5
Short Communication/ Kratko saopštenje	5	2.8
History of Medicine/ Istorija medicine	5	2.8
Letter to the Editor/Pismo uredniku	2	1
Book Review/ Prikaz knjige	6	3.3
Total/ Ukupno	185	100.0

articles whose authors or co-authors were from abroad revealed that their number in 2014 was 28 (15.1%).

Of the most important events for the Journal that occurred during 2014, we must mention the reconstruction of national and international Editorial board at the beginning of the year [3], entered by several new members, prominent experts from various fields of medicine, then obtaining a new IF for 2013 (at the end of July) that increased from the previous 0.21 in 2012 to 0.269 (the increase of 28%), as well as marking of the 70th birthday of the Journal (in September) [4]. For that occasion bibliography of all articles published in the Journal over the past 70 years was prepared in an electronic form (on CDs) and a film about the Journal that can be found on our website.

Taking into account the above-mentiond, we can say that 2014 was successful for our Journal, even according to some indicators and more successful than previous years. With the hope that this trend of success will go on in the New Year 2015, I want to thank for very fruitful cooperation to all the editors, reviewers and authors of the VSP. In particular, I would emphasize a significant contribution of our reviewers to improving the quality of articles published in the Journal providing it better positioning in the international scientific scene. The names of reviewers who were involved in reviewing the manuscripts received in the past year are given in Table 2.

Od važnijih događaja za časopis koji su se odigrali u toku 2014. godine, svakako treba spomenuti rekonstrukciju domaćeg i međunarodnog uređivačkog odbora početkom godine [3], u koji je ušlo nekoliko novih članova, istaknutih stručnjaka iz različitih oblasti medicine, zatim dobijanje novog IF za 2013. godinu (krajem jula) čija je vrednost povećana sa prethodne 0,21 na 0,269 (povećanje za 28%), kao i proslavu 70. rođendana časopisa (u septembru) [4]. Za tu priliku izdata je u elektronskom obliku (na CD-u) bibliografija svih radova objavljenih u časopisu tokom proteklih 70 godina. Takođe, urađen je i film o časopisu koji se može pogledati na našem sajtu.

Uzimajući u obzir napred navedeno, možemo slobodno reći da je 2014. godina bila uspešna za naš časopis, čak prema nekim pokazateljima i uspešnija od prethodnih godina. Sa nadom da će se ta tendencija uspešnosti nastaviti i u Novoj 2015. godini želim da se zahvalim na dosadašnjoj veoma plodnoj saradnji svim urednicima, recenzentima i autorima VSP-a. Posebno bih istakla značajan doprinos recenzenata u podizanju kvaliteta radova koji se objavljuju na stranicama časopisa, a time i u njegovom boljem pozicioniranju na međunarodnoj naučnoj sceni.

Imena recenzenata koji su bili angažovani za recenziranje radova za VSP u protekloj godini data su u Tabeli 2.

Table 2

Reviewers of the Vojnosanitetski pregled in 2014 / Recenzenti Vojnosanitetskog pregleda u 2014. godini

Aćimović Slobodan	Beleslin Branko	Čovičković Šternić Nada	Dragojević Simić Viktorija
Aldawood S. Abdulaziz	Berisavac Milica	Čutović Tatjana	Dragović Tamara
Aleksić Dragan	Bokonjić Dubravko		Drapšin Miodrag
Aleksić Petar	Brkić Zlata	Ćuk Vladimir	Duka Miloš
Antić Branislav	Bulat Petar		Dulović Olga
Antonijević Biljana	Bumbaširević Marko	Daković Dragana	
Arsenijević Nebojša		Dankuc Dragan	Djordjević Brižita
Arsenović Ranin Nevena	Carević Momir	Davidović Lazar	Djurović Branka
Arsović Nenad	Cartea María Elena	Dedić Gordana	Djordjević Snežana
	Cvijanović Vlado	Dimić Nadežda	Djukanović Ljubica
Baletić Nenad		Dinčić Evica	Djukić Mirjana
Balint Bela	Čabarkapa Milanko	Dobrić Silva	Djurić Tatjana
Bančević Vladimir	Čekanac Radovan	Doder Radoje	Djurović Aleksandar
Baškot Branislav	Čolić Miodrag	Dopsaj Violeta	Djurović Branislav

Gazivoda Dragan
Glibetić Marija
Grdinić Aleksandra

Hajduković Zoran
Hajjar M. Waseem
Haroche Julien

Ignjatović Mile
Ilić Dragan
Ilić Radoje
Ilić Tihomir
Ivanović Mirjana

Jakovljević Mihajlo
Jakovljević Vladimir
Janković Borisav
Janković Slavenka
Janković Slobodan
Jovanović Dragana
Jovanović Ida
Jovanović Miloš
Jović Jasna
Jović Nebojša
Jović Stošić Jasmina
Jovičić Bojan

Kandolf Sekulović Lidija
Kanjuh Vladimir
Konstantinović Ljubica
Konstantinović Vitomir
Kostić Vladimir
Kostov Miloš
Kot Jacek
Kovačević Nada
Kozarski Jefta
Kozomara Ružica
Krivokapić Zoran
Krstev Srmena
Kulesher R. Robert
Kumar Kushwaha Jitendra
Kundaković Tatjana

Lakić Dragana
Lazić Miodrag
Lazić Srđan
Lazić Zoran
Lečić Toševski Dušica
Lepšanović Zorica
Lukač Marija

Magić Zvonko
Maksić Đoko
Mandić Gajić Gordana
Manojlović Nebojša
Marić Nađa
Marjanović Ivan
Marjanović Marjan
Marković Dejan
Martinović Milica
Matić Smiljana
Medenica Ivica
Meštrović Arijana
Micić Dragan
Mićić Sava
Mihaljević Biljana
Mikić Dragan
Mikov Momir
Milenković Marina
Milenković Svetislav
Milovanović Dragan
Milović Novak
Minić Predrag
Mirković Darko
Mirković Ljiljana
Mirović Veljko
Mitić Igor
Mujović Nebojša
Mitrović Jovanović Ana

Nagorni Ljudmila
Nešković Konstantinović Zora
Nežić Duško
Nikolić Branka
Nikolić Đurović Marina
Nikolić Ljiljana
Nikolić Ljubiša
Novaković Marijan
Nožić Darko

Obradović Dragana
Obradović Slobodan
Opinćal Stošić Tatjana
Ostojić Gordana

Paunić Mila
Paunović Katarina
Pavlović Drašković Biljana
Pavlović Milorad
Pekić Sandra
Peković Sandra
Perić Aleksandar
Peruničić Jovan
Petronić Marković Ivana
Petronijević Milan
Petrova Guenka
Petrović Silvana
Popović Nada
Popović Zoran
Potpara Tatjana

Rabrenović Milorad
Rabrenović Violeta
Radaković Sonja
Rađen Slavica
Radojčić Ljiljana
Radosavljević Vladan
Rafajlovski Saša
Raičević Ranko
Resan Mirko
Risović Dušica
Ristić Anđelka
Ristić Arsen
Ristić Ljubiša
Roganović Zoran
Rutter Victoria

Sabo Ana
Sekulović Leposava
Sen Indrani
Sharma Shalini
Shoenfeld Yehuda
Simić Snežana
Slavković Slobodan
Slavković Zoran
Spasić Slavica
Spasojević-Kalimanovska Vesna
Stamatović Dragana
Stamenković Dragoslav
Stamenković Dušica
Stamenković Miroslav
Stančić Ivica
Stanić Vojkan
Stanković Goran
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Stefanović Dara
Stefanović Dušan
Stepanović Jelena
Stevanović Goran
Stimmelmayr Michael
Stojanov Marina
Stojanović Miodrag
Stošić Sanja
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Šarac Momir
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SHORT COMMUNICATIONS

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Anismus as a cause of functional constipation – Experience from Serbia

Anizam kao uzrok funkcionalne opstipacije – iskustvo iz Srbije

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Abstract

Backround/Aim. Anismus is paradoxal pressure increase or pressure decrease less than 20% of external anal sphincter during defecation straining. This study analyzed the presence of anismus as within a group of patients with the positive Rome III criteria for functional constipation. We used anorectal manometry as the determination method for anismus. **Methods.** We used anorectal water-perfused manometry in 60 patients with obstructive defecation defined by the Rome III criteria for functional constipation. We also analyzed anorectal function in 30 healthy subjects. **Results.** The presence of anismus is more frequent in the group of patients with obstructive defecation compared to the control group (a highly statistically significant difference, $p < 0.01$). Furthermore, we found that the Rome III criteria for functional constipation showed 90% accuracy in predicting obstructive defecation. We analyzed the correlation of anismus with the presence of weak external anal sphincter, rectal sensibility disorders, enlarged piles, diverticular disease and anatomic variations of colon. We found no correlation between them in any of these cases. **Conclusion.** There is a significant correlation between anismus and positive Rome III criteria for functional constipation. Anorectal manometry should be performed in all patients with the positive Rome III criteria for functional constipation.

Key words:
constipation; manometry; risk factors; serbia.

Apstrakt

Uvod/Cilj. Anizam predstavlja paradoksalno povećanje pritiska ili smanjenje pritiska ispod 20% u nivou spoljnjeg analnog sfinktera pri defekacionom napinjanju. U radu je analizirana zastupljenost anizma kao uzroka funkcionalne opstipacije u grupi bolesnika sa pozitivnim tzv. rimskim (Roma) III kriterijumima za funkcionalnu opstipaciju. Korišćena je anorektalna manometrija, te je na taj način analiziran i njen klinički značaj u dijagnostici anizma. **Metode.** Metoda anorektalne manometrije korišćena je kod 60 bolesnika koji su imali funkcionalnu opstipaciju definisanu pomenutim rimskim kriterijumima, kao i kod 30 zdravih osoba (kontrolna grupa). **Rezultati.** Zastupljenost anizma bila je visoko statistički značajnija u grupi bolesnika sa funkcionalnom opstipacijom u odnosu na kontrolnu grupu ($p < 0.01$). Ustanovljeno je da rimski III kriterijumi za funkcionalnu opstipaciju tačno predviđaju anizam kod 90% bolesnika. Analizirana je korelacija anizma sa insuficijencijom spoljnjeg analnog sfinktera, rektalnim senzibilitetom, uvećanim hemoroidalnim spletovima, divertikulumima i anatomskim varijacijama kolona. Nije utvrđeno postojanje udruženosti anizma sa pomenutim entitetima. **Zaključak.** Postoji značajna korelacija anizma sa simptomima funkcionalne defekacije, tj. pozitivnim rimskim (Rome) III kriterijumima za funkcionalnu opstipaciju. Anorektalna manometrija trebalo bi da bude standardna metoda kod bolesnika sa funkcionalnom opstipacijom koji imaju pozitivne rimske (Rome) kriterijume za funkcionalnu opstipaciju.

Ključne reči:
opstipacija; manometrija; faktori rizika; srbija.

Introduction

Anismus is a paradoxical pressure increase or pressure decrease less than 20% of the external anal sphincter (EAS) during defecation straining [1–4]. It is an acquired disorder that can occur in children as a new behavioral pattern in order to avoid discomfort related to passage of large-volume stools or pain during defecation in patients with fissures or inflamed piles [2, 3, 5]. It can also occur as a consequence of sexual or physical abuse [2, 6–8].

The aim of the study was to establish the frequency and correlation of anismus as a cause of functional constipation when the positive Rome III criteria are present.

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The Rome III criteria for functional constipation must include two or more of the following: straining during at least 25% of defecations; lumpy or hard stools in at least 25% of defecations; sensation of incomplete evacuation for at least 25% of defecations; sensation of anorectal obstruction/blockage for at least 25% of defecations; manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor); fewer than three defecations *per* week; loose stools are rarely present without the use of laxatives; insufficient criteria for irritable bowel syndrome; (criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis) [1, 3].

Decreased rectal sensitivity and increased EAS pressure can cause obstructive defecation. In constipated patients we can find enlarged piles, diverticular disease, the ptotic or long colon [1]. Therefore, we also investigated the correlation of anismus with rectal sensibility disorders, EAS competence, enlarged piles, diverticular disease, ptotic or long colon.

Methods

We had 90 patients, 60 with symptoms of functional constipation (positive Rome III criteria for functional constipation) and 30 healthy subjects in the control group.

All the patients had normal endoscopic or large bowel enema study findings and no evidence for metabolic, inflammatory or neoplastic processes that can cause constipation.

We used water-perfused anorectal manometry procedure (Medtronic device). We followed standards for performing anorectal manometry [5, 9, 10].

The data we received were analyzed by SPSS 16.0 software for Windows.

We used descriptive statistic methods, χ^2-test and Fisher's test.

Values less than 0.05 were considered statistically significant.

Results

In the group of patients with functional constipation, anismus had 54 out of 60 (90%) patients which is highly statistically significant ($p < 0.01$) compared to the control group where we found anismus in 4 out of 30 (13.33%) patients (Table 1).

Table 1

The presence of anismus in the group of patients with the positive modified criteria for functional constipation and in the control group

Anismus	Group of patients	Control group	Total
Yes	54	6	60
No	6	24	30
Total	60	30	90

In the group of patients with anismus EAS insufficiency had 34 out of 54 (64.81%) patients. In the control group EAS insufficiency had 3 out of 6 (50%) patients with anismus, which was not statistically significant ($p > 0.05$).

In the group of patients with anismus, rectal sensibility disorders had 20 out of 54 (37%) patients. In the control group sensibility disorders had 1 out of 6 (16.66%) patients with anismus, which was not statistically significant.

Enlarged piles had 23 out of 54 (42.59%) patients with anismus, while 1 patient out of 6 (16.66%) patients with anismus in the control group had enlarged piles. No statistically significant difference was found.

Colonoptosis or dolichocolon had 20 out of 54 (37%) patients with anismus. In the control group 4 out of 6 patients with anismus had colonoptosis or dolichocolon or both. No statistically significant difference was found.

Diverticular disease had 10 out of 54 (54%) patients with anismus and none out of 6 (0%) patients with anismus in the control group. No statistically significant difference was found.

Discussion

Dyssinergic defecation significantly affects quality of life [8, 9]. Therefore it is necessary to diagnose this problem in order to apply appropriate treatment strategy.

Anorectal manometry is a very important method for assessment of patients with constipation [10–19]. We tested internal and external anal sphincter resting pressures, rectoanal inhibitory reflex (presence and adaptability) and rectal sensibility [5, 10].

According to the Mayo Clinic study (1,000 patients with constipation), 28% of the patients had defecatory disorders, i.e. anismus [20]. Another study that included 100 patients with the positive Rome II criteria for functional constipation showed that 46% of the patients had dyssinergic defecation i.e. anismus [20]. There are studies with up to 59% of patients with anismus [21–23].

Our results showed that 90% of the patients with the positive Rome III criteria for functional constipation had anismus, which was highly statistically significant relative to the control group.

We did not find any correlation between anismus and rectal sensibility disorders, EAS insufficiency, diverticular disease, enlarged piles and dolichocolon or colonoptosis.

We did not find data about these correlations in published papers.

Conclusion

The results of our study show than 90% of all the patients with positive Rome III criteria for functional constipation had anismus diagnosed by anorectal manometry.

This high percentage suggests necessity to perform anorectal manometry in all patients with the positive Rome III criteria for functional constipation.

By using this approach we could make the early diagnosis of outlet obstruction (anismus) and apply appropriate treatment strategy like biofeedback (re-educaton) therapy which gives very good results.

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Index of orthodontic treatment need in children from the Niš Region

Indeks potrebe za ortodontskim lečenjem kod dece niškog regiona

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Abstract

Background/Aim. The Index of Orthodontic Treatment Need (IOTN) is a scoring system for malocclusion that consists of the two independent components: Denal Health Component (DHC) and Aesthetic Component (AC). IOTNs are usually used in the countries with dental healthcare financed by the government through the national healthcare system or healthcare insurance. The aim of the study was to determine IOTN in primary school children from the town of Niš and to asses percent of children with any kind of orthodontic treatment. **Methods.** The study involved 301 school children, 11–14 (12.4 ± 1.1) years old. The IOTN was used by the two examiners in order to evaluate the treatment need. **Results.** The results of the study showed that 111 (37%) out of 301 examined children had orthodonic treatment (33.33% boys and 66.67% girls) and they were excluded from the study. Out of final sample of 190 school children, considering DHC of the IOTN, 27.4% of the children showed great (grades 4–5), 41.0% moderate (grade 3) and 31.6% slight or no treatment need (grade 1–2). Considering IOTN AC, 15.3% of the children showed great (grade 8–10), 24.3 % moderate (grade 5–7) and 60.4% slight or no treatment need (grade 1–4). **Conclusion.** The need for orthodontic treatment in school children in the town of Niš, Serbia, is similar to the need in most European countries, despite the fact that the number of children orthodontically treated is much higher compared to most of European countries.

Key words:
orthodontics, corrective; malocclusion; child; data interpretation, statistical.

Apstrakt

Uvod/Cilj. Indeks potrebe za ortodontskim lečenjem (IOTN) je indeks za procenu izraženosti malokluzija koji se sastoji od dve nezavisne komponente: komponente zdravlja zuba (DHC) i estetske komponente (AC). Indeks IOTN najčešće se primenjuje u zemljama u kojima se stomatološka služba finansira od strane države preko zdravstvenih fondova i sistema zdravstvenih institucija. Cilj ovog rada bio je da se odredi IOTN kod dece iz osnovnih škola u Nišu i da se utvrdi procenat dece koja imaju istoriju ortodontskog lečenja. **Metode.** Studijom je bilo obuhvaćeno 301 dete, uzrasta od 11 do 14 godina, koje su ispitala 2 ispitivača. **Rezultati.** Rezultati istraživanja pokazali su da je 111 (37%) ispitane dece imalo istoriju ortodontskog lečenja (33,33% dečaka i 66,67% devojčica) i oni su bili isključeni iz studije. Od preostale 190 dece, na osnovu analize DHC IOTN 27,4% imalo je veliku (stadijum 4–5), 41,0% umerenu (stadijum 3) i 31,6% malu ili nikakvu potrebu (stadijum 1–2) za ortodontskim tretmanom. Analizom AC IOTN 15,3% ispitane dece imalo je veliku (stadijum 8–10), 24,3% umerenu (stadijum 5–7) i 60,4% malu ili nikakvu potrebu (stadijum 1–4) za ortodontskim tretmanom. **Zaključak.** Indeks IOTN kod dece iz Niša sličan je onom kod dece u većini evropskih država, uprkos činjenici da je broj dece koja su ortodontski lečena u Nišu znatno veći nego u evropskim zemljama.

Ključne reči:
ortondoncija, korektivna; malokluzija; deca; statistička interpretacija podataka.

Introduction

In the Republic of Serbia, Healthcare Fund provides free mobile appliances for orthodontic treatment for children under 18. Orthodontic treatment with fixed appliances will be charged depending on the institution in which the treatment is carried out. In the City of Niš, in public institutions, generally, there are waiting lists for orthodontic treatment with mobile appliances. Waiting time for the treatment is from two to three months.

The orthodontic treatment is not obligatory and it depends on personal desires of children and their parents. Thus, educating parents and children in this sense even in primary schools, would certainly contribute to rising the awareness

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among parents and children about the existing orthodontic irregularities. It would influence the increment of the number of patients who request orthodontic treatment. Assessment of the severity of malocclusion and estimating the need for treatment is not always easy and depends on many factors: age, gender, dentition, knowledge, and experience of the orthodontist, but of course also on the financial situation of patients [1].

Many studies are dealing with the assessment of the need of orthodontic treatment by patients and orthodontists [2–6]. There is a significant difference in the assessment of patients and specialists in orthopedics of jaws, except when it comes to very severe forms of irregularities.

The first quantitative method for the assessment of malocclusion was developed by Massler and Frankel in 1951 [7]. Since then a large number of occlusal indexes was developed. Several contemporary orthodontics methods are used for assessing the severity of malocclusion, such as: Index of Orthodontic Treatment Need (IOTN) [4], Peer Assessment Rating Index (PAR) [8] and the Index of Complexity, Outcome and Need (ICON) [9]. The IOTN and ICON are most commonly used. The results of the measurement needs for treatment obtained by these methods in certain ethnic groups largely coincide [10]. The IOTN is due to its simplicity more frequently used especially among researchers from the Middle East [11–15].

The IOTN is a scoring system for malocclusion, developed by Brook and Shaw [4] in 1989. It consists of the two independent components. The Dental Health Component (DHC) is a five-grade index that records the dental health need for orthodontic treatment. The Aesthetic Component (AC) records the aesthetic need for orthodontic treatment using a ten-grade standardized ranking scale of colored photographs showing different levels of dental attractiveness.

These indexes are usually used in the countries with dental healthcare financed by the government through the national healthcare system or healthcare insurance (Denmark, Finland, Norway, and Great Britain). The leading idea is to take care of patients with severe orthodontic anomalies first and to limit the free of charge orthodontic services to severe cases of malocclusions. This can considerably narrow the waiting list [3].

Up to now, in the city of Niš there were no studies on the IOTN. The aim of this study was to determine the IOTN among children from the city of Niš aged 11–14 and to find the percentage of children with the history of orthodontic treatment. The results would help determine the facts about the prevalence of malocclusion and the efficiency of the existing healthcare services.

Methods

The study was approved by the Ethical Committee of the Faculty of Medicine, University of Niš, Serbia. With the help of schoolteachers, families of the examined children were contacted to obtain authorisation.

We examined 301 children, from 4 primary schools in Niš (139 boys and 162 girls). Their average age was 12.4 ± 1.1 years. A group of 111 children of the initial sample was excluded from the study because of a previous or current orthodontic treatment. The final sample included 190 school children, 102 boys and 88 girls. Their average age (± standard deviation) was 12.28 ± 1 years. The sample was chosen in order to give us reliable data for school children population from Niš.

The two orthodontists were collecting data. Before starting investigation, the necessary calibrations using plaster models were done with the examiners to provide the validity of the results. The clinical examinations were performed in school dental ordinations. In one session not more than 20 children were examined to avoid tiredness of the examiners. Following the World Health Organization (WHO) criteria and recommendations for oral health examinnations, WHO – type periodontal probe and No. 5 plain mouth mirror were used. The used indices were IOTN, DHC, and AC. The DHC consists 5 grades. Grade 1 and 2 represent slight or no treatment need, grade 3 moderate and grade 4 and 5 represent great need of orthodontic treatment. AC consists a scale of 10 color photographs showing 10 levels of dental attractiveness starting with most attractive dentition (grade 1). Grade 1 to 4 represent slight or no treatment need, grades 5 to 7 moderate and grades 8 to 10 represent great need for orthodontic treatment.

To test intra-examiner agreement, 65 of the referred population were re-examined, 6 weeks after their initial examination. The assignment of grades was also done by two examiners to test inter-examiner agreement. Kappa statistics [16] was used to evaluate the consistency of both intra-examiner and inter-examiner agreement.

The data were recorded on examination record forms and processed and stored in the access database. Statistical analysis was undertaken using the Statistical package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 12.0. We analised the IOTN results regarding gender using the χ^2-test. The differences greater than ($p < 0.05$) were considered statistically significant.

Results

The kappa values of the intra-examiner reproducibility for the DHC and AC were 0.88 and 0.80, respectively. On the other hand, the kappa values of the inter-examiner for the DHC and AC were 0.84 and 0.78.

The distribution of the results of the orthodontic treatment need in relation to DHC IOTN is shown in Table 1. Considering DHC IOTN 27.4% of school children from Niš showed great (grades 4–5), 41.0% moderate (grade 3) and 31.6% slight or no treatment need (grade 1–2). There were no statistically significant gender differences in the determined treatment need using the DHC ($\chi^2 = 1.78$; $p = 0.183$). The distribution of the results of the orthodontic treatment need in relation to the AC IOTN is shown also in Table 1. Considering the IOTN AC, 15.3% of school children from Niš showed great (grade 8–10), 24.3 % moderate (grade 5–7) and 60.4% slight or no treatment need (grade 1–4). No statistically significant gender differences in treatment need determined using the AC were found ($\chi^2 = 0.37$; $p = 0.543$).

Table 1

Influence of gender on Dental Health Component (DHC) and Aesthetic Component (AC) of treatment need frequency [expressed as Index of Orthodontic Treatment Need (IOTN) grade]

IOTN component (grade)	Male (n = 102) n (%)	Female (n = 88) n (%)	Total (n = 190) n (%)
DHC*			
1and 2	32 (31.5)	28 (31.8)	60 (31.6)
3	38 (37.3)	40 (45.4)	78 (41.0)
4 and 5	32 (31.4)	20 (22.7)	52 (27.4)
AC†			
1–4	55 (54.5)	59 (67.0)	114(60.4)
5–7	29 (28.7)	17 (19.3)	46 (24.3)
8–10	17 (16.8)	12 (13.6)	29 (15.3)

χ^2= 1.78; p = 0.183; χ^2= 0.37; p = 0.543 (no statistically significant gender differences).
***grade: 1–2 – slight or no treatment need; 3 – moderate treatment need; 4 and 5 – great treatment need**
† grade: 1–4 – slight or no treatment need; 5–7 moderate treatment need; 8–10 great treatment need.

Discussion

The conducted study is one of the first epidemiological studies on malocclusions using IOTN on the territory of the town of Niš. The obtained results allow comparisons with the other regions of Serbia as well as with the results obtained in Europe and other parts of the world. The present results are not totaly representative because of the fact that 37% of the examined children had the history of orthodontic treatment and they were excluded from the study.

In this study, the intra-examiner kappa values were 0.88 and 0.80 for the DHC and AC, respectively. The intra-examiner kappa values were 0.84 and 0.78 for the DHC and AC, respectively. When these values were analyzed, almost perfect agreement was obtained for the DHC and substantial agreement for the AC.

Taking into consideration IOTN DHC, our result of 27.4% of the children with the great need for orthodontic treatment is similar to the results obtained in the Southern Italy, (27.3%) [17], and in Spain, (21.8%) [18], while substantially smaller than those obtained in Sweden (37%) [19], Turkey (38.8%) [20] and Malaysia (47.9%) [21]. Significantly lower DHC IOTN value is found in Iran (18.4%) [22] and the Western Sahara (18.1%) [23]. According to AC IOTN our results 15.3% of the children with the great need for orthodontic treatment is similar to those obtained in the Western Sahara [23] (13.7%), while higher values are obtained in Malaysia (22.8%) [21]. Most of the authors, however, received very low values of AC IOTN: in Iran 8.7% [22], Spain 4.4% [18], Turkey 4.8% [20], Sweden 2.3% [19]. In our study there are no gender differences in the distribution of the orthodontic treatment need. These results are in the line with the results of many studies [17, 20, 23].

The percentage of children with the history of orthodontic treatment (37%) is incredibly high compared to the results obtained in the Western Europe [18, 24, 25]. In the UK the percentage of orthodontically treated children aged 15–16 is 14%, France 2.4%, and 26.6% in Spain. This is a fact which is important to know when interpreting the results obtained after determining the IOTN only in children who did not have the history of orthodontic treatment.

Conclusion

The use of the Index of Orthodontic Treatment Need in epidemiological studies can be useful for comparing the need for orthodontic treatment in different populations and planning and improving the healthcare system of the society. The need for orthodontic treatment in school children in the town of Niš, Serbia, is similar to the need in most European countries, despite of the fact that the number of children orthodontically treated is much higher as compared to European countries.

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Effect of diode laser cyclophotocoagulation in treatment of patients with refractory glaucoma

Efekat ciklofotokoagulacije diodnim laserom na lečenje bolesnika sa refraktornim glaukomom

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Abstract

Background/Aim. Refractory glaucoma is glaucoma resistant to conventional management (maximally tolerated medical therapy, one or more glaucoma surgeries) and glaucoma in cases of neovascularisation after panretinal photocoagulation or cryoablation. The aim of the study was to determine the intraocular pressure (IOP) lowering efficacy of transscleral diode laser cyclophotocoagulation (DCPC) treatment in the management of pain and IOP in patients with refractory glaucoma. **Methods.** This nonrandomized, retrospective study, included 95 patients (95 eyes) with refractory glaucoma treated at the University Eye Clinic, Clinical Center of Vojvodina, Novi Sad, Serbia, between November 2007 and November 2012 in accordance with the established protocols (16–18 spots, 270°, up to 5J of energy). All the eyes were treated with transscleral DCPC (Iris Medical OcuLight SLx, Iridex Co, Mountain View, USA). Patient's symptoms, bests corrected visual acuity and IOP were recorded 7 days, and 1, 3 and 6 months after the DCPC treatment. **Results.** Out of 95 patients (95 eyes) enrolled in this study 24 (25.2%) were with primary (the group I), and 71 (74.5%) with secondary (the group II) glaucoma. The mean baseline IOP in these two groups was similar: 36.08 ± 8.39 mmHg for the first group and 37.36 ± 8.19 mmHg in the second group. Measurement of the mean IOP in the group I showed the following results: on the day 7 it was 13.96 ± 8.30 mmHg (62.1% decrease of the baseline value), on the day 30 it was 18.44 ± 8.85 mmHg (48.9% decrease regarding the baseline value), after 3 months it was 22.44 ± 7.36 mmHg (37.8% decrease regarding the baseline value), and after 6 months it was 25.92 ± 7.65 mmHg (28.2% decrease regarding the baseline value). Measurement of IOP in the group II showed the following results: on the day 7 it was 15.77 ± 9.73 mmHg (57.8% decrease of the baseline value), on the day 30 it was 20.14 ± 10.20 mmHg (46.1% decrease regarding the baseline value), after 3 months it was 23.46 ± 9.83 mmHg (37.2% decrease regarding the baseline value) and after 6 months it was 27.23 ± 9.87 mmHg (27.2% decrease regarding the baseline value). Pain was the main symptom in 70 (73.6%) patients before the treatment and it persisted in only 4 (4.2%) of our patients. Other complaints (burning, stinging, foreign body sensation) were experienced by 39 (41%) of the patients, postoperatively. A total of 52 (54.7%) patients had no complaints after the treatment. **Conclusion.** Our study confirmed that transscleral DCPC is a useful, effective and safe procedure with predictable amount of IOP decrease, which makes it the treatment of choice for refractory glaucoma.

Key words:
ophthalmologic surgical procedures; glaucoma; laser coagulation; lasers; intraocular pressure; treatment outcome.

Apstrakt

Uvod/cilj. Refrakorni glaukom spada u grupu glaukoma koji ne reaguje na konvencionalnu terapiju. Cilj ove studije bio je da se odredi efekat sniženja intraokularnog pritiska (IOP) kod bolesnika sa refraktornim glaukomom nakon transskleralne ciklofotokoagulacije diodnim laserom. **Metodi.** Ova nerandomizirana, retrospektivna studija obuhvatila je 95 očiju sa refraktornim glaukomom lečenih dioda laser ciklofotokoagulacijom na Klinici za očne bolesti Kliničkog centra Vojvodine u periodu 2007–2012, prema ustanovljenom protokolu (16–18 pečata, 270°, do 5J energije). Simptomi, vidna oštrina i IOP su praćeni 7 dana, a zatim 1, 3 i 6 meseci nakon lečenja. **Rezultati.** Ukupno 25 bolesnika (95 očiju) bilo je uključeno u studiju, 24 (25,2%) bolesnika sa primarnim (1. grupa) i 71 (74,5%) bolesnik sa sekundarnim (2. grupa) glaukomom. Srednji IOP pre terapije kod obe grupe bio je sličan: 36,08 ± 8,39 mmHg za prvu i 37,36 ± 8,19 mmHg za drugu grupu. Srednje vrednosti IOP za prvu grupu tokom perioda praćenja bile su: 7.

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dana 13,96 ± 8,30 mmHg (62,1% sniženja), 30. dana 18,44 ± 8,85 (48,9% sniženja), nakon 3 meseca 22,44 ± 7,36 mmHg (37,8% sniženja), nakon 6 meseci 25,92 ± 7,65 mmHg (28,2% sniženja). Srednje vrednosti IOP za drugu grupu tokom perioda praćenja bile su: 7. dana 15,77 ± 9,73 mmHg (57,8% sniženja), 30. dana 20,14 ± 10,20 mmHg (46,1% sniženja), nakon 3 meseca 23,46 ± 9,83 mmHg (37,2% sniženja), i nakon 6 meseci 27,23 ± 9,87 mmHg (27,2% sniženja). Bol je pre terapije bio prisutan kod 70 (73,6%) bolesnika, a nakon tretmana kod samo 4 (4,2%) bolesnika. Tegobe kao što su pečenje, osećaj stranog tela, bockanje, postoperativno su bile prisutne kod 39 (41%) bolesnika. Posle lečenja, tegobe nisu imala 52 (54,7%) bolesnika. **Zaključak.** Naša studija je potvrdila da je transskleralna ciklofotokoagulacija diodnim laserom koristan i efikasan metod u smanjenju IOP, što ga čini terapijom izbora za refraktorni glaukom.

Ključne reči:
hirurgija, oftalmološka, procedure; glaukom; koagulacija laserom; laseri; intraokularni pritisak; lečenje, ishod.

Introduction

Refractory glaucoma is glaucoma resistant to conventional management (maximally tolerated medical therapy, one or more glaucoma surgeries) and glaucoma in cases of neovascularisation after panretinal photocoagulation or cryoablation [1].

Refractory glaucoma are generally treated with cyclodestructive procedures such as: surgical excision of ciliary body, cycloirradiation, cycloelectrolysis, cyclodiathermy, cyclocryotherapy, ultrasound or microwave cyclodestruction and with Neodymium Yttrium Aluminum Garnet (Nd:YAG) and diode laser cyclophotocoagulation (DCPC) [2].

Beside refractory primary open and angle closure glaucoma indications for cyclodestructive procedures are: neovascular, post-traumatic, aphakic/pseudophakic glaucoma especially with anterior chamber intraocular lenses (IOL), severe congenital glaucoma with multiple failed surgeries, post-penetrating keratoplasty glaucoma, post-retinal detachment surgery glaucoma, silicone oil induced glaucoma, inflammatory glaucoma.

Mechanism of action of cyclophotocoagulation includes decrease of aqueous production and increase of aqueous outflow [3]. Destruction of the ciliary epithelium combined with destruction of ciliary blood vessels and coagulative necrosis, leads to decrease in aqueous production [4]. In many cases inflammation after the treatment leads to short-term hypotension [5].

Neuroepithelial defects created after laser treatment, and creation of transscleral flow similar to cyclodialysis, are responsible for increase of aqueous outflow which is related to the extent of treatment [6]. Diode laser causes destruction of the pigmented and nonpigmented ciliary epithelium and capillaries in the ciliary processes with pigment clumping, coagulative necrosis, and extensive destruction of ciliary muscle with a moderate reduction in vascularity [7]. Some histopathologic studies have shown that diode laser produces most of its coagulative effect on the ciliary body stroma [8]. Even though it is not completely understood, it seems that there is an increase of uveoscleral outflow through the enlarged extracellular spaces from the anterior chamber into the suprachoroidal space [9].

Diode and Nd:YAG lasers require the presence of ciliary body pigment epithelium for the absorption of laser energy [10]. A diode laser (810 nm) has a greater melanin absorption compared to a Nd:YAG laser (532 nm), requiring lesser energy *per spot* [11]. Data about dosage and laser treatment protocol-related response vary in available literature [1, 12, 13]. A totally delivered energy, the number of laser burns *per* session and pulse power and duration were analyzed in numerous studies, but the results were inconclusive and contradictory. However, most of the results confirmed that refractory glaucoma can be successfully managed on a long-term basis with single or repeated diode laser cyclophotocoagulation [14].

Recently, contact diode laser cryoablation has emerged as the preferred treatment because cryoablation and Nd:YAG laser cyclophotocoagulation are associated with a greater risk of hypotony and phthisis due to excessive ciliary body destruction [15–19].

The aim of the study was to determine the intraocular pressure (IOP) lowering efficacy of transscleral DCPC treatment in the management of pain and IOP in patients with refractory glaucoma.

Methods

This nonrandomized, retrospective study included 95 patients (95 eyes) with refractory glaucoma treated at the University Eye Clinic, Clinical Center of Vojvodina, Novi Sad, Serbia, between November 2007 and November 2012. The study was conducted in accordance with the Declaration of Helsinki. The patients were divided into two groups: the group I – patients with primary glaucoma [primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG) and group II – patients with secondary glaucoma (neovascular glaucoma, glaucoma post pars plana vitrectomy and traumatic glaucoma)].

All the eyes were treated with transscleral DCPC (Iris Medical OcuLight SLx, Iridex Co, Mountain View, USA). Inclusion criteria were: painful eyes or eyes with other ocular symptoms (burning, itching, foreign body sensation) with elevated IOP and best corrected visual acuity (BCVA) lower than 0.1 according to Snellen. All anti-glaucoma therapeutic modalities (topical, systemic medications), except cyclocryo destructive procedures were tried and rendered unsuccessful. All the patients received retrobulbar or peribulbar anesthesia with 3–5 mL injection of lidocaine hydrochloride alone or in combination with bupivacaine hydrochloride. Cyclophotocoagulation treatment employed diode infrared laser of 810 nm

of wavelength. The average power used was 2.5 W, with 1.5 seconds of duration. Contact tip of G-probe was positioned 1.2 mm behind surgical limbus and 16–18 spots spread over 270° *per* session were made. The sound of "pop" or "snap" at the treatment site was used as indicator for tissue disruption within the ciliary body. To prevent potential inflammatory reactions topical 1% dexamethasone, every one to two hours while awake, and atropine sulfate 1%, twice a day for the first seven days, were applied in all the patients.

When the patients required repeated treatment due to insufficient reduction in IOP, spots were made in untreated quadrants behind limbus.

The patient's symptoms, BCVA and IOP were recorded 7 days, and 1, 3 and 6 months after the DCPC treatment.

For statistical analyses we used Microsoft Excel software with standard statistical parameters and methods – numerical data were presented using minimum, maximum and average values) standard deviation (SD) and 95% confidence interval (CI). Student's *t*-test was used to make comparison between the groups and to compare IOP values.

Results

A total of 95 patients (95 eyes) were enrolled in this study, of whom 24 (25.2%) were with primary (the group I) and 71 (74.5%) with secondary (the group II) glaucoma. In the group I, there were 20 (21%) patients with POAG and 4 (4.2%) patients with PACG. In the group II 53 (55.7%) patients had neovascular glaucoma, 11 (11.5%) patients had glaucoma after pars plana vitrectomy and 7 (7.3%) patients had traumatic glaucoma.

There was a predominance of males in both groups (55.7% *vs* 44.3%). The mean age of patients was 61.5 years (SD ± 15.4; range 13–86 years). Forty-five (47.3%) patients were with no light perception (L-). BCVA ≤ 0.1 was found in 50 (52.7%) patients. There was no significant difference between the treatment groups in the mean age, gender and visual acuity. Pain was the chief complaint and the main reason for treatment in 70 (73.6%) patients (20 patients in the group I and 4 patients in the group II), while other complaints (burning, stinging, foreign body sensation) were the main reason for treatment in 25 (26.4%) patients (4 patients in the group I and 21 in the group II). The mean baseline IOP in the two groups was similar: 36.08 ± 8.39 mmHg for the group I and 37.36 ± 8.19 mmHg in the group II. The demographic characteristics and the baseline IOP values are shown in Table 1.

Table 1

Demographics and baseline characteristics of the patients

Variable	Groups of patients	
	Primary glaucoma	Secondary glaucoma
Age (years), $\bar{x}$ ± SD (min-max)	57.16 ± 10.03 (33–79)	63.12 ± 14.46 (13–86)
Gender, n (%)		
male	13 (54.16)	40 (56.33)
female	11 (45.83)	31 (43.66)
BCVA, n (%)		
0.03–0.1	8 (33.33)	22 (31)
L+P+–0.02	3 (12.5)	17 (23.94)
L-	13 (54.17)	32 (45.07)
Complaints		
pain	20 (83.33)	50 (70.42)
other	4 (16.66)	21 (29.58)
Baseline IOP (mmHg), $\bar{x}$ ± SD	36.08 ± 8.39	37.36 ± 8.19

BCVA – best corrected visual acuity; IOP – intraocular pressure.

Mean IOP measurement in the group I showed the following results: on the day 7 it was 13.96 ± 8.30 mmHg (62.1% decrease regarding the baseline volume), on the day 30 it was 18.44 ± 8.85 mmHg (48.9% decrease regarding the baseline value), after 3 months it was 22.44 ± 7.36 mmHg (37.8% decrease from the baseline value), and after 6 months it was25.92 ± 7.65 mmHg (28.2% decrease regarding the baseline value) (Figure 1).

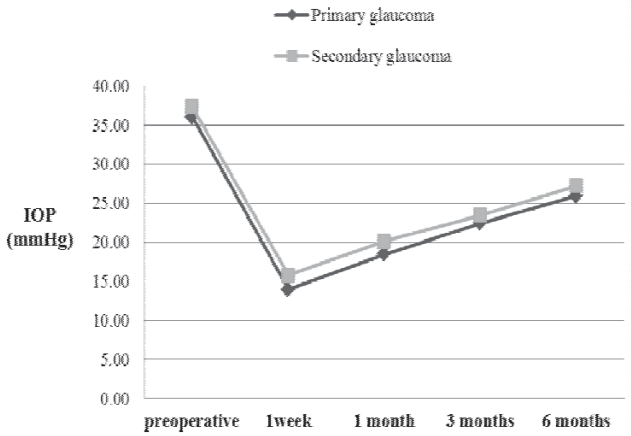

Fig. 1 – Mean intraocular pressure (IOP) by the treatment groups.

Measurement of IOP in the second group showed the following results: on day 7 it was 15.77 ± 9.73 mmHg (57.8% decrease regarding the baseline value), on day 30 it was 20.14 ± 10.20 mmHg (46.1% decrease regarding the baseline value), after 3 months it was 23.46 ± 9.83 mmHg (37.2% decrease regarding the baseline value), and after 6 months it was 27.23 ± 9.87 mmHg (27.2% decrease regarding the baseline regarding) (Figure 1).

During a 6-month follow-up IOP was significantly lower regarding the baseline values in both groups ($p < 0.001$), but there was no significant difference between the two groups.

After the treatment pain persisted in only 4 (4.2%) patients. Other complaints (burning, stinging, foreign body sensation) were postoperatively experienced by 39 (41%) patients. A total of 52 (54.7%) patients had no complaints after the treatment (Figure 2).

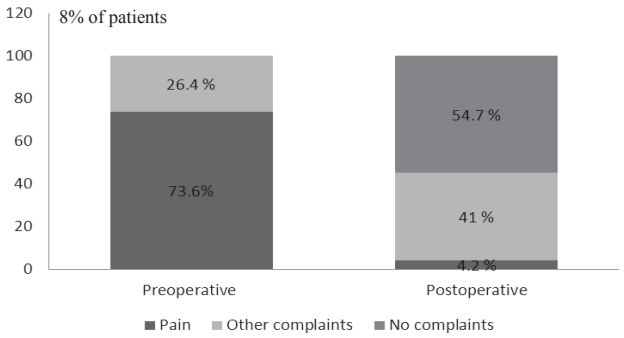

Fig. 2 – Change in chief complaints during the treatment.

Discussion

Transscleral cyclophotocoagulation with a diode laser has gained popularity and has practically replaced the Nd:YAG laser and cryo method for treatment of refractory glaucoma due to comparable efficacy. However, some studies have found that the therapeutic effect can be lost over time and in some cases repeated treatment is necessary [20].

There are two factors that determine the laser power – energy and the duration of application. The energy *per* application should be kept under 5 J. A longer duration allows the thermal energy to spread through the tissue and reach the ciliary epithelium [12].

We obtained good results with settings of 2,500 mW and 1.5 seconds of duration (3.75 J), reserving the higher energy levels for repeated procedures and lower settings for eyes with more heavily pigmented irises.

Long-term study of Ataullah et al. [21] in the Manchester Royal Eye Hospital used 1,500 mW with 2.5 seconds of duration. Six months after DCPC IOP reduction was 42% regarding the baseline value. We found a reduction in IOP six months after the treatment by 28.2% (the group I) and 27.2% (the group II) regarding the baseline values.

Noureddin et al. [13] showed an IOP decrease in 36 refractory glaucoma eyes from 35.8 mmHg to 19 mmHg (47% regarding the baseline values) which is a higher IOP decrease than our study presented. This difference can be explained by the fact that they performed a 360 degrees cyclophotocoagulation compared to 270 degrees of treatment in our study.

The other study of Hawkins and Stewart [22] showed an IOP decrease by 36% after DCPC, from 32.5 mmHg preoperative to 21.8 mmHg six months after the treatment. That is comparable to the results of our study.

Egbert et al. [23] showed a 20% of IOP decrease six months after DCPC in the treatment of refractory POAG. In that study 360 degrees of laser treatment was performed and the energy was 1,500 mW. Our study showed a decrease in IOP in the patients with primary glaucoma of 28.2% regarding the baseline value.

A retrospective analysis of Murphy et al. [14] including 263 eyes with refractory glaucoma after transscleral DCPC, showed that 89% of the patients reached 30% drop in IOP. This overall IOP decrease was similar to our study results. They had found 3% of patients with pain after the treatment. In our study 4.2% of the patients had persistent pain postoperatively due to IOP increase unresponsive to the repeated procedures.

In a multicenter study, 30 eyes of 30 patients with refractory glaucoma were followed for a median of 2 years after DCPC. Seventeen to 19 applications were made over 270 degrees, 2 seconds duration and 1,500–2,000 mW power. IOP fell from a mean baseline pressure of 36.1 mmHg to a mean of 21.6 mmHg and remained essentially unchanged for the duration of the study [24]. After a 6-month follow-up our study showed comparable results.

Conclusion

Our study confirmed that transscleral diode laser cyclophotocoagulation is a useful, effective and safe procedure with predictable amount of intraocular pressure decrease, which makes it the treatment of choice for refractory glaucoma.

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Influence of disease activity on functional capacity in patients with rheumatoid arthritis

Uticaj aktivnosti bolesti na funkcijski status bolesnika sa reumatoidnim artritisom

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Abstract

Background/Aim. Progressive erosive changes in cartilage and bone in rheumatoid arthritis (RA) ultimately lead to joint deformities and disability which may be early, severe and permanent. Consequently, there is the reduction of functional ability and changes in the quality of life. The aim of this study was to estimate the impact of disease activity on functional status of patients with RA. **Methods.** A prospective investigation included 74 patients with RA who were treated in the Rheumatology Clinic of the "Niška Banja" Institute. Assessment of functional status (capacity) was measured by the Health Assessment Questionnaire (HAQ) with the values from 0 to 3 that patients fill out on their own. The patients were then divided into three groups: the group I with the HAQ values from 0.125 to 1.000, the group II with the values from 1.125 to 2.000 and the group III with the values from 2.125 to 3.000. Disease activity was measured by Disease Activity Score (DAS28). The assessment also included sedimentation rate (SE) influence, IgM rheumatoid factor (RF) and C-reactive protein (CRP) positivity, age, and disease duration. **Results.** The patients with the most severe functional damage estimated by the HAQ – the group III, had the highest values of DAS28 SE (7.4 ± 0.8) compared to the group II (6.5 ± 1.2) and the group I (3.4 ± 1.2). The group III also showed the highest values of DAS28 CRP (7.1 ± 0.8) compared to the group II (6.7 ± 0.8) and the group I (3.6 ± 0.4). Compared with the patients with small and moderate functional damage, the patients in the group III had positive IgM RF and CRP as well as higher SE values more frequently and the difference was statistically significant. In the univariate logistic model, the tested parameters of DAS28 SE, DAS 28 CRP, SE, RF and CRP represent significant predictors of functional disability. The most significant factors that increase the odds of patient having the most severe functional damage include DAS28 SE which increases the odds by 5.5 times (OR = 5.450, 95% CI = 3.211–7.690, p = 0.001), DAS28 CRP by 5.1 times (OR = 5.111, 95% CI = 2.123–10.636, $p <$ 0.01), and the presence of increased CRP (OR = 5.219, 95% CI = 1.305–18.231, p = 0.019) by 5.2 times. **Conclusion.** Functional status evaluated by the HAQ is a standard for assessment of RA due to its convenience and good correlation with parameters of disease activity. The most significant factors that increase the odds that the patient has the greatest functional damage are DAS28 SE, DAS28 CRP and the presence of CRP.

Key words:
arthritis, rheumatoid; severity of illness index; questionnaires; prognosis.

Apstrakt

Uvod/Cilj. Progresivne erozivne promene hrskavice i kosti u reumatoidnom artritisu (RA) u krajnjem ishodu dovode do deformacije zglobova i invalidnosti koja može biti rana, teška i trajna. Posledično dolazi do smanjenja funkcijske sposobnosti i kvaliteta života. Cilj rada bio je ispitati uticaj aktivnosti bolesti na funkcijski status bolesnika sa RA. **Metode.** Prospektivnim ispitivanjem obuhvaćeno je 74 bolesnika sa RA, lečenih bolnički u Klinici za reumatologiju Instituta „Niška Banja". Procena funkcijskog statusa (sposobnosti) merena je upitnikom Health Assessment Questionnaire (HAQ), koji su bolesnici samostalno popunjavali (Health Assessment Questionnaire sa vrednostima od 0-3), a zatim su podeljeni u 3 grupe: grupa I sa vrednostima HAQ 0,125–1,000; grupa II sa vrednostima HAQ 1,125–2,000 i grupa III sa vrednostima HAQ od 2,125–3,000. Aktivnost bolesti procenjivana je indeksom aktivnosti bolesti (*Disease Activity Score* – DAS28). Analiziran je i uticaj brzine sedimentacije eritrocita (SE), pozitivnosti IgM reumatoidnog faktora (RF) i C-reaktivnog proteina (CRP), godina života i trajanja bolesti. **Rezultati.**

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Bolesnici koji su imali najteže funkcijsko oštećenje procenjeno HAQ-om (grupa III) imali su najviše vrednosti DAS28 SE (7,4 ± 0,8) u odnosu na grupu II (6,5 ± 1,2) i grupu I (3,4 ± 1,2), kao i najviše vrednosti DAS28 CRP (7, 1 ± 0,8) u odnosu na grupu II (6,7 ± 0,8) i grupu I (3,6 ± 0,4). Ispitanici grupe III imali su statistički značajno češće pozitivan IgM RF i CRP, višu vrednost SE, u odnosu na ispitanike sa manjim i umerenim funkcijskim oštećenjem. U univarijantnom logističkom modelu, ispitivani parametri DAS28 SE, DAS28 CRP, SE, RF i CRP predstavljali su značajne prediktore funkcijske nesposobnosti. Najznačajnije faktore koji povećavaju šansu da ispitanik ima najteže funkcijsko oštećenje predstavljali su DAS28 SE i to 5,5 puta (OR = 5,450, 95% CI = 3,211–7,690, p = 0.001), DAS28 CRP 5,1 puta (OR = 5,111, 95% CI = 2,123–10,636, p < 0,01), i prisustvo povišenog CRP-a (OR = 5,219, 95% CI = 1,305–18,231, p = 0,019) 5,2 puta. **Zaključak.** Funkcijski status procenjen upitnikom HAQ pokazao se kao standard pri oceni reumatoidnog artritisa zbog praktičnosti i dobre korelacije sa parametrima aktivnosti bolesti, gde su se kao najznačajniji faktori izdvojili indeks aktivnosti bolesti DAS28 SE, DAS28 CRP prisustvo CRP.

Ključne reči:
artritis, reumatoidni; bolest, indeks težine; upitnici, prognoza.

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic autoimmune disease which is characterised by symmetric inflammatory changes of synovial joints. During the course of the disease, progressive erosions in cartilage and bone appear, finally leading to characteristic deformities of joints and possible disability, which can be early one, severe and permanent [1]. Consequently, the patients' quality of life deteriorates including both self care and everyday activities and there is also a decrease in functional ability and productivity concerning professional activities, which leads to economical consequences because of treatment, rehabilitation and possible surgical methods of treatment. Success in the treatment of RA significantly depends on good and prompt assessment of disease activity [2]. RA activity determines the speed of the disease advancement and its potential for the development of anatomical and functional disorders [3].

Because of the variables of signs and symptoms manifestations, clinical trials use summary indices which overcome the problems of validity, reliability and sensitivity to changes, noticed in some characteristics [4, 5]. For the time being, the best tools for this assessment in individual patients are the Disease Activity Index and its validated modifications which include the Disease Activity Score (DAS) and DAS28 [4] developed by the European League Against Rheumatism (EULAR) [6]. Those indexes show a significant correlation with functional abilities, as well as with the outcome of the disease – radiographic progression of the disease [3–5].

The aim of this study was to examine the influence of disease activity on the functional status of RA patients.

Methods

This prospective study included 74 RA patients with the diagnosis established according to a revised American College of Rheumatology (ACR) criteria from 1987. The patients were hospitalized at the Rheumatology Clinic of the "Niška Banja" Institute. There were 57 (77%) women and 17 (23%) men. The average age of patients was 58.3 ± 8.6 years, and the average duration of the disease 7.8 ± 6.6 years. Assessment of the functional status (ability) was performed by the Health Assessment Questionnaire (HAQ) with the values from 0 to 3, which the patients filled out themselves. The patients were then divided into three study groups: group I – the subjects with smaller degree of functional damage with HAQ values 0.125–1.000, the group II with HAQ values 1.125–2.000 – subjects with moderate functional damage and the group III – subjects with complete functional disability and HAQ values from 2.125–3.000. The disease activity was assessed by the disease index activity DAS28, calculated on the basis of the number of painful and swollen joints out of a total of 28 examined, sedimentation rate (SE) for DAS28 SE, C-reactive protein (CRP) values for DAS28 CRP and assessment of general state of the patients by the use of the visual analogue scale (VAS, 0–100). DAS 28 values higher than 5.1 suggest a high disease activity, the values from 3.2 to 5.1 suggest moderate disease activity and the values from 2.6 to 3.2 suggest low disease activity. DAS28 value less than 2.6 suggests remission. Analysis also included SE rate, positivity of IgM Rheumatoid factor (RF) and CRP, age and disease duration. Analyzed data were presented by absolute and relative numbers (category variables), arithmetic mean and standard deviations (continuous numeric features). Comparison of numeric variables distributed by the type of normality, was performed by analysis of variance (ANOVA) test, while variables which were not distributed by the type of normality were compared by Kruskal-Wallis test. Mann Whitney *U*-test and Bonferroni test were used in the *Post hock* procedure. The definition of risk factors was done by univariate logistic regression. Statistical significance is regarded to be at the level of $p < 0.05$, defined by the statistical package SPSS (version 18).

Results

A statistically significant difference (ANOVA), was noticed in the DAS 28 SE variable ($F = 53.797$, $p < 0.001$), and in SE variable ($F = 8.253$, $p = 0.001$). *Post hock* analysis showed that DAS28SE and DAS28 CRP values were statistically significantly higher in the group III, as compared to the group II and the group I, as well as that the values of the same parameters in the group II were higher than in the group I.

A significance of SE value difference was also noticed, but only between the group III and the group I ($F = 8.253$, $p = 0.001$).

In the univariate logistic model, the examined parameters of DAS28 SE, DAS28 CRP, SE, RF and CRP represent significant predictors of functional disability. The most significant factors which increase the chance for a patient to be in the HAQ III group, i.e. to have the most severe functional damage include DAS 28 SE which increases the odds by 5.5 times (OR = 5.450, 95% CI = 3.211–7.690, p = 0.001), DAS28 CRP by 5.1 times (OR = 5.111, 95% CI = 2.123–10.636, $p < 0.01$), and the presence of CRP (OR = 5.219, 95% CI = 1.305–18.231, p = 0.019) by 5.2 times. As the significant risk factor at the level $p < 0.001$, RF singled out by increasing the odds that the patient has functional disability by 2.1 times.

ties, as well as with the disease outcome – radiographic disease progression [3–5].

The interaction between the disease activity and joint damage are the main factors which influence the functional ability.

Investigation of the relationship between the disease activity, joint destruction and functional capacity is very common in clinical investigations. This provides data on the degree to which the disease activity and current joint damage influence the functional ability of RA patients and their quality of life which has certain psychosocial and economic significance [2]. Functional capacity measured by Health Assessment Questionnaire Disability Index (HAQDI) deterio-

Table 1

Patient characteristics, significance of numerical differences of continuous variables between the examined groups (I–III) with respect to the Health Assessment Questionnaire (HAQ)

Variables	Groups of patients ($\bar{x} \pm SD$)							
	I		II		III		F	p
Age (years)	55.9	7.7	58.5	8.6	60.5	9.4	1.205	0.306
Disease duration (years)	5.5	3.8.	7.7	6.9	10.2	9.1	1.541	0.221
DAS28 CRP	3.6	0.4	6.7	0.8	7.1	0.8	10.084	†< 0.001^{A,B,C}
DAS28 SE	3.4	0.9	6.5	1.2	7.4	0.8	53.797	†< 0.001^{A,B,C}
SE	15.1	7.5	36.4	20.3	50.8	28.5	8.253	‡0.001^{B}

DAS – disease activity score; CRP – C-reactive protein; SE – sedimentation rate;
Group I –HAQ values from 0.125 to 1.000
Group II – HAQ values from 1.125 to 2.000
Group III – HAQ values from 2.125 to 3.000
A (I *vs* II), B (I *vs* III), C (II *vs* III)
†*p*-value of ANOVA test, ‡ *p*-value of Kruskal-Wallis test.

Table 2

Univariate logistic regression, predictors of functional disability

Factors		OR	95% CI	p
DAS28 SE		5.45	3.211–7.690	0.001
DAS28 CRP		5.111	2.123–10.636	0.01
SE		1.561	1.021–3.156	0.04
CRP	[0]	1	/	/
	1	5219	1.305–18.231	0.019
RF	[0]	1	/	/
	1	2.111	1.210–4.150	< 0.001

[]–The reference category; OR – odds ratio, 95% CI-95% confidence interval;
***p*-statistical significance at the level $p < 0.05$; DAS – disease activity score;**
SE – sedimentation rate; CRP - C-reactive protein; RF –rheumatoid factor.

Discussion

Success in RA treatment largely depends on the right evaluation of the disease activity, when efficient administration of medicaments is possible, which change the disease course [2].

Accurate measurement of the RA activity is not at all simple, and in the last 15 years it has become obvious that due to the varaibility of symptoms and signs manifestation [4], it is not sufficient to determine only the number of painful and swollen joints and perform the basic laboratory analysis. It is necessary to monitor the collective indexes of the disease activity which overcome the problems with validity, reliability and sensitivity to changes noticed in some characteristics [4, 5]. For the time being, the best tools for its assessment in individuals are the disease activity Score and its validated modifications DAS and DAS28 developed by the European League Against Rheumatism (EULAR) [6]. Those indexes show a significant correlation with functional abilirates during the disease, If left untreated, 20–30% of RA patients will become permanently disabled for work within 3 years from the diagnosis, and after 10 years with the disease 80% of patients will be permanently incapable for work and become handicapped.

Functional disability assessment is the fundamental measurement in RA [7], considering the chronic nature of this disease. The influence of the changes developed in RA on everyday activities, working ability, need for surgical treatment, increased mortality rate, suggest the convenience of the use of such investigation and is a significant addition to physical examination of the patient.

The HAQ, filled out by patients themselves, is a measure of the functional loss of everyday activities, such as dressing up, eating, using the toilet, shopping or house work. HAQ usually increases faster at the beginning of the disease [8]. Among the early reports, HAQ becomes a regular measure of the progression, damage and limited range of motion in RA, especially during the years of follow-up.

Investigations which deal with the influence of the disease activity on functional status often have controversial results, and this diversity of the results is explained by the variability of symptoms and signs manifestations in patients with RA, prone to frequent and even daily variations.

Drossaers-Bakker et al. [9] investigated the relationship of the functional status which is represented by the HAQ score and the disease activity measured by DAS during the period of 12 years in 132 patients. At the beginning of the investigation there was a strong correlation of HAQ and DAS, that was maintained even after three years. In the following years, joint damage presented by Sharp's score had greater influence on HAQ, but at the end of the investigation, after 12 years of follow-up, the disease activity presented by DAS was the main factor of the functional disability represented by HAQ [9].

Our results also show that subjects with the most severe functional damage estimated by HAQ – the group III, have the highest disease activity presented by DAS 28 SE whith the values 7.4 ± 0.8 compared to the group II (6.5 ± 1.2) and the group I (3.4 ± 1.2), as well as the highest values of DAS 28 CRP 7.1 ± 0.8 compared to the group II (6.7 ± 0.8) and the group I (3.6 ± 0.4). The findings have a high statistical significance. The subjects in the group II have a higher disease activity in comparison to those in the group I (statistically significant difference ANOVA, DAS28 SE ($F = 53.797$, $p < 0.001$) and DAS28 CRP ($F = 10.084$, $p < 0.001$).

In the univariate logistic model, the most significant factor which increases the odds for a patient to be in the HAQ group III, i.e. to have the most severe functional damage is DAS 28 SE which increases these chances by 5.5 times (OR = 5.450, 95% CI = 3.211–7.690, $p = 0.001$). DAS28 CRP increases the odds for the subject to have the most severe functional damage by 5.1 times (OR = 5.111, 95% CI = 2.123–10.636, $p < 0.01$), and presence of CRP (OR = 5.219, 95% CI = 1.305–18.231, $p = 0.019$) by 5.2 times. RF was singled out as a significant risk factor at the level of $p < 0.001$, increasing the odds for the subject to have functional disability by 2.1 times.

In the five-year follow-up, Combe et al. [10] concluded that the final HAQ disability is caused by the initial value of the HAQ, pain, Ritchie index, the number of painful joints, disease activity score, SE, CRP and erosions. Using a multivariate analysis, they emphasized the following prognostic risk factors of HAQ disability: initial HAQ score, Ritchie index, SE, CRP, and the presence of erosions as the most significant prognostic factors of the functional disability.

Investigation by Courvaisir et al. [11] in a 10-year follow-up, defined the correlation between HAQ and disease activity which was presented by DAS and pain, both at the beginning and after five and 10 years.

The significance of investigation of the functional ability is also suggested by the Early Rheumatoid Arthritis Study (ERAS) which included 732 patients and showed that deterioration of the functional status later in the course of the disease was caused by a high HAQ at the beginning of the investigation [12].

Some studies showed that functional status at the early stages of the disease was first of all influenced by the disease activity, and that in later stages poor functional status was the consequence of joint damage [2].

Our results suggest that the subjects with the most severe functional damage, the group III, have a statistically significantly higher SE value (increases the odds for the subject to be in the HAQ group III by 56%), frequently positive RF as significant risk factor at the level of $p < 0.001$, increasing the odds for the subject to be in the HAD group III by 2.1 times, compared to subjects with smaller and moderate functional damage. Gender did not significantly influence the functional ability.

Investigation of the influence of age and duration of the disease on the functional ability showed that older age and longer disease significantly contribute to the loss of the functional ability (patient's age observed as continued variable), increases the odds for the patient to be in the HAQ group III by almost 60% (OR = 1.572, 95% CI = 1.111–1.946, $p < 0.001$), disease duration (continuously) by 80% (OR = 1.792, 95% CI = 1.550–1.930, $p < 0.001$). These results are in accordance with investigations by Sokka et al. [13] who concluded that older age contributed to the decrease of the functional ability and with a study by Scott et al. [14] who compared the results of several research centers and showed that functional disability increases with longer disease and the increase is constant.

Investigation that involved 706 patients, studied the influence of demographic, laboratory and radiology parameters on HAQ. The loss of functional ability was significantly influenced by the number of painful and swollen joints, older age, longer disease duration and higher SE values. The crucial factor for the functional ability loss was female gender. RF and joint damage did not have significant influence [15].

A study on 110 patients with RA showed a statistically highly significant correlation between HAQ with older patients, longer disease duration, progress on the walking path, longer morning stiffness, as lower values of Erythrocyte number and statistically significant correlation between HAQ and lower hemoglobin values and higher SE and CRP values [16].

HAQ index was proved to be one of the best indicators of the long-lasting prognosis in RA-patients with high HAQ score who have increased mortality rate, working disability, pain and psychosocial changes.

Original DAS and DAS28 remain valid, reliable and sensitive indicators of the disease activity that can be used for the estmation of the total RA activity. They are relatively successful in determining the number of patients who will actually be affected by the consequences of RA [3].

Conclusion

The Health Assessment Questionaire proved to be the standard in the evaluation of the functional status of rheumatoid arthritis patients due to its practicality and good correlation with parameters of disease activity, where the disease activity index DAS28 is singled out as the most significant factor.

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ORIGINAL ARTICLE

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Follicular lymphoma patients with a high FLIPI score and a high tumor burden: A risk stratification model

Bolesnici sa folikularnim limfomom, visokim FLIPI skorom i velikom tumorskom masom: model za određivanje rizika

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Abstract

Background/Aim. The widely accepted Follicular Lymphoma International Prognostic Index (FLIPI) divides patients into three risk groups based on the score of adverse prognostic factors. The estimated 5-year survival in patients with a high FLIPI score is around 50%. The aim of this study was to analyse the prognostic value of clinical and laboratory parameters that are not included in the FLIPI and the New Prognostic Index for Follicular Lymphoma developed by the International Follicular Lymphoma Prognostic Factor Project (FLIPI2) indices, in follicular lymphoma (FL) patients with a high FLIPI score and high tumor burden. **Methods.** The retrospective analysis included 57 newly diagnosed patients with FL, a high FLIPI score and a high tumor burden. All the patients were diagnosed and treated between April 2000 and June 2007 at the Clinic for Hematology, Clinical Center of Serbia, Belgrade. **Results.** The patients with a histological grade > 1, erythrocyte sedimentation rate (ESR) ≥ 45 mm/h and hypoalbuminemia had a significantly worse overall survival ($p = 0.015$; $p = 0.001$; $p = 0.008$, respectively), while there was a tendency toward worse overall survival in the patients with an Eastern Cooperative Oncology Group (ECOG) > 1 ($p = 0.075$). Multivariate Cox regression analysis identified a histological grade > 1, ESR ≥ 45 mm/h and hypoalbuminemia as independent risk factors for a poor outcome. Based on a cumulative score of unfavourable prognostic factors, patients who had 0 or 1 unfavourable factors had a significantly better 5-year overall survival compared to patients with 2 or 3 risk factors (75% *vs* 24.1%, $p = 0.000$). **Conclusion.** The obtained results suggest that from the examined prognostic parameters histological grade > 1, ESR ≥ 45 mm/h and hypoalbuminemia can contribute in defining patients who need more aggressive initial treatment approach, if two or three of these parameters are present on presentation.

Key words:
lymphoma; follicular; antineoplastic combined chemotherapy protocols; prognosis.

Apstrakt

Uvod/Cilj. Široko prihvaćeni internacionalni prognozni indeks za folikularni limfom (FLIPI) svrstava bolesnike u tri grupe rizika na osnovu skora nepovoljnih prognoznih faktora. Procenjeno 5-ogodišnje preživljavanje bolesnika sa visokim FLIPI skorom je oko 50%. Cilj ove studije bio je analiza prognostičke vrednosti kliničkih i laboratorijskih parametara koji nisu uključeni u FLIPI i FLIPI2 indekse, kod bolesnika sa visokim FLIPI skorom i velikom tumorskom masom. **Metode.** Ova retrospektivna analiza obuhvatila je 57 novodijagnostikovanih bolesnika. Svi bolesnici dijagnostikovani su i lečeni u periodu između aprila 2000. i juna 2007. godine na Klinici za hematologiju Kliničkog centra Srbije, Beograd. **Rezultati.** Značajno lošije preživljavanje imali su bolesnici sa histološkim gradusom > 1 ($p = 0{,}015$), sedimentacijom eritrocita (SE) ≥ 45 mm/h ($p = 0{,}001$) i hipoalbuminemijom ($p = 0{,}008$), dok je tendencija lošijeg preživljavanja postojala kod bolesnika sa *Eastern Cooperative Oncology Group* (ECOG) > 1 ($p = 0{,}075$). Multivarijantnom Cox regresionom analizom identifikovani su histološki gradus > 1, SE ≥ 45 mm/h i hipoalbuminemija kao nezavisni prognostički faktori za nepovoljan ishod. Na osnovu kumulativnog skora nepovoljnih prognostičkih faktora, bolesnici koji su imali 0 ili 1 nepovoljan prognostički faktor imali su značajno bolje petogodišnje ukupno preživljavanje u poređenju sa bolesnicima sa 2 ili 3 faktora rizika (75% *vs* 24,1%, $p = 0{,}000$). **Zaključak.** Rezultati našeg ispitivanja pokazuju da od testiranih prognostičkih parametara histološki gradus > 1, SE ≥ 45 mm/h i hipoalbuminemija mogu doprineti izboru bolesnika koji zahtevaju inicijalno agresivniji modalitet lečenja, ukoliko su na prezentaciji prisutna dva ili tri od ovih parametara.

Ključne reči:
limfom, folikularni; lečenje kombinovanjem antineoplastika; prognoza.

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Introduction

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma with the median survival of 8–10 years [1, 2]. The disease has a variable course, some patients have a slowly progressive disease, while the others have a rapidly progressive disease with the survival of around one year. Up to 15 years ago, the efforts to find an appropriate therapeutic strategy resulted in a prolonged event-free survival (EFS) and higher treatment response rate for these patients, but all of them were unsuccessful at prolonging the overall survival (OS) of these patients [3–7].

The first step towards the for many years elusive aim of prolonging OS in FL was recorded when interferon was included in the treatment of patients with FL [8]. The use of interferon in FL ceased due to its impact on the deterioration of quality of life, the necessity of its application in high doses and along with chemotherapy, as well retrieving the new drug, antiCD20 antibody [9]. The introduction of rituximab as the standard treatment for FL patients in combination with chemotherapy brought much better therapeutic results, including prolonging of OS [10–13]. The optimal first line immunochemotherapy is not yet defined, but is one of the purposes of on-going Primary Rituximab and Maintenance (PRIMA) studies [14].

In spite of the progress in treatment of FL, a significant portion of patients with FL still have poor outcome. During the past decades, a number of potential prognostic factors and risk models in patients with FL were studied with the aim of identifying patients at risk for poor outcome, but only the Follicular Lymphoma International Prognostic Index (FLIPI), which was established in 2004, was widely used as predictor of survival [15–19]. The FLIPI, consisting of age, stage, number of nodal sites, hemoglobin level and lactate dehydrogenase (LDH), identifies patients with a low risk (0–1 risk factors), intermediate risk (2 risk factors) and high risk (3–5 risk factors) with the expected 5-year overall survival of around 90%, 80% and 50%, respectively [19]. After the introduction of immunochemotherapy as the standard first line treatment of FL and after encouraging results in terms of survival, the need for new investigations with the aim of defining the risk profile of FL patients treated with immunochemotherapy became apparent. Thus, the recent study performed by Federico et al. [18] defined the new prognostic index FLIPI2 (consisting of age, β-2 microglobulin, longest diameter of the largest node involved, bone marrow involvement and hemoglobin level), as the appropriate prognostic index for FL patients treated with immunochemotherapy [20]. Nowadays, FLIPI is commonly used as enrolment criteria or stratification factor in clinical trials. Still, there is no evidence of risk adapted treatment strategy based on FLIPI indexes.

In this study on the group of high FLIPI risk patients with a high tumor burden who are theoretically at highest risk for poor outcome, we tried to identify a subgroup that probably require the more effective treatment approach. For the purpose of this analysis, we investigated routinely performed pathohistological, clinical and biochemical parameters that are not included in the FLIPI indexes. Also, we compared the outcome of patients treated with chemotherapy and immunochemotherapy.

Methods

Case Selection

This retrospective analysis was performed on 57 newly diagnosed FL patients at high risk according to FLIPI and with a high tumor burden. High tumor burden is defined as the presence of at least one of the following criteria: systemic symptoms (> 10% weight loss, temperature > 38°C for more than 5 days, abundant night sweats); performance status (PS) greater than 1 according to the Eastern Cooperative Oncology Group (ECOG) scale; elevated LDH level; β2-microglobulin level greater than 3 mg/L; single lymph node larger than 7 cm; spleen enlargement with a craniocaudal diameter greater than 200 mm; organ failure; pleural effusion or ascites; symptomatic compressive syndrome; the existence of 3 lymph nodes in 3 distinct nodal areas with a diameter greater than or equal to 3 cm [13]. All the patients were diagnosed and treated in our institution between April 2000 and December 2006. In all the cases, the diagnosis of FL was confirmed by immunophenotyping and classified according to the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues in specialized Laboratory of Hematopathology [21]. The patients with histological grade 1, 2 and 3A according to Mann and Berard [22] criteria were eligible for this study.

Patients who were previously treated for another malignancy were not included in this study, nor those with high FLIPI risk without high tumor burden, since according to the institutional treatment guidelines in that period, they underwent “watch and wait”.

Medical records were reviewed to determine the FLIPI, bulky disease (the diameter of tumor > 7 cm), erithrocyte sedimentation rate (ESR), serum albumin level, ECOG performance status (ECOG PS) and the treatment outcome.

Treatment recommendations

All the patients were treated according to the institutional standard of care at the time of diagnosis. In the first line treatment, 32 patients received cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or cyclophosphamide, vincristine, prednisone (CVP) chemotherapy and 25 patients received R(rituximab)-CHOP or R(rituximab)-CVP immunochemotherapy. The patients who responded after four cycles of chemotherapy/immunochemotherapy proceeded with the treatment to complete 6 to 8 cycles, depending on the treatment response (complete or partial remission) and treatment tolerance. Patients with refractory disease or relapse after the initial chemotherapy received fludarabine-based second line therapy in combination with cyclophosphamide (FC) or mitoxantrone and dexamethasone (FMD), of whom 11 received additional rituximab. Six patients who transformed to diffuse large B-cell lymphoma received etoposide, cisplatinum, ara-c, methylprednisolone (ESHAP) regimen.

Statistical methods

The patients who achieved complete or partial remission were considered to have responded to the therapy. The early relapsed were those who initially responded to the therapy and relapsed inside 12 months after achieving remission. The association between the treatment modality and the response/early relapse rate was determined using the χ^2-test.

The overall survival was measured from the date of diagnosis until the date of death from any cause, or until the last follow up visit. The event-free survival was measured from the date of diagnosis to that of disease progression, relapse, death from any cause or the last follow-up visit.

The receiver operating curve (ROC) was used to determine the optimal cut-off value for laboratory parameters in the prediction of the overall survival for our group of patients. If the optimal cut-off value was not found, the analysis was performed using literature cut-off values.

Survival functions were estimated using the Kaplan-Meier method and compared using the log-rank test. A multivariate analysis was performed to evaluate the potential predictive value of the examined characteristics as a risk factor.

Table 1

Baseline characteristics of the patients

Characteristics	Patients, n (%)
Age (years), mean (range)	54 (range 35–74)
≤ 60	35 (61.4%)
> 60	22 (38.6%)
Stage of tumor	
II	1 (1.8%)
III	10 (17.5%)
IV	46 (80.7%)
Histology grade	
1	29 (50.9%)
2	19 (33.3%)
3a	9 (15.8%)
Bulky disease	
no	22 (38.6%)
yes	35 (61.4%)
ECOG PS	
≤ 1	39 (68.4%)
> 1	18 (31.6%)
ESR	
< 45 mm/h	25 (43.9%)
≥ 45 mm/h	32 (56.1%)
Albumin level	
low	28 (49.1%)
normal	29 (50.9%)

ECOG PS – Eastren Cooperative Oncology Group Performance Status; ESR – erythrocyte sedimentation rate.

Results

Baseline characteristics

The median follow-up was 58 months, from 6 to 122 months. The median age of the patients was 54 years (range 35–74 years). Twenty-two (38.6%) patients were older than 60 years.

Histological grade 1, 2 or 3a was present in 29 (50.9%), 19 (33.3%) and 9 (15.8%) patients, respectively. Bulky disease was present in 22 (38.6%) patients. ECOG PS > 1 on presentation had 18 (31.6%) patients.

The cut-off point for ESR identified by ROC analysis was 45 mm/h. Twenty-five (43.9%) patients had an ESR higher than the cut-off value. The ROC analysis could not identify the optimal cut-off value for albumin level. For the purpose of further analysis, 35 g/L was taken as the cut-off value [19]. Hypoalbuminemia was present in 28 (49.1%) of the patients.

The baseline characteristics of the patients are summarized in Table 1.

The outcome of the patients

A total of 51(89%) patients responded to the therapy. Early relapse occurred in 16 (31%) patients. Twenty-eight (49.1%) patients lived for 5 years or longer.

A higher response rate (RR) was observed in the group of patients treated with immunochemotherapy, but the difference was not statistically significant (92% *vs* 87.5%, χ^2, $p > 0.05$). In those who responded to the initial treatment with chemotherapy, a statistically higher percentage of early relapse occurred (42.9% *vs* 17.4%, χ^2, $p < 0.05$).

In survival analysis, the patients initially treated with immunochemotherapy had significantly longer EFS (5-year EFS, 40% *vs* 12.5%; $p = 0.016$) (Figure 1A), and OS (5-year OS, 68% *vs* 34.3%; $p = 0.022$), (Figure 1B) compared to the patients treated with chemotherapy.

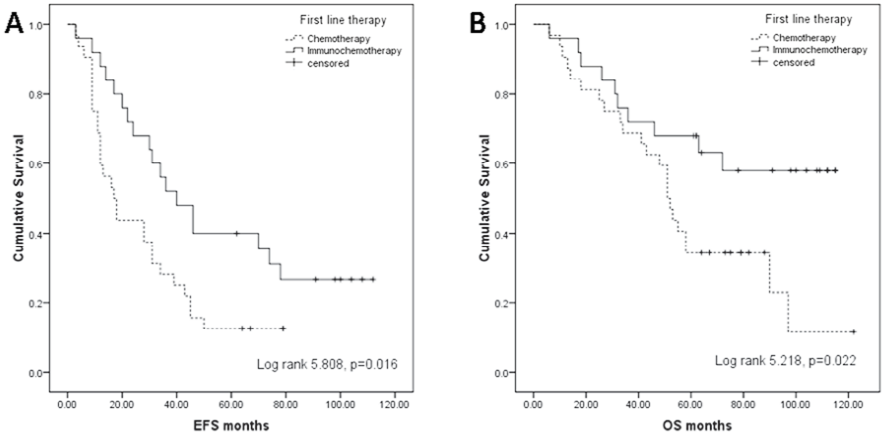

Fig. 1 – Comparison of the survival based on the first line treatment, chemotherapy *vs* immunochemotherapy: A) Event-free survival (EFS); B) Overall survival (OS)

Analysis of risk factors for poor outcome

Univariate analysis

Univariate analysis indicated that the patients with a histological grade > 1, ESR ≥ 45 mm/h and hypoalbuminemia had significantly shorter overall survival ($p = 0.009$; $p = 0.001$; $p = 0.008$, respectively) (Figure 2). There was a tendency to worse overall survival in the patients with an ECOG > 1 ($p = 0.075$). There was no difference in the outcome based on the presence of bulky disease on presentation ($p = 0.672$).

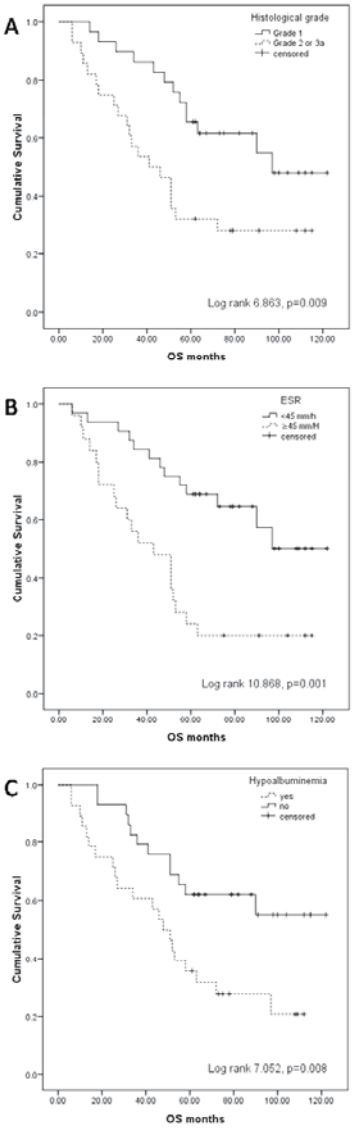

Fig. 2 – Overall survival (OS) depending on the disease characteristics:
A) Histological grade; B) Erythrocyte sedimentation rate (ESR); C) Albumin level.

Risk stratification model

Based on the cumulative score of the identified unfavourable prognostic factors, a risk stratification model was developed. Twenty-eight (49.1%) patients who had 0 or 1 unfavourable factor had significantly longer overall survival compared to 29 (50.9%) patients with 2 or 3 risk factors (5-year OS 75% *vs* 24.1%; $p = 0.000$) (Figure 3A), regardless frontline treatment with chemotherapy (5-year OS 62.5% *vs* 6.3%; $p = 0.000$) (Figure 3B) or immunochemotherapy (5-year OS 91.7% *vs* 46.2%; $p = 0.004$) (Figure 3C).

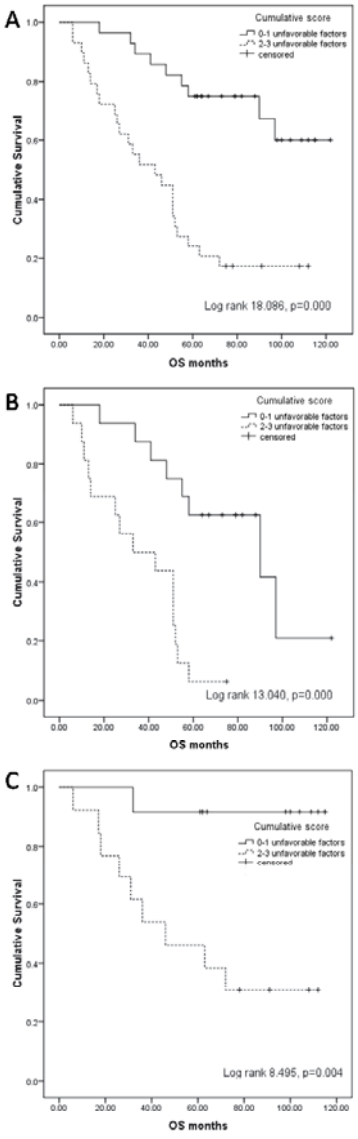

Fig. 3 – Overall survival (OS) based on the cumulative score of unfavourable prognostic factors, 0–1 *vs* 2–3:
A) The whole group of patients; B) The patients treated with chemotherapy; C) The patients treated with immunochemotherapy.

Multivariate Analysis

Multivariate analysis revealed that a histological grade > 1, ESR ≥ 45 mm/h and hypoalbuminemia were independent prognostic factors for shorter OS.

Discussion

Numerous clinical studies have now identified many clinical, biochemical and molecular findings as prognostic factors for a poor outcome in patients with FL [17–20, 23–25]. The

multicenter study that compared the influence of different clinical and biochemical findings on the outcome, established the FLIPI index for the risk stratification of newly diagnosed FL patients [18, 19]. Federico et al. [20] identified risk factors in FL patients treated with immunochemotherapy and designed the New Prognostic Index for Follicular Lymphoma developed by the International Follicular Lymphoma Prognotic Factor Project (FLIPI2). However, the primary endpoint in this study was EFS, while in the Solal-Celigny et al. [19] study, the primary endpoint was OS. Recent gene profiling analysis has suggested that the survival of patients with newly diagnosed follicular lymphoma can be affected by the host molecular signature, termed an immune response-1 (IR-1), which originates from non-malignant cells present in tumor tissue [26, 27]. The first studies that investigated the presence of CD68 positive lymphoma associated macrophages as the surrogate of IR-1 identified it as biological predictor of a poor outcome, but latter studies revealed that adding rituximab to standard chemotherapy overcame its negative impact on survival [28, 29]. Thus, prognostic value of biomarkers in follicular lymphoma has to be assessed in future studies with uniform methodology.

The results of our study on high FLIPI risk patients with high tumor burden confirmed the benefit in terms of early relapse rate and 5-year EFS of adding rituximab to chemotherapy in previously untreated FL patients. Also, addition of rituximab to chemotherapy brought a significant improvement in 5-year OS. These results are in accordance with results from randomized trials that reported an improvement in progression-free survival (PFS) or time to progression (TTP) and OS, associated with the addition of rituximab to standard chemotherapy in the first line treatment of FL [10–13]. Still in both groups of patients in our study as well as in the previous reports, a significant percent of patients remain with poor outcome. Therefore nowadays the main purpose of investigators is to identify patients with poor prognosis who maybe require the more aggressive therapeutic approach from the beginning.

In our study, by analysing the values of routinely performed pathohistological, clinical and biochemical parameters not included in the FLIPI indices, histological grade > 1, ESR ≥ 45 mm/h and hypoalbuminemia were identified as independent risk factors for a poor outcome in high FLIPI risk patients. According to the literature, in researches on unselected groups of patients, the prognostic role of these factors is the subject of controversy. Martin et al. [30] identified histological grade 3 as the independent risk factor for failure free and overall survival. However, a later research by Ott et al. [31] found that patients with grade 3a, as well as those with grade 1 or 2, are experiencing an indolent course of the disease, while patients with grade 3b are experiencing an aggressive course of the disease, similar to diffuse large B-cell lymphoma. Hans et al. [32] concluded that patients with grade 3a and more than 50% of centroblasts are experiencing an aggressive course similar to patients with grade 3b. Elevated ESR was identified as the risk factor in patients with FL in the prerituximab era [18, 19]. On the contrary, this was not the case in the study by Federico et al. [20]. Hypoalbuminemia was identified as risk factor in the Italian intergroup trial, but this was not the case in later studies, which defined FLIPI indices [18–20].

Treatment personalization is needed to achieve a successful balance of treatment effectiveness and toxicity. Based on the cumulative score of the identified negative prognostic parameters on presentation in our group of patients, the risk stratification model that we developed effectively identifies patients who clearly needed more effective treatment. However, the model is not eligible for the use in all newly diagnosed FL patients since the cut-off values are derived from parameters of high FLIPI risk patients with high tumor burden and it can not be tested even in other FLIPI risk groups with high tumor burden.

By now, in the younger population, several studies have been conducted using the aggressive approach in the first line and in relapse in high risk FL patients [23, 33–38]. The autologous stem cell transplantation (ASCT) in first remission brought improvement in disease-free survival (DFS) or PFS, but there is still no clear evidence of prolonging OS. However, only one study with ASCT in first remission was initiated in the rituximab era [38]. The allogeneic transplantation was examined in relapsed FL and it proved potentially curative, but the first reports on allogeneic transplantation with myeloablative regimens did not resolve whether there is a benefit in OS, mainly due to the high treatment related mortality (21–40%) [39–42]. Thus, the main focus at the present moment is to explore the efficacy of rituximab maintenance therapy in first remission with or without ASCT, as well the efficacy of radioimmunochemotherapy and allogeneic stem cell transplantation with the reduced-intensity conditioning (RIC) protocols, based on rituximab and fludarabine [43–46].

Conclusion

The results obtained in this study suggest that from examined prognostic parameters histological grade > 1, ESR ≥ 45 mm/h and hypoalbuminemia could contribute in defining a group of patients who need the more aggressive initial treatment approach, if two or three of these parameters exist on presentation. To our opinion, new prospective studies with more precise pretreatment risk stratification seem to be needed in order to define the best treatment strategy for high-risk follicular lymphoma patients.

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Social functioning of elderly persons with malignant diseases

Socijalno funkcionisanje starijih osoba obolelih od malignih bolesti

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Abstract

Background/Aim. Malignant disease, its treatment and consequences of treatment can often lead to social marginalization and reduced quality of life. The aim of this research was to determine how elderly patients with malignant diseases function in their social environment. **Methods.** Sociodemographic questionnaire and interview were used to investigate a group of 49 elderly persons undergoing adjuvant chemotherapy treatment against early carcinomas (P1), and a group of 51 elderly persons with advanced stages of cancer undergoing systemic chemotherapy (P2). There were two cycles of assessment: one just before the beginning of the first cycle of adjuvant or systemic chemotherapy, and the other three months later. The research paradigm was based on the relation between individual treatment and the impact of the malignant disease on functional and social incompetence. The obtained findings were compared with the group of 50 healthy elderly people (K) who share the same relevant features but do not suffer from malignant diseases. **Results.** It was found that most healthy older people live in share house, whereas those who suffer from malignant diseases mostly live in separate households. In both groups of patients and healthy group older people are mostly taken care of by their children. Individuals in both groups of patients have been frequently visited by their relatives during initial stages of treatment, unlike the elderly people in the control group. However, the difference did not reach a statistical significance. Three months after the beginning of chemotherapy, there was a statistically relevant difference in favor of the group undergoing adjuvant treatment. Home visits eventually become less frequent, whereas communication by telephone becomes more frequent. It was also found that visits by friends and neighbors are statistically more frequent among subjects who undergo adjuvant treatment, both before the treatment began and three months later when compared to other groups. **Conclusion.** Our research shows that elderly people are subject to social exclusion, especially those with malignant diseases. Special care should be dedicated to monitoring of social functioning during treatment of patients with malignant disease considering the detected trend of deterioration and significance for further recover and cure.

Key words:
old age assistance; neoplasms; patient care; social support; social behavior.

Apstrakt

Uvod/Cilj. Maligne bolesti, njihovo lečenje, kao i posledice tretmana, mogu često dovesti do socijalne marginalizacije i pogoršanja kvaliteta života. Cilj našeg istraživanja bio je da se proceni funkcionisanje starijih osoba obolelih od malignih oboljenja u njihovoj socijalnoj sredini. **Metode.** Primenjen je sociodemografski upitnik i metod intervjua na grupi od 49 starih osoba na lečenju od ranog karcinoma koje se nalaze na adjuvantnom hemioterapijskom lečenju (P1). Drugu grupu (n = 51) činile su stare osobe koje su se nalazile u odmaklom stadijumu bolesti i na sistemskom hemioterapijskom lečenju (P2). Istraživanje je sprovedeno kroz dva testiranja: prva procena vršena je neposredno pre otpočinjanja prvog ciklusa adjuvantne ili sistemske hemioterapije, a druga procena tri meseca kasnije. Istraživačka paradigma bila je zasnovana na relaciji individualnog lečenja i posledica koje maligna bolest izaziva u oblastima funkcionalne i socijalne inkompentencije. Dobijeni rezultati poređeni su sa kontrolnom grupom od 50 starijih osoba (K), istih karakteristika, ali bez malignog oboljenja. **Rezultati.** Utvrđeno je da većina starijih zdravih ispitanika živi u zajedničkim domaćinstvima sa decom, dok ispitanici iz grupa obolelih od malignih bolesti češće žive u samostalnim zajednicama. U sve tri grupe brigu o starima najčešće su vodila deca. „Česte“ posete rodbine imale su obe grupe obolelih na početku lečenja, za razliku od kontrolne grupe starijih osoba. Ipak, ova razlika nije bila statistički značajna. U drugoj proceni, tri meseca od početka lečenja, dobijena je statistički značajna razlika u korist grupe na adjuvantnom lečenju. Kako vreme prolazi smanjivale su se kućne posete, a povećavala komunikacija telefonom. Takođe, utvrđeno je

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da su posete prijatelja i komšija statistički značajno učestalije kod ispitanika koji su na adjuvantnom lečenju, kako pre otpočinjanja tretmana, tako i tri meseca nakon lečenja, u odnosu na ostale ispitivane grupe. **Zaključak.** Naše istraživanje pokazalo je da je socijalna isključenost prisutna u starijem dobu, a posebno kod obolelih od malignih bolesti. Posebnu pažnju potrebno je posvetiti praćenju socijalnog funkcionisanja tokom lečenja obolelih od malignih bolesti, s obzirom na uočenu tendenciju njegovog pogoršanja i značaj za dalji oporavak i izlečenje.

Ključne reči:
stare osobe, pomoć; neoplazme; nega bolesnika; socijalna podrška; socijalno ponašanje.

Introduction

Elderly people suffering from malignant diseases pose a huge medical, economic and social problem in every society, including Serbian. Bearing in mind that 60% of patients suffering from malignant diseases fall into this group efforts to integrate them into social environment seem quite justified [1, 2]. Successful social integration of these people implies their participation in family life and social environment, which is of immense importance for society [3, 4].

Malignant disease, its treatment and the consequences of treatment can often lead to social marginalization and reduced quality of life [5–7]. Regardless of the evident progress in prevention, diagnostics and treatment of malignant diseases, most people still think that the words like "cancer" or "malignant disease" mean suffering, pain and death. Prejudice against cancer causes intensive psychological/emotional reactions and raise deepest existential fears, i.e. fear of death, of suffering and pain, uncertainty, change person's perception of future and life, raise fear of separation from beloved ones and from his/her social environment, fear of marginalization and of being stigmatized [7, 8].

The stigma of malignant diseases comes from the historical and cultural idea of the unfortunate outcome, painful procedures used in diagnostics and treatment, as well as bad prognosis [9, 10]. The stigma that patient's family and the patient himself/herself will experience certainly depend on the environment in which the family lives, their level of education, culture, religion, prejudice and misapprehensions associated with malignant diseases [9, 11].

Malignant disease can cause certain changes which pose potential threats and obstacles in everyday life of old persons and causes difficulties in their everyday functioning. People suffering from malignant diseases have their life plans shattered, experience changes in body schemes and in self-respect, change in social roles and lifestyle, concerns about money and financial status, and their everyday habits and other aspects of life become different (diet, physical ability, mobility, personal hygiene, communication, interpersonal relations etc.) [8, 11].

Malignant disease and adverse effects of its treatment pose risk factors in the development of functional, cognitive and depressive symptomatology and psychiatric morbidity [6, 10, 12]. The group which is particularly exposed to a higher risk of social exclusion and psychiatric morbidity comprises patients in late stages of malignant diseases, with bad performance status and bad pain control [13–15].

This research included patients whose cancer treatment had just begun, both adjuvant and systemic, and whose performance status and quality of life were good. Adjuvant cancer treatment follows radical surgeries in which the entire tumor mass has been recently removed, or radiation therapy delivered with curative intent. Systemic treatment is applied in different stages of malignant disease [16]. Depending on the stage of the disease and specific results expected after the treatment, it is possible to apply several kinds of systemic treatment [17, 18]. The aim of cancer treatment is to extend the patient's life, to improve the quality of his/her life and to reduce the symptoms of the disease. Recent researches have shown that adjuvant or systemic chemotherapy in elderly patients can be of benefit in terms of survival and overall quality of life [13, 14, 19, 20].

Malignant disease and its treatment can further make worsen the problems and changes caused by the process of ageing (e.g. chronic diseases, changes in physical appearance, weakness of muscles, changes in bones, weak eyesight, poor hearing, decline of cognitive functions) [21, 22].

Investigation of behaviour, social problems and difficulties of patients with malignant diseases performed in other countries in the past two decades were mostly focused on younger adults, which is the reason why there is a gap in understanding of complex psychosocial needs of old persons and of problems they are facing [23–25]. Geriatric medicine has recently become particularly focused on special education and rehabilitation. Effects which follow old age, quality of life of old people and effects of rehabilitation are being researched.

The aim of this paper was to determinate social functioning of elderly people suffering from malignant diseases and the possibilities for their social integration. Our research paradigm was based on the relation between individual treatment and the effects of malignant disease in the domains of functional and social competence.

Methods

The research was conducted during the years 2011 and 2012 at the Medical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Belgrade. There were 150 subjects of both sexes included in this research, aged between 65 and 79. There were 3 groups of examinees: the group of 49 older persons (P1) undergoing adjuvant chemotherapy treatment against early carcinoma; the group of 51 older persons with advanced stage cancer undergoing systemic chemotherapy (P2) and the control group (K) of 50 healthy older people. There were two criteria for the groups of patients: aged 65 and over, malignant disease diagnosed by histopathological verification, retained communicativeness, mobility and the

absence of mental or physical limitations. Both patients and the control group were uniform in terms of sex, age and education. The subjects of the control group were mainly recruited from the neighbours and acquaintances of the authors, with certain difficulties, since most of the healthy people refused to be tested and compared with malignant patients. First evaluation cycle was done just before the beginning of the first cycle of adjuvant or systemic chemotherapy and was repeated three months after the beginning of the treatment. The results obtained for malignant patients were compared with those pertaining to a group of healthy old persons (K) who shared the same features, but did not suffer from malignant diseases.

Our research was approved by the Ethics Committee of the Institute for Oncology and Radiology of Serbia and its Scientific Committee. All the subjects signed consent forms.

The sociodemographic questionnaire, previously described in the reference of Berat [3], and interview were used in this research. The sociodemographic questionnaire covered basic demographic features: sex, age, marital status, place of living and level of education. The interview provided answers concerning social estimate: telephone communication with relatives, visits by relatives and friends, living in the same household, eldercare. Medical records of malignant patients were checked to retrieve data about the diagnosis, clinical stage of the disease, type of treatment and associated illnesses.

Descriptive statistics was used to present the significant parameters and dependence on the parameter itself: frequency, percentage, mean, median, standard deviation (SD) and range. For the dependence of the parameters Pearson's χ^2 test, Fisher's exact test, Kruskal Wallis test and Wilcoxon rank sum test were used to check the differences. The level of significance was set to $p = 0.05$.

Results

Sociodemographic characteristics of the patients from both groups of malignant patients and the healthy control group are represented in Table 1. Although the majority of elderly people from this study were women, both sexes were distributed in the same ratio in all the groups. The youngest subject was 65 years old, and the oldest one was 79, while the median age was 69.5. Most of the subjects in all the three groups were aged 65. The level of education was also equally distributed in all the three groups, showing that more than half of the patients had secondary school. Marital status showed that more than 60% of patients were married, and more than one quarter widowed. Predominantly, the patients from both groups and elderly people from the healthy group were from the urban and suburban communities.

Table 1

Sociodemographic characteristics of the patients

Patient's characteristics	Total n (%)	P1 n (%)	P2 n (%)	K n (%)	Test
Gender					
men	29 (19.33)	9 (18.37)	11 (21.57)	9 (18)	$\chi^2 = 0.25$; $p = 0.88263$
women	121 (80.67)	40 (81.63)	40 (78.43)	41 (82)	
Education					
primary school	39 (26)	13 (26.53)	13 (25.49)	13 (26)	
secondary school	78 (52)	25 (51.02)	27 (52.94)	26 (52)	$\chi^2 = 0,037$ $p = 1$
equivalent to US Community college	15 (10)	5 (10.2)	5 (9.8)	5 (10)	
university	18 (12)	6 (12.24)	6 (11.76)	6 (12)	
Marital status					
domestic partnership	2 (1.33)	0 (0%)	1 (1.96)	1 (2)	
widowed	40 (26.67)	11 (22.45)	13 (25.49)	16 (32)	
divorced	10 (6.67)	4 (8.16%)	4 (7.84)	2 (4)	
married	91 (60.67)	30 (61.22)	32 (62.75)	29 (58)	
single	7 (4.67)	4 (8.16)	1 (1.96)	2 (4)	
Type of community					
urban	104 (69.33)	40 (81,63)	36 (70,59)	28 (56)	
suburban	36 (24)	5 (10,2)	9 (17,65)	22 (44)	
rural	10 (6.66)	4 (8,16)	6 (11,76)	0 (0)	
Age (years)					
average (± SD)	70.39 (± 4.29)	70.43 (± 4.36)	70.37 (± 4.28)	70.38 (± 4.32)	$\chi^2 = 0.002$ $p = 0.9989$
median (range)	69.5 (65–79)	70 (65–79)	69 (65–79)	69.5 (65–79)	

P1 – elderly ongoing adjuvant chemotherapy (n = 49); P2 – elderly ongoing systemic chemotherapy (n = 51); K – healthy elderly (n = 50).

Most subjects from the group of old patients with early carcinoma who underwent adjuvant treatment suffered from breast carcinoma (26 out of 49, 53%) and from colorectal carcinoma (19 out of 49, 38%). On the other hand, most subjects from the group of old people with disseminated diseases who underwent systemic treatment suffered from breast carcinoma (18 out of 51, 35%) and gynecologic carcinoma (15 out of 51, 29%).

As presented in Table 2, there was a statistically significant difference in the frequency of category 'living in the same household' between the groups. Most older people with no malignant diseases came from the suburban areas and usually lived in the same household with their children, whereas the patients with malignant diseases more often

lived single in independent households (Fisher's exact test P1 *vs* K: $p = 0.00327$, and Fisher's exact test P2 *vs* K: $p = 0.00515$) (Table 2).

Table 3 shows that the majority of subjects in both groups of patients (P1 and P2) were most frequently visited by their children at the beginning of the treatment. On the other hand, the older people from the control group were rarely visited by their children, but the difference was not statisticaly significant. In the second evaluation cycle, three months after the therapy had begun, there was a statistically significant difference in the categories of answers among the groups ($p = 0.00141$). Our results show a statistically significant decrease of "Often" visits, and consecutive increase of "Rare" visits by relatives in both P1 and P2 groups, compared to the control group (P1 *vs* K, Fisher's exact test: $p < 0.001$ and Fisher's exact test P2 *vs* K: $p = 0.0486$). As time went on, home visits become less frequent, and telephone communication increased.

Table 4 represents the results concerning telephone communication. In the first evaluation cycle, there was a statistically significant difference in the frequency of categories of answers between the groups, whereas there was no statistically relevant difference in the second evaluation cycle. In

Table 2

Elderly people living in the same household

Living in the same household	Total n (%)	P1 n (%)	P2 n (%)	K n (%)	Fisher's exact test
With children	59 (39.33)	14 (28.57)	15 (29.41)	30 (60)	$p = 0.00605$
With others (parents, brother, sister etc.)	4 (2.67)	1 (2.04)	2 (3.92)	1 (2)	
Single	84 (5)	32 (65.31)	33 (64.71)	19 (38)	
Other	3 (2)	2 (4.08)	1 (1.96)	0 (0)	

P1 – elderly ongoing adjuvant chemotherapy (n = 49); P2 – elderly ongoing systemic chemotherapy (n = 51); K – healthy elderly (n = 50).

Care for the older people was most often provided by their children, that was the case in all the three groups independent from their health status (Figure 1).

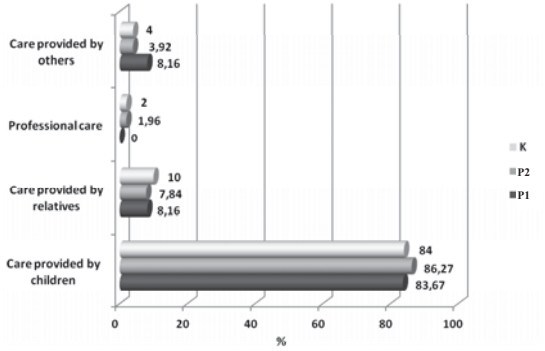

Fig. 1 – Care for elderly healthy people (K) and malignant patients (P1, P2).

Table 3

Visits by relatives to the elderly patients

Cycle	Total n (%)	P1 n (%)	P2 n (%)	K n (%)	Fisher's exact test
1st					
often	39 (26)	15 (30.61)	16 (31.37)	8 (16)	$p = 0.19083$
rarely	81 (54)	28 (57.14)	24 (47.06)	29 (58)	
almost never	29 (19.33)	6 (12.24)	10 (19.61)	13 (26)	
never	1 (0.67)	0 (0)	1 (1.96)	0 (0)	
2nd (after 3 months)					
often	31 (20.67)	12 (24.49)	11 (21.57)	8 (16)	$p = 0.00141$
rarely	98 (65.33)	36 (73.47)	33 (64.71)	29 (58)	
almost never	17 (11.33)	0 (0)	4 (7.84)	13 (26)	
never	3 (2)	1 (2.04)	2 (3.92)	0 (0)	

P1 – eldery ongoing adjuvant chemotherapy (n = 49); P2 – eldery ongoing systemic chemotherapy (n = 51); K – healthy elderly (n = 50).

Table 4

Telephone communication with the elderly patients

Cycle	Total n (%)	P1 n (%)	P2 n (%)	K n (%)	Test
1st					
never	2 (1.33)	1 (2.04)	1 (1.96)	0 (0)	Fisher's exact test $p = 0.00417$
often	30 (20)	14 (28.57)	11 (21.57)	5 (10)	
rarely	34 (22.67)	15 (30.61)	13 (25.49)	6 (12)	
when necessary	84 (56)	19 (38.78)	26 (50.98)	39 (78)	
2nd (after 3 months)					
often	20 (13.33)	6 (12.24)	9 (17.65)	5 (10)	Pearson χ^2 $\chi^2 = 2.162$ $p = 0.70604$
rarely	22 (14.67)	8 (16.33)	8 (15.69)	6 (12)	
when necessary	107 (71.33)	35 (71.43)	33 (64.71)	39 (78)	

P1 – elderly ongoing adjuvant chemotherapy (n = 49); P2 – elderly ongoing systemic chemotherapy (n = 51); K – healthy elderly (n = 50).

the first evaluation cycle there was a statistically relevant difference in frequency of categories of answers between the groups undergoing adjuvant treatment (P1) and the group of healthy subjects (K) (P1 *vs* K Fisher's exact test: $p < 0.001$). The control group showed that telephone communication described as 'when necessary' was more frequent than in the group of subjects undergoing adjuvant treatment (P1), which more frequently opted for 'often' and 'when necessary'. Adult children and other relatives often call to learn about the condition of the patient during initial stages of therapy, but in the course of time, the calls 'when necessary' become more frequent (first *vs* second evaluation cycle, Wilcoxon signed rank test with continuity correction: $p = 0.0005$)

Table 5 shows a statistically relevant difference in the frequency of categories of answers among the groups. It was particularly obvious at the beginning of the treatment and remained the same three months after the treatment, and the results refered to the group undergoing adjuvant treatment (P1) and to the control group (K), which was statistically relevant (first evaluation cycle P1 *vs* K: $p = 0.00298$, and the second evaluation cycle P1 *vs* K: $p = 0.00119$). This result suggests that friends, neighbours and colleagues pay frequent visits and offer their help to subjects suffering from malignant diseases. There was no statistically relevant difference when other groups were compared.

nies suffering and death, and people suffering from either curable or incurable malignant diseases are usually placed on the margins of the social care.

Reduced social contacts can be seen from the data obtained after the analysis of visits to relatives, friends, neighbours or colleagues, regular telephone communication, etc. As the results show, concern about a suffering friend or neighbour is more frequent when therapy begins, but as the treatment continues and the disease progresses, telephone communication becomes prevalent. This confirms that highest concern and support for the old patient remain to be a duty of the family. The results of the control group of older people that do not suffer from malignant diseases show that friends and neighbours do not visit them frequently and confirm that the older population becomes increasingly alienated. This kind of alienation is becoming increasingly frequent in Serbia, as well as in other countries. Our research shows that most of the older people with no malignant diseases come from suburban areas and most often live in the same household with their children. Most subjects are taken care of by their children. The scientific literature shows that adult children are the most important source of support and social relations, next to spouses, and that emotional support during illness is even more important than financial support [4, 6]. Married old people are happier, they cope with the

Table 5

Visits by friends and neighbours to the elderly patients

Cycle of assessment	Total n (%)	P1 n (%)	P2 n (%)	K n (%)	Fisher's exact test
1st cycle					
often	20 (13.33)	13 (26.53)	5 (9.8)	2 (4)	
rarely	69 (46)	23 (46.94)	23 (45.1)	23 (46)	$p = 0.01472$
almost never	58 (38.67)	13 (26.53)	21 (41.18)	24 (48)	
never	3(2)	0 (0)	2 (3.92)	1 (2)	
2nd (after 3 months)					
often	4 (2.67)	0 (0)	2 (3.92)	2 (4)	
rarely	95 (63.33)	39 (79.59)	33 (64.71)	23 (46)	$p = 0.00766$
almost never	46 (30.67)	9 (18.37)	13 (25.49)	24 (48)	
never	4 (2.67)	1 (2.04)	2 (3.92)	1 (2)	

P1 – elderly ongoing adjuvant chemotherapy (n = 49); P2 – elderly ongoing systemic chemotherapy (n = 51); K – healthy elderly (n = 50).

Discussion

Malignant disease, the way it is treated and long rehabilitation often exclude the patient from his/her social environment and in the end significantly reduce social contacts. The results pertaining the frequency of visits and the extent to which communication with social environment is retained confirm this view.

The results showed that both elderly people suffering from malignant diseases, so as healthy ones were often subject to so exclusion. Home visits and interest in patient's health were more frequent when the therapy began, but eventually, this interest and care often faded, which was particularly the case in the group of subjects suffering from disseminated diseases. The patients suffering from malignant diseases remind others of the fact that possibilities for therapy are limited and that life is transient. Serbian culture detreatment more easily and live longer than their peers who are divorced or widowed [4, 13, 26].

According to Gelder et al. [27] most of older persons live in their own homes, almost half of them live with spouse, and almost 10% of the older live with their children. Some of them live alone and are lonesome. These unsatisfactory social forms are typical of most Western countries, while in certain other cultures, for example Chinese or Indian, old people enjoy much respect and can often expect to live with their children. In Western countries, most middle-aged people want to live in a separate household, but this kind of independence will take its toll when they become weak and helpless, because there will be less assistance [4, 28]. Our research shows that older people in the group P1 had much more support from friends and neighbours when the treatment began, and this difference was statistically significant when compared to the other groups. This is in accordance

with research carried out by other authors [8, 28]. As time passes, home visits become less frequent, whereas telephone communication becomes more frequent. Our research also shows that social contacts become reduced even in the control group of older people with no malignant diseases. Numerous factors impacted the quality of life of older people in the former Yugoslavia. Many years of financial crisis, drop in living standards, poverty, unemployment and alienation made life difficult for old people, which had an impact on their mood and social ties [3, 29].

Another research with similar results was carried out by Đurđević and Nikolić [8] and it covered 100 subjects suffering from malignant diseases out of who 90% maintained close relations with their friends, and the highest degree of satisfaction was to keep close ties with family members and siblings. Additionally, 33% of the subjects faced difficulties when planning their budget, and 25% of them was in the need of other people's support. A study by Thomé and Hallberg [30] on people with and those with no malignant diseases, both groups aged above 75, shows that people with malignant diseases have a significantly lower quality of life, whereas their health, social, business and emotional functioning is worse compared with healthy subjects. Women with malignant diseases develop more health symptoms, face more financial difficulties and have less social support than healthy ones. Novaković and Pečenica [29] investigated neglect of old people in Bosnia and Herzegovina analyzing 2,000 subjects between 1993 and 2004. The results show that relatives of old persons contact them on a daily basis in 31.57% of cases, once a week in 18.68% of cases, never in 4.45% of cases, and sometimes in 45.30% cases. Relatives of 10.44% of the elderly provide financial support, domestic assistance in 6.24% of cases, farming assistance in 3%, and 28.17% of the old refuse any kind of assistance or support. Generally, contacts with children and relatives are insufficient and foster loneliness. Almost 80% of old people do not have enough support from their relatives.

In case of people suffering from malignant diseases, social support encompasses both emotional and instrumental support, e.g. transportation, cooking meals for them or assistance in everyday activities. Inadequate levels of any of these forms of social support increase risk of psychosocial problems and difficulties, which has a particular impact on persons suffering from disseminated diseases [4, 18, 29]. Petrak et al. [31] compared demographic features of Istria with other regions in Croatia, their health status, satisfaction with life, needs and availability of various care services, and found out that satisfaction with one's life was lower if self-perception of one's health was worse, functional ability is weaker and if there was a lack of emotional and instrumental support. Data obtained from the foreign scientific literature show that social services input is provided mainly to the over-65s, who are three times more likely to receive social service than community health service [32]. Interviews with our subjects and their family members show that most of them rely on health services, and that most of them are not even aware of other kinds of services or support. These data show that education of the old raise their awareness of the network of social support wchich should be further developed.

In most cases older people are afraid they might become a burden to the others, that they might become dependent on other people's assistance, of effects of the treatment, pain and other symptoms of the disease which might have a negative impact on their life quality. They also express fear that they will not finish certain tasks, fear of death and dying. It is widely known that old people who were successful in several fields, who lived active lives and have more social contacts are mostly healthier [4, 10]. The literature also shows fewer cases of psychiatric morbidity during the treatment of patients with malignant diseases who enjoy higher degree of social participation [13–15].

In the field of special education and rehabilitation, geriatric assessment involves assessments of life habits (level of achievement), kinds of necessary assistance and the degree of pleasure (personal hygiene, general physical abilities, interpersonal relations, mobility, maintaining the household etc.), assessment of socioeconomic status and social support [3, 8, 22]. These factors are important for assessing whether an old person can live independently and the extent to which he/she needs experts' assistance. By identifying financial sources we can assess their income, i.e. superannuation, or if there are other sources of support and to determine if they are sufficient for living expenses. Assessment of the environment involves living conditions, i.e. location, proximity and availability of various services, such as clinics, post office, supermarket etc. and their impact on the person's independence [4, 33].

Conclusion

The results of this study confirm that malignant diseases and their treatment often contribute to the exclusion of elderly patients from their social environment and in the end seriously reduce his/her social contacts. This exclusion becomes increased with time during chemotherapy, and is present as a decrease in the frequency of visits by their relatives, as well as friends and neighbours, comparing to the social contacts of healthy elderly people. The probable cause of this reduction of social contacts is unreadiness of the relatives and friends to cope with the long lasting malignant disease of the elderly.

These findings point to the importance of the special education and rehabilitation care of old people with malignant diseases, based on early identification of psychoemotional and social difficulties, requiring preventive interventions. Interventions should be focused on informing patients and their families about the available support within society, about proper life habits (diet, physical activity, recreation, personal hygiene etc.), psychosocial interventions by way of encouraging to take personal care and maintenance of social contacts, legal and financial advice, contacts with social services, contacts with various associations and non-government organizations. Adequate geriatric assessment in the period after the beginning of the treatment and palliative care would enable continuous monitoring and adequate treatment in future on-

cological clinical practice, which would improve the quality of life of old persons, may increase social competence and integration. Future research should be focused on the assessment of certain psychosocial interventions and their impact on the quality of life of old persons. Studies on old persons who manage to recover from malignant diseases could help us complete the picture about the problems and difficulties of old people after the treatment.

Conflicts of Interest

The authors indicate no potential conflicts of interest.

Author contributions

All the authors contributed to the design of the review, extraction and compiling of the data, drafting and critical revision of the manuscript.

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Long term complications of ventilation tube insertion in children with otitis media with effusion

Dugotrajne komplikacije implantacije ventilacionih cevčica u lečenju hroničnog sekretornog otitisa u dečjem uzrastu

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Abstract

Background/Aim. Otitis media with effusion (OME) is characterized by the prolonged presence of fluid (longer than 12 weeks) of different viscosity in the middle ear, without perforation of the eardrum or signs of acute inflammation. The conservative treatment does not always provide satisfactory recovery, so surgical treatment may be unavoidable. The aim of the study was to determine the incidence, type and frequency of complications caused by ventilation tube insertion as a part of treatment for OME in children, and specifically, to evaluate the evolution of these changes over the extended period of time. **Methods.** During a 5-year period (1986–1991), 84 children with chronic bilateral OME, aged from 6 months to 12 years, were enrolled in the study and treated with ventilation tube insertion. All the patients were periodically checked every 6 months over a 3–8 year period following the intervention (otomicroscopic examination, audiometry, tympanometry), and reexamined in 2013 (22–27 years after the primary surgical intervention). **Results.** The complications observed in this study (51%) were atrophic scarring of the tympanic membrane, myringo- and tympanosclerosis, retraction of the eardrum, persistent perforations, granulation tissue formations, development of chronic otitis and sensorineural hearing loss. **Conclusion.** The incidence of complications after ventilation tube insertion was 51% in this study. Atrophic scars and myringosclerosis were the most prominent complications. Despite high complications rate ventilation tube insertion still remains the treatment of choice in children with otitis media with effusion.

Key words:
otitis media with effusion; otologic surgical procedures; middle ear ventilation; treatment outcome; child.

Apstrakt

Uvod/Cilj. Hronični sekretorni otitis definiše se kao produženo prisustvo sekreta (duže od 12 nedelja) različite gustine u srednjem uvu, bez perforacije na bubnoj opni ili znakova zapaljenja. Kako konzervativno lečenje često ne daje zadovoljavajuće rezultate, hirurška intervencija može biti neizbežna. Cilj ovog rada bio je da se odredi incidencija, tip i učestalost komplikacija nakon hirurškog lečenja (implantacije ventilacionih cevčica) kao dela lečenja dece sa ovim oboljenjem, kao i da se proceni evolucija ovih promena u produženom vremenskom periodu. **Metode.** Tokom petogodišnjeg perioda (1986–1991) 84 dece sa obostranim sekretornim otitisom, uzrasta od 6 meseci do 12 godina bilo je uključeno u studiju i lečeno implantacijom ventilacionih cevčica. Sva deca su praćena i periodično kontrolisana 3–8 godina nakon intervencije (otomikroskopski pregled, audiometrija, timpanometrija) i ponovo pregledana tokom 2013. godine, odnosno 22–27 godina nakon primarne hirurške intervencije. **Rezultati.** Registrovane komplikacije u ovoj studiji (51%) bile su atrofični ožiljci, timpano- i miringoskleroza, različiti stepeni retrakcije bubne opne, granulaciono tkivo, razvoj hroničnog otitisa i pojava senzorineuralne nagluvosti. **Zaključak.** Učestalost pojave komplikacija nakon implantacije ventilacionih cevčica vrlo je visoka, u našoj studiji iznosila je 51%. Najčešće komplikacije bili su atrofični ožiljci na bubnoj opni i miringoskleroza. Iako je broj komplikacija veliki, implantacija ventilacionih cevčica i dalje ostaje terapija izbora u lečenju dece sa hroničnim sekretornim otitisom.

Ključne reči:
otitis media, serozni; hirurgija, otološka, procedure; uvo, srednje, aeracija; lečenje, ishod; deca.

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Introduction

Otitis media with effusion (OME) is characterized by the prolonged presence of fluid of different viscosity in the middle ear, without perforation of the eardrum or signs of acute inflammation. This fluid (secretion) can cause limited mobility of tympanic ossicular chain. It is most commonly seen in childhood, between the ages of 7 months and 6 years, with a higher prevalence during winter months [1]. The disease has usually slow and silent course with the symptoms that are vague and in most cases not clinically significant, while its etiology still remains unclear. When the condition is misdiagnosed or not treated adequately, it can lead to serious consequences and impair function of statoacustic apparatus. Considering the fact that the condition is almost always bilateral, long lasting hearing loss can have great impact on psychokinetic and speech development in childhood. Children with persistent OME are usually hyperactive, inattentive, with different behavioral problems and usually have decreased quality of life compared to their peers [2, 3].

Conservative treatment does not always provide adequate recovery. In these cases, surgical treatment may be inevitable, including ventilation tube insertion, with or without adenoidectomy. Myringocentesis and ventilation tube insertion are still commonly performed in everyday ear, nose and throat practice, and the possibility of complications is evident; therefore, it is very important to identify advantages and disadvantages of this surgical procedure.

Possible late complications of ventilation tube insertion reported in the literature are: persistent otorrhea, persistent perforation of the eardrum, atrophic scars, tympano- or myringosclerosis with or without ossicular chain fixation, granulation tissue, cholesteatoma, and sensorineural hearing loss [4, 5]. Some authors reported various eardrum changes following this procedure in as much as 80% of cases [5]. It is important to note that many of these complications may result from the disease itself.

The aim of this study was to determine the incidence, type and frequency of complications caused by ventilation tube insertion as a part of treatment for OME in children, and specifically, to evaluate the evolution of these changes over the extended period of time.

Methods

During a 5-year period (1986–1991), 84 children with chronic bilateral OME, aged from 6 months to 12 years, were enrolled in the study and treated with ventilation tube insertion. In most cases (in 157 of 165 ears), "Tübingen" gold prosthesis was implanted, most commonly in anterior inferior quadrant (86.06%), and in rest of the cases in anterior superior quadrant (13.94%). In 30.3% of cases, reimplantation was performed, while 14.54% of patients underwent the intervention more than twice. Average aeration time was 8 months and 21 days. All the patients were periodically checked, every 6 months, over a 3–8 year period following the intervention (otomicroscopic examination, audiometry, tympanometry), and reexamined in 2013 (22–27 years after the primary surgical intervention). A total of 71 patients came to reexamination visit.

Statistical analysis included descriptive methods of recording absolute and relative frequencies of the observed features, as well as hypothesis testing and determining the level of significance using Pearson's $\chi 2$ test and Fisher's exact test. The level of correlation was determined using the contingency coefficient (C).

Results

The study found that incidence of various complications of ventilation tube insertion after extended period of time was 51%.

In the early postoperative period, atrophic areas formed, usually occupying small areas (up to 3 mm), except in 4 cases were they involved almost half of the eardrum, and 4 other cases were they involved the entire surface of the tympanic membrane. Furthermore, there were 2 cases of eardrum perforation due to the atrophic scarring. At the last examination, all cases showed atrophic areas localized exclusively in the anterior inferior quadrant of the eardrum, involving area of up to 3 mm in diameter.

In the early postoperative period, mild retraction of the tympanic membrane was also observed, involving anterior part of the membrane in 3 cases, and posterior superior quadrant in 3 other cases. On the later reexamination, from 2 cases, which both had retraction situated in upper portion of the membrane, one of them had a form of retraction pocket.

Tympanosclerotic scars at sites of previously implanted ventilation tubes were observed in 25 cases at previous follow-up examinations, and 15 of them spread more extensively over the membrane, involving less than half of its surface. In adulthood, these scars were present at the exact locations and with the same extent as in the past period.

In the cases of 6 verified persistent perforations, there were no observable signs of inflammatory process in the ear, and myringoplasties were performed at adolescent age. In 5 remaining cases, chronic suppurative otitis developed; 3 patients had severe sensorineural hearing loss, in 3 cases extensive polypous granulomatous process of the middle ear's mucosa was confirmed, while 2 patients developed cholesteatoma (one with protympanic localization, and the other with extensive features).

All of these cases were treated with surgical procedures (in one case with 2 reinterventions). On the latter reexamination, in adulthood, only 2 patients had pathological findings, one case of the radical trepanation, and one tympanic membrane perforation. In the rest of the cases, otologic findings showed no abnormalities. On reexamination, we observed new case of chronic suppurative otitis in adulthood, which was surgically treated at other hospital (Table 1).

In 80 (48.48%) ears in early adolescence and 76 (54.28%) in adulthood no complications were observed. The patients did not have any symptoms and their otomicroscopic, audiometric and tympanometric findings were normal.

Table 1

Complications 3–8 years and 22–27 years after the implantation

Complications	Ear, n (%)	
	after 3–8 years	after 22–27 years
Atrophy of the eardrum	48 (29.09)	15 (10.71)
Tympanosclerosis	42 (25.45)	35 (25.00)
Persistent perforation	11 (6.66)	3 (2.14)
Retraction	6 (3.63)	2 (1.42)
Granulation tissue	3 (1.81)	/ /
Sensorineural hearing loss	3 (1.81)	3 (2.14)
Cholesteatoma	2 (1.21)	/ /
No complications	80 (48.48)	76 (54.28)

Figure 1 clearly shows a significant correlation between repeated myringocentesis on the same ear and later occurrence of atrophy and tympanosclerosis of eardrum. In regard to the incidence of remaining complications, frequencies were low, and with statistical testing, these differences compared to the number of myringocentesis with ventilation tube insertion in the same ear, showed no significant difference ($p < 0.05$).

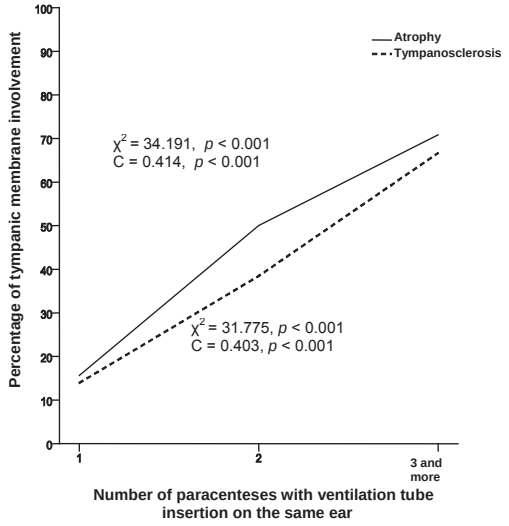

Fig. 1 – A correlation between the frequencies of atrophy/tympanosclerosis of the tympanic membrane and the number of myringocenteses with ventilation tube insertion in the same ear.

Discussion

Although the earlier presumption that implantation of ventilation tubes in children with bilateral OME has a beneficial effect on hearing, it was shown that the procedure is only of short duration efficacy, and researchers failed to prove that it has any impact on speech and language development in these children [6–8].

Atrophic areas on the tympanic membrane are the most frequent complication of ventilation tube insertion in our study. They appear when the tissue repair is inadequate due to the lack of middle layer of the membrane, and they are localized to the site of previous tube implantation. In the cases of reimplantation, this complication was more frequent. The prevalence of segmental atrophy in ears where ventilation tubes were implanted can vary between 16% and 74%, while certain percent of these changes is seen in ears that had never been implanted (up to 30%) [9, 10]. Progression of these scars is possible in the first couple of years after the extraction, which can lead to more serious complications in the future if middle ear ventilation remains poor – retraction pocket formation, atelectasis, and cholesteatoma. According to our results, these scars are in most cases minimal and without change, with rare tendency of further development. After a longer follow-up period, a significant number of these changes resolved.

Atrophic scars and pars flaccida retraction pockets were not common in early postoperative period, and in adulthood the occurrence was even lower. The observed low incidence of development is probably due to the normalization of middle ear ventilation in most cases after implantation. These changes are also considered to be complications of the disease itself by some authors [11].

Tympano(myringo)sclerosis is the second most common complication. It represents hyaline degeneration and calcification of the fibrous layer beyond the mucosa. In cases of reimplantation these changes appeared more frequently, and progressed in 10 of 42 cases in the first couple of years after the intervention, which is in accordance with reported findings by other authors [12]. After this period, these scars become stabile and permanent, and lose the tendency both of progression and regression. It is debated in literature whether these changes are sequelae of the disease itself or represent a complication of previously implanted ventilation tube. The estimated risk ratio for the development of myringosclerosis at the site of previously implanted ventilation tube is 24.5% [9].

In our opinion, persistent perforations, in half of the cases when they are "dry", with normal otomicroscopic findings in the tympanic cavity, represent the treatment optimum because they allow for prolonged aeration. The reported prevalence of this complication in the literature is around 3% [13]. In these cases, myringoplasty should be delayed until the adolescent period, with regular follow-ups. In cases of chronic otitis or cholesteatoma development, the surgery should be performed earlier.

The observed causal connection between the ventilation tube insertion and latter occurrence of cholesteatoma in 2 cases is still unsolved. The possible causes are epithelial migration in tympanic cavity over the edges of the perforation and retraction pocket formation on the atrophic tympanic membrane after the extraction. The prevalence of this serious complication is reported to be 1.1% [14]. It is considered that implantation of ventilation tubes can be complicated by the development of cho-

lesteatoma or it is a sequelae of the disease itself. The incidence of cholesteatoma formation is significantly higher in patients with poor Eustachian tube function. The development of cholesteatoma is most probably sequelae of both the disease and surgical intervention. Although a serious complication, chronic otitis can be managed and stabilized till adulthood if diagnosed and surgically treated in a timely manner.

Conclusion

The incidence of complications after ventilation tube implantation is very high, reaching 51% in our cases, but they are mostly mild with no significant pathological or functional consequences. Atrophy and tympano (myringo) sclerosis are the most common complications. Several years after the intervention, these changes can progress, but they tend to stabilize as time passes. Persisting perforations, cholesteatoma and sensorineural hearing loss are uncommon but serious complications that require surgical treatment. Considering that myringocentesis with ventilation tube implantation leads to functional and morphological healing of the ear and that serious complications are rare, this intervention still represents treatment of choice for chronic otitis media with effusion.

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Disease relapses in multiple sclerosis can be influenced by air pollution and climate seasonal conditions

Uticaj zagađenja vazduha i klimatskih uslova na pojavu relapsa multiple skleroze

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Abstract

Background/Aim. Environmental factors may influence the disease activity in patients with relapsing-remitting multiple sclerosis (MS). The aim of this study was to evaluate the influence of air pollution and seasonal climate factors of any on number of relapses in MS patients during a consecutive 5 years of observation. **Methods.** We retrospectively analyzed data of MS patients from the town of Niš, hospitalized at the Clinic of Neurology, Clinical Center Niš, Serbia, from 2005 to 2009. Climate data: mean daily sun shining; mean monthly sun shining, mean whole daily cloudiness, daily cloudiness at 7 a.m, 2 p.m. and 9 p.m. and air pollution expressed by NSR (New Source Review) were obtained from the Meteorology Observatory Niš. **Results.** During a 5-year of observation there were 260 relapses in 101 MS patients. The number of relapses showed a significantly negative correlation with the number of days with NSR < 2 (ϱ = -0.31; $p < 0.01$) and a positive correlation with the mean whole daily cloudiness ($p < 0.05$), mean daily cloudiness at 7 a.m. ($p < 0.05$) and 2 p.m. ($p < 0.01$). We found a significantlly positive correlation ($p < 0.05$) between the reduced number of relapses during the period of high vitamin D season, i.e. July–October. There was a statistically significant increase ($p < 0.01$) of the number of relapses during spring ($\bar{x}$ = 6.53; SD = 3.98) compared to the other three seasons. The joint presence of lower number of days with NSR < 2 during low vitamin D season (January–April) correlated with a statistically significant increase of the number of relapses in MS patients (F = 5.06, $p < 0.01$). **Conclusion.** The obtained results confirmed the influence of air pollution and climate seasonal conditions on disease relapses in MS patients based on a long-term observation. Lower numbers of days with low air pollution during the periods with low vitamin D (January–April), especially with increased cloudiness at 2 p.m, induce a higher risk of MS relapses in southern continental parts of Europe.

Key words:
multiple sclerosis; recurrence; air pollution; climate; sunlight; vitamin d.

Apstrakt

Uvod/Cilj. Nekoliko istraživanja ukazalo je na mogućnost uticaja klimatskih faktora na aktivnost bolesti u relapsno-remitentnoj multiploj sklerozi (MS). Cilj istraživanja bio je da se ispita uticaj zagađenja vazduha i sezonskih klimatskih faktora na pojavu relapsa bolesti u dužem vremenskom periodu. **Metode.** Retrospektivno i detaljno statistički analizirali smo podatke o broju relapsa MS bolesnika iz Niša i okoline, hospitalizovanih u Klinici za neurologiju Kliničkog centra Niš, od 2005. do 2009. godine. Praćeni su klimatski faktori: srednja mesečna osunčanost, srednja dnevna oblačnost, dnevna oblačnost u 7, 14 i 19 časova i stepen zagađenja vazduha meren po metodu *New Source Review* (NSR), a na osnovu podataka Meteorološke stanice Niš. **Rezultati.** Tokom pet godina praćenja 101 bolesnika registrovano je 260 relapsa MS čija pojava je imala statistički značajnu negativnu korelaciju sa brojem dana sa niskim nivoom zagađenja vazduha, NSR < 2 (ϱ = -0,31 $p < 0,01$) i pozitivnu korelaciju sa povećanim brojem dana sa povećanom ukupnom dnevnom oblačnošću ($p < 0,05$), kao i oblačnošću u 7 ($p < 0,05$) i 14 časova ($p < 0,01$). Prosečan broj dana sa NSR > 8 bio je statistički značajno veći od broja dana sa NSR < 2 tokom 2005, 2006 i 2009. ($p < 0,05$). U periodu visokog nivoa viatamina D (jul–oktobar) utvrđena je statistički značajna korelacija sa sniženjem učestalosti relapsa ($p < 0.05$). Broj relapse u proleće ($\bar{x}$ = 6,53; SD = 3,98) bio je statistički značajno veći ($p < 0,01$) u odnosu na leto ($\bar{x}$ = 3,27; SD = 2,49), jesen ($\bar{x}$ = 2,93; SD = 1,62) i zimu ($\bar{x}$ = 4,60; SD = 2,64). U periodima karakterističnim za snižene nivoe vitamina D (januar–april), uz istovremeno prisustvo NSR < 2 primećen je statistički značajan porast broja relapsa MS (F = 5.06, $p < 0,01$). **Zaključak.** Tokom dužeg vremenskog perioda klimatski faktori utiču na aktivnost MS. Veći broj dana sa povećanom zagađenošću vazduha u sezoni niskog nivoa vitamina D (januar–april), posebno u slučaju povećane oblačnosti u 14 časova, značajno povećavaju rizik od pojave relapsa MS u jugoistočnim kontinentalnim delovima Evrope.

Ključne reči:
multipla skleroza; recidiv; vazduh, zagađenje; klima; sunčeva svetlost; vitamin d.

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Introduction

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory-demyelinating disease of the central nervous system (CNS). It is postulated that, beside genetic susceptibility, environmental factors may play a crucial role in the disease origin [1]. Epidemiological studies have found that risk to develop MS and the disease prevalence is enhanced with the latitude and by changing the residence from the equator to northern areas [2, 3]. The inverse correlation between risk to develop MS and previous sunshine exposure is found in several studies in the USA [4], Norway [5], Canada [6] and Australia [7].

Environmental factors also can have impact on the disease activity influencing relapse triggering[1] and the disease seasonal variability [8–11]. A higher frequency of relapses is often associated with lower vitamin D serum levels, lower sunshine ultraviolet (UV) radiation exposition and high frequency of infections [11]. UV radiation is the prime determinant of the circulated serum vitamin D level and it highly depends on the regional weather conditions[12]. Soilu-Hanninen et al.[13] have found that lower serum vitamin D level during relapse could be in relation to remission in MS patients while Simpson et al.[14] have shown that higher vitamin D serum levels are associated with lower relapse risk in MS patients.

The effects of air pollution on the pulmonary and cardiovascular systems have been well-established in a series of major epidemiological and observational studies, but newer data indicated a possible association with diseases of the CNS, including stroke, Alzheimer's disease, Parkinson's disease and neurodevelopmental disorders. Emerging evidence indicated that air pollution could provoke neuroinflammation, oxidative stress, microglial activation, cerebrovascular dysfunction and alterations in the blood-brain barrier [15]. Air pollution and poor air quality are related to the risk of multiple sclerosis in women, as well as exacerbation of symptoms as shown in a study correlating outdoor air particulate matter (PM) and the occurrence of MS in women in the Atlanta area. PM is a particulate matter from smoke, dirt and dust from factories, farming and roads, mold, spores, and pollen and can affect the immune system making those exposed more susceptible to infections. PM has an influence on systemic immune response and inflammation. Ambient air pollutants are known to induce systemic immune responses and to enhance existing peripheral inflammation. Ambient air quality and monthly MS relapse occurrence in south-western Finland were compared showing that the risk of relapse was by over fourfold increased when the concentration of PM was at the highest quartile [16, 17].

The majority of other investigated climate factors (maximal and minimal air temperature, air humidity, level of precipitations or atmospheric pressure) did not show a significant correlation with the relapse frequency in MS patients [18–20].

There are only few studies investigating this topic and increasing queries from MS patients. Since geographic determinants and country industrial and economic development can influence the obtained results, it is necessary to investigate insolation, air pollution and other climate factors on MS in different parts of the world to gather conclusive information. This is why the aim of this study was to investigate if there is a correlation between the frequency of relapses in MS patients during the year and climate factors which may influence sunshine accessibility.

Methods

This cross-sectional retrospective study included patients with the established diagnosis of MS with relapsing-remitting disease course according to the McDonald criteria [21] independently on disease duration. We analyzed the disease activity expressed through the relapse frequency in patients hospitalized at the Clinic of Neurology, Clinical Center Niš, Serbia (referral institution covering the area with ~ 2 million inhabitants) from 2005 to 2009. Serbia is a typical non-EU developing country at the southern Europe with typical four seasonal climates. Only patients settled in the urban parts and rural suburbs, of the Niš municipality localized in south-east Serbia (43.3000°N, 21.9000°E) were enrolled into the study.

The exclusion criteria were treatment with immunomodulatory drugs during the observational period and clear evidences of proceeding infection prior to disease relapse. MS relapse was defined as the onset of new objective neurological symptoms/signs or worsening of existing neurological disability, not accompanied by metabolic changes, fever or other signs of infection, and lasting for a period of at least 48 h accompanied by objective change of at least 0.5 in the EDSS [22] score. The diagnosis of MS relapses was established by the neurologist – MS specialist. We analyzed the annual distribution of relapses recorded during 12 months of the year. The study design was approved by the local Ethic Committee and performed in accordance with the Declaration of Helsinki.

Sunshine accessibility was evaluated by the records of meteorology data from the Meteorology Observatory Niš. Over the 5 years (2005–2009) each month we collected monthly data about: mean sun shining expressed by the number of daily sunny hours; monthly sun shining (total hours number); mean whole daily cloudiness; daily cloudiness at 7 am, 2 pm and 9 pm expressed as one tenth (1/10) of the cloudiness of the visible sky and the air pollution expressed by direct air pollutions and their precursors measured as recommended by Environmental Protection Agency (EPA) and its New Source Review (NSR) permits [23]. Air pollution was expressed by the number of days with NSR less than two (low level of air pollution) and the number of days with NSR more than eight (high level of air pollution).

Several epidemiologic studies have shown that there are seasonal, month by month, variations in vitamin D levels not corresponding with classic climate periods that could be divided in three seasons: low (January–April), high (July–October) and medium (May, June, November, December). We used this definition to additionally stratify our data in addition to classic seasonal periods [24–26].

Statistical analysis was performed using Spearman`s coefficient of linear correlation to find a potential correlative connection between the number of monthly relapses and examined parameters. We have used ANOVA test (one way and two way) to test the influence of environmental parameters on

the number of relapses during the seasons and performed consequent *post hoc* analysis of the multiple comparisons by Tamhane test. To evaluate monthly variations in relapse number we performed Kolmogorov-Smirnov test to check normality of sample parameters within a 5-year observational period.

Results

Out of 230 MS patients hospitalized at our Clinic who had 497 disease relapses, the inclusion criteria were met in 101 patients, settled in the town of Niš and its suburbs, with 260 relapses recorded during a 5-year observational period. There were 22 males and 79 females with the average age 39.3 years (18–60 years) with no statistically significant differences in age. There were 74 patients settled in the urban parts of Niš and 27 patients settled in rural suburbs. We did not found any statistically significant differences in monthly number of relapses between sexes, nor between the patients settled in rural and urban environment.

The average number of relapses by month and year during the investigated seasonal periods, is shown in Figure 1. The cumulative number of relapses (during 5 years of observation) ranked according to seasonal periods with high, medium and low levels of vitamin D (according to Bell et al. [24]) was significantly higher in the period with low vitamin D level compared to other two seasonal periods ($p < 0.01$) as shown in Figure 1. We found a significant positive correlation ($p < 0.05$) between reduced number of relapses during the period of high vitamin D season [24] i.e. July–October. Statistical analysis using χ^2 test to calculate the difference between the expected and observed number of relapses during seasonal periods with high, medium and low vitamin D levels, showed a significant decrease in the number of relapses during the season defined as high vitamin D season (Table 1). Correlation analysis used to compare the number of relapses in different classic climate seasons showed the influence of seasonal variations on the relapse number during a 5-year observational period with a statistically significant increase ($p < 0.01$) relapses of number during spring ($\bar{x}$ = 6.53; SD = 3.98) compared to the other three seasons: summer ($\bar{x}$ = 3.27; SD = 2.49), autumn ($\bar{x}$ = 2.93; SD = 1.62) and winter ($\bar{x}$ = 4.60; SD = 2.64).

Air pollution data (Figure 2) analysis showed the that average number of days *per* month with NSR > 8, during the

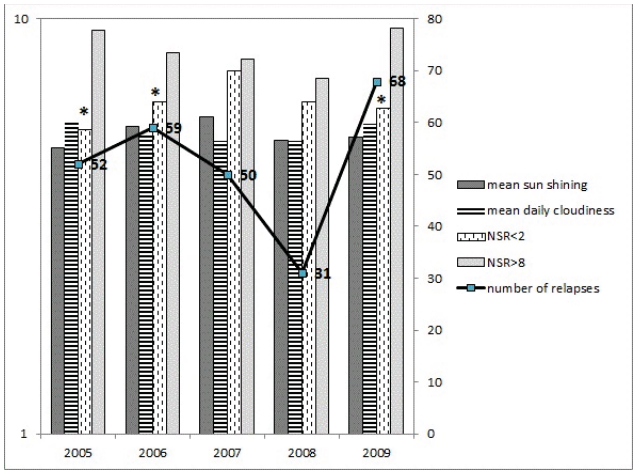

Fig. 2 – Correlation of the average number of relapses with air pollution and climate factors during the observational period (5 years)

Left Y axis – absolute number of values for parameters investigated: the mean sun shining expressed by the number of daily sunny hours, mean whole daily cloudiness expressed as one tenth (1/10) of cloudiness of the visible sky, air pollution expressed by direct air pollutions and their precursors measured as recommended by the Environmental Protection Agency (EPA) and its New Source Review (NSR) permits; Right Y-axis – average number of relapses *per* year; * - statistically significant correlation ($p < 0.01$).

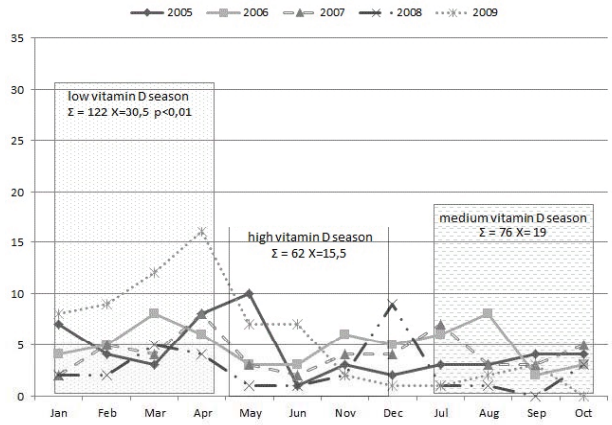

Fig. 1 – Relapse rate by months and years according to the seasonal periods

Y-axis – absolute number of relapses; X-axis – months during year; Σ – sum of relapses; x – mean number of relapses.

Table 1

Number of relapses during the periods according to vitamin D level

Annual period according to vitamin D levels	Relapse number (sum 2005–2009)		
	observed	expected	other
Low vitamin D	122	86.7	35.3
Medium vitamin D	76	86.7	-10.7
High vitamin D	62	86.7	-24.7
Σ 2005–2009	260		

$\chi^2 = 22.77$; df 2 ; $p < 0.001$.

observational period, was higher than the number of days with NSR < 2 with a statistically significant difference in 2005, 2006 and 2009 ($p < 0.05$). The number of relapses showed a significantly negative correlation with the number of days with NSR < 2 ($\rho = -0.31$; $p < 0.01$), indicating the increased number of relapses during the periods with small number of days with low air pollution. ANOVA test and the consequent *post hoc* analysis of multiple comparisons using the Tamhen test showed a joint presence of two factors, i.e. low number of days with NSR < 2 during the low vitamin D season (January–April) inducing statistically significant increase in the number of relapses in MS patients ($F = 5.06$, $p < 0,01$).

The mean daily sun shining expressed by the number of daily sunny hours and the mean whole daily cloudiness expressed through one tenth part of the visible sky was stabile during the observation (Figure 2). Both sunshine parameters measured (the number of sunshine hours per day and the sum of sunshine hours/day/months) did not influenced the number of relapses recorded.

The results of Spearman's linear correlation analysis between the number of monthly relapses and the examined climate parameters are presented in Table 2. Monthly relapse number showed a statistically significant positive correlation with the mean whole daily cloudiness ($p < 0.05$), the mean daily cloudiness at 7 am ($p < 0.05$) and mean daily cloudiness at 2 pm ($p < 0.01$).

Table 2

Correlations of the monthly number of relapses with the investigated climate factors

Climate factors	ρ	*p*
Mean sun shining (number of hours/day)	-0.18	0.1809
Monthly sun shining (sum of hours/day/months)	-0.18	0.1796
Daily cloudiness (as 1/10 of the visible sky)	0.29	0.0240*
Mean daily cloudness (at 7 am as 1/10 of the visible sky)	0.28	0.0325*
Mean daily cloudness (at 2 pm as 1/10 of the visible sky)	0.34	0.0074#
Mean daily cloudness (at 9 pm as 1/10 of the visible sky)	0.24	0.0655
Number of days/year with NSR < 2	-0.32	0.0115#
Number of days/year with NSR > 8	0.21	0.1081

NSR – New Source Review; ρ - correlation coefficient; *- $p < 0.05$; # - $p < 0.01$.

Discussion

There are several ambient environmental factors most frequently considered to influence different relapse rates in MS patients such as sun shining, rainfall, ozone or air pollution [17] and cycle fluctuations of infections[11]. Tremlett et al. [11] investigated a connection between MS and ambient factors and found a significant connection between the relapse rate and UV radiation induced erythemal level. Instead of cloudiness they analyzed the level of rainfall and did not find any statistically significant connection. The same study analyzed the influence of air pollution (expressed by aerodynamic particulate of a defined diameter – PM10) on the relapse rate and could not finding clear statistical connection.

The results of our study did not confirm any connection between the disease activity and direct sunshine accessibility measured by the number of sunshine hours *per* day and the sum of sunshine hours/day/months but showed the indirect connection with sunshine accessibility through the degree of cloudiness. The first connection between sun shining and MS was pointed out by Sir Donald Acheson et al. [4] in 1960 while later findings pointed out that sunshine influence on MS is indirect and correlate with vitamin D levels and its immunomodulatory effects. Immunomodulatory effects of vitamin D in MS were confirmed by the results of experimental and human investigations [27–30]. The influence of vitamin D on MS even could be independent from the level of sunshining which has been confirmed by epidemiological studies in Eskim populations who should have high risk for MS according to the low level of sunshining, but have been found to have low MS morbidity [31]. Nevertheless some recent studies have shown evidence that sunshine supress the clinical signs of animal model of MS – experimental autoimmune encephalomyelitis independent on vitamin D level [32].

According to the fact that sunshine UV accessibility is not determined only by insolation intensity and duration but also by the structures on the sunshine way to the earth, this result may be explained by a higher absorption and/or scattering of sunshine UV rays by clouds and air pollutants [33–35]. Our finding of a statistically significant correlation between the number of relapses and the mean whole daily cloudiness, mean daily cloudiness at 7 a.m. and 2 p.m. and the degree of air pollution (lower number of monthly days with NSR < 2) is in accordance with this.

There are numerous studies with controversial results about seasonal variation in the MS disease activity. Some of them have found the presence of seasonal variability in the number of relapses in MS patients [8–11, 36, 37] while other did not find a clear seasonal character of the disease [18, 38, 39]. Embry et al.[40] study supported the finding of seasonal fluctuations by a correalation with the number of gadolinium contrast enhancing lesions on MRI which tend to get lower in the period when serum 25(OH)D is higher which is in accordance with the findings of seasonal variations in vitamin D levels (beeing lower during winter and higher during summer) [41].

Our results clearly demonstrated statistically significant increase in the number of relapses during spring compared to the other three seasons: summer, autumn and winter during 5 years of observation. This confirmed the

findings of Tremllet et al. [11] who have found a lower frequency of relapse appearing in summer than in winter in the context of the evident positive correlation between serum levels of vitamin D and relapse frequency, but also in the context of a higher frequency of upper respiratory tract infections. On the other hand, our results support observations that the classic climate four-season approach do not necessarily correlate with the influence of vitamin D since there is almost a 2-month difference between 25(OH)D decrease and the appearance of MS worsening or increased number of relapses and *vice versa* [40]. This was the main reason why we decided to implement two types of season division approaches: classic climate seasons and seasons according to the average levels of vitamin D [24–26]. Both approaches showed a significant seasonal influence on MS relapse rate but only seasonal variations according to the average levels of vitamin D showed a significant joint impact with cloudiness and air pollution on disease relapse rates during 5 years of observation. Unfortunately, one of the main biases of our study was unavailability of patient's blood samples, due to retrospective nature of the study, to tests real levels of 25(OH) D in our patient cohort.

Conclusion

The impact of air pollution on MS relapse rate, found in our study is in accordance with a recent observation that air pollution could influence neuroinflammation, blood brain barrier functions and neurodegenerative processes in the CNS. The most important finding of our investigation is that a lower number of days with low air pollution during the periods with low vitamin D (January–April), especially with increased cloudiness at 2 p.m, increase risk of MS relapses in the southern continental parts of Europe. Because of this and with respect to conflicting data about seasonal variations (with unclear definition of vitamin D seasonal impact) and the influence of sun shining, climate factors and air pollution, in conclusion we would suggest that further studies investigating any of these factors role in MS, should always take into account the joint effect of several environmental factors through a longer time period.

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ORIGINAL ARTICLE

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Quality of analgesia after lower third molar surgery: A randomised, double-blind study of levobupivacaine, bupivacaine and lidocaine with epinephrine

Kvalitet analgezije nakon hirurškog vađenja donjih umnjaka: randomizovana, duplo slepa studija efikasnosti levobupivakaina, bupivakaina i lidokaina sa adrenalinom

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Abstract

Background/Aim. Surgical extraction of lower third molars is followed by mild or severe postoperative pain which peaks at maximal intensity in the first 12 hours and has a significant impact on a patient's postoperative quality of life. The use of long-acting local anaesthetics is a promising strategy to improve postoperative analgesia. The aim of the present study was to investigate analgesic parameters and patient satisfaction after using 0.5% levobupivacaine (Lbup), 0.5% bupivacaine (Bup) and 2% lidocaine with epinephrine 1:80,000 (Lid + Epi) for an inferior alveolar nerve block following lower third molar surgery. **Methods.** A total of 102 patients (ASA I) were divided into three groups, each of which received either 3 mL of Lbup, Bup or Lid + Epi. The intensity of postoperative analgesia was measured using a verbal rating scale (VRS). The total amounts of rescue analgesics were recorded on the first and during seven postoperative days. Patients satisfaction was noted using a modified verbal scales. **Results.** A significantly higher level of postoperative pain was recorded in Lid + Epi group compared to Bup and Lbup groups. No significant differences were seen between Bup and Lbup, but a significant reduction in the need for rescue analgesics was seen postoperatively in both Lbup and Bup (50%) in comparison with Lid + Epi (80%) in the first 24 hours. The same significant trend in rescue analgesic consumption was recorded for seven postoperative days. Patients' overall satisfaction was significantly lower for Lid + Epi (10%) than for Lbup (56%) and Bup (52%). **Conclusion.** The use of a new and long-acting local anaesthetic 0.5% levobupivacaine is clinically relevant and effective for an inferior alveolar nerve block and postoperative pain control after third molar surgery. In our study Lbup and Bup controled postoperative pain more efficiently after lower third molar surgery compared to Lid + Epi.

Key words:
tooth extraction; molar, third; bupivacaine; lidocaine; anesthesia, dental; pain, postoperative; questionaires.

Apstrakt

Uvod/Cilj. Hirurško vađenje donjih impaktiranih umnjaka praćeno je bolom umerenog do jakog intenziteta, sa maksimalnim intenzitetom tokom prvih 12 sati, koji ima značajan uticaj na kvalitet života pacijenata u postoperativnom periodu. Upotreba dugodelujućih lokalnih anestetika predstavlja obećavajuću strategiju za poboljšanje postoperativne analgezije. Cilj ove studije bio je da se ispitaju analgetički parametri i zadovoljstvo pacijenata postignutom analgezijom u postoperativnom periodu nakon primene 0,5% levobupivakaina (Lbup), 0,5% bupivakaina (Bup) i 2% lidokaina sa epinefrinom (1: 80,000) (Lid + Epi) za sprovodnu anesteziju donjeg alveolarnog nerva prilikom hirurškog vađenja donjih umnjaka. **Metode.** Ukupno 102 pacijenta (ASA I) bila su podeljena u tri grupe u zavisnosti od primljenog anestetika: 3 mL Lbup, 3 mL Bup ili 3 mL Lid + Epi. Intenzitet postoperativne analgezije registrovan je primenom verbalne rangirajuće skale (VRS). Zabeležena je ukupna količina primenjenih analgetika nakon prvog i sedmog postoperativnog dana. Zadovoljstvo pacijenata ocenjivano je na osnovu modifikovanih verbalnih skala. **Rezultati.** Značajno jači intenzitet postoperativnog bola zabeležen je u grupi Lid + Epi, u poređenju sa grupama Lbup i Bup. Značajno smanjenje potrebe za analgeticima u postoperativnom periodu zabeleženo u grupama Lbup i Bup (50%) u poređenju sa grupom Lid +

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Epi (80%) nakon 24 časa. Značajno smanjenje potrebe za postoperativnim analgeticima u grupama Lbup i Bup zabeleženo je i nakon 7 dana. Potpuno zadovoljstvo pacijenata postignutom analgezijom bilo je značajno slabije u grupi Lid + Epi (10%) u poređenju sa grupama Lbup (56%) i Bup (52%). **Zaključak.** Upotreba novog dugodelujućeg lokalnog anestetika 0,5% levobupivakaina klinički je relevantna i efikasna za sprovodnu anesteziju donjeg alveolarnog nerva i kontrolu postoperativnog bola nakon hirurškog vađenja donjih umnjaka. U našoj studiji Lbup i Bup bili su efikasniji u kontroli postoperativnog bola nakon hirurškog vađenja donjih umnjaka u poređenju sa Lid + Epi.

Ključne reči:
zub, ekstrakcija; umnjaci; bupivakain; lidokain; anestezija, stomatološka; bol, postoperativni; upitnici.

Introduction

Surgical extraction of impacted lower third molars is considered the standard clinical model in pain studies, due to the evidence of moderate to severe postoperative pain which leads to increased pain perception and causes patient dissatisfaction [1]. Postoperative pain levels have also been found to have a significant impact on the quality of life after third molar surgery [2]. Thus, the successful control of postoperative pain is a prerequisite for general patient compliance with oral-surgical procedures.

The standard protocol for pain control in third molar surgery involves the preoperative administration of local anaesthetics along with the intermediate action and postoperative use of analgesics. However, intermediate anaesthetics are not analgesics during the periods of the most intensive postoperative pain experienced (6–8 hours), leading to the faster onset of postoperative pain and increased consumption of postoperative analgesics. Furthermore, any failure in postoperative pain control may contribute to the develoment of central sensitisation [3], a state of hyperexcitability in the central nervous system that may even persist for 30 days after third molar surgery [4]. It has been demonstrated that the use of long-acting local anaesthetics for the prolonged blockage of nociceptive impulses arising from the site of surgery may be a promising strategy for improving postoperative analgesia [5].

Bupivacaine (Bup) was a widely used, long-acting local anaesthetic which provided relatively fast relief and prolonged block anaesthesia and delayed onset of postoperative pain [6]. However, due to clinical reports citing life-threatening cardiac issues and its neurotoxic effects, it became evident that bupivacaine had a narrow safety margin, especially after an unwanted intravascular injection [7–10]. On the other hand, levobupivacaine (Lbup) is a long-acting local anaesthetic with chemical and physical properties identical to bupivacaine but with lower toxicity seen in *in vitro*, *in vivo* and human volunteer studies [11–14]. Comparative clinical studies evaluating equivalent doses of 0.5% Lbup and Bup for peripheral nerve blocks have suggested that clinical parameters were similar or even better with 0.5% levobupivacaine [15–18]. In dentistry, one human volunteer study compared the anaesthetic properties of 0.5% Bup and 0.5% Lbup, both associated with epinephrine (1 : 200,000), and found no significant differences between the two anaesthetics in achieving onset time and duration of soft tissue and pulpal anaesthesia for an inferior alveolar nerve block [19].

The aim of the study was to investigate analgesic parameters and patient satisfaction after using 0.5% Lbup, 0.5% Bup and 2% lidocaine with epinephrine (1 : 80,000) (Lid + Epi) for inferior alveolar nerve block in patients undergoing lower third molar surgery.

Methods

The study was performed at the Clinic for Oral Surgery, Faculty of Dental Medicine, University of Belgrade, with institutional approval from the Ethical Commitee (No. 36/32). The patients were classified as having physical status 1 according to the American Society of Anesthesiologists (ASA) classification. Exclusion criteria were: age under 18, pregnant women, nursing mothers, smokers, patients with any signs of acute or chronic pain in the orofacial region and any antibiotic or analgesic intake within seven days preoperatively. Specific inclusion criteria were patients with fully impacted lower third molars (more than two-thirds of the crown covered with alveolar bone, confirmed by radiographic analysis) with no signs of acute pericoronitis or any acute infection. The patients were studied using a double-blind, controlled design and were randomly allocated to three groups receiving either 3 mL of 2% lidocaine with 1 : 80,000 epinephrine (Lidokain-Adrenalin 2%®, Galenika, Serbia) – Lid + Epi; 3 mL of 0.5% bupivacaine (Marcaine®, AstraZeneca, United Kingdom) – Bup; 3 mL of 0.5% levobupivacaine (Chirocaine®, Abbott, USA) – Lbup.

Random assignments were carried out by an independent investigator according to a computer-generated randomisation list with sealed numbered envelopes. The patients received a total of 3.0 mL of local anaesthetic in the following manner: 2.0 mL for the inferior alveolar nerve block, 0.5 mL for the lingual nerve block and 0.5 mL for the buccal nerve block. No premedication was given. Since 0.5% Bup and 0.5% Lbup were not available in dental cartridges, they were drawn from 10 and 20 mL vials by a clinical pharmacist not involved in the study. The same surgeon performed all the blocks. The time from the application of anaesthetic to the beginning of surgery was limited to 15 minutes. If additional anaesthesia was given due to a prolonged onset time or the presence of intolerable intraoperative pain, anaesthesia was considered unsuccessful and the patients were excluded from the study. Additional anaesthesia was achieved by administering 2% lidocaine with epinephrine (1 : 80,000) (Lidokain-Adrenalin 2%®, Galenika, Serbia). At the end of surgery, the patients were given a study questionnaire with detailed instructions for collecting the protocol parameters of postoperative analgesia. Regular postoperative follow-ups were scheduled for the first and seventh days after the surgery.

The questionnaires were returned back seven days after the surgery, when the patients' sutures were removed.

The postoperative analgesia protocol consisted of clear instructions for analgesic consumption (ibuprofen 400 mg *per os*, Brufen®, Galenika, Serbia) in the case of pain experienced at the surgical site of moderate to severe intenstity, identified at the level of ≥ 4 according to the Verbal Rating Scale (VRS). The VRS consists of a list of six-point scale phrases (0 – no pain; 1 – just notable pain; 2 – weak pain; 3 – moderate pain; 4 – severe pain; 5 – excrutiating pain) which represent the levels of pain intensity. The patients were instructed to grade pain intensity at fixed time points 2, 4, 6, 8, 12, 24 and 48 hours postoperatively. Also, the patients were instructed to record the total amount of analgesics taken in the first 24 hours and over seven days postoperatively.

In order to evaluate the patients satisfaction with the administered analgesia and the overall satisfaction with the treatment, a five-point verbal scale was used: 1 – poor, 2 – fair; 3 – good; 4 – very good; 5 – excellent. The patients evaluated the duration of anaesthesia using a three-point verbal scale: 1 – not enough; 2 – enough; 3 – too long.

Statistical analysis was performed using the statistical software SPSS, version 18.0. The results were presented as the mean ± standard deviation (SD), while χ^2 test was performed to determine the differences in gender and the patient's satisfaction with the treatment and analgesia. Age, weight, the duration of operative procedure and analgesic uptake were compared using parametric one-way ANOVA with *post-hoc* Tukey test. When normal data distribution was not present, non-parametric Kruskal-Wallis and Mann-Whitney tests were used. The difference of $p < 0.05$ was considered significant. The group size was estimated based on a pilot study. In order for the study to have 80% power, with type I errors of 0.05 and assumed differences detected at 40%, the total sample size required was 82 patients. The sample size was calculated using the statistical program G*Power 3.1. (Heinrich-Heine-University, Dusseldorf, Germany).

Results

The flow diagram demonstrates randomisation of patients enrolled in the study (Figure 1). Initially, 125 patients were examined but 102 met the enrollement criteria. The patients were randomised into three groups of 34 each and received either levobupivacaine, bupivacaine or lidocaine with epinephrine. Due to discontinued intervention and the lost of follow-ups, 3, 7, and 7 patients from Lid + Epi, Bup and Lbup groups, respectivelly, were excluded from the study. The subjects' demographic and clinical data are summarised in Table 1.

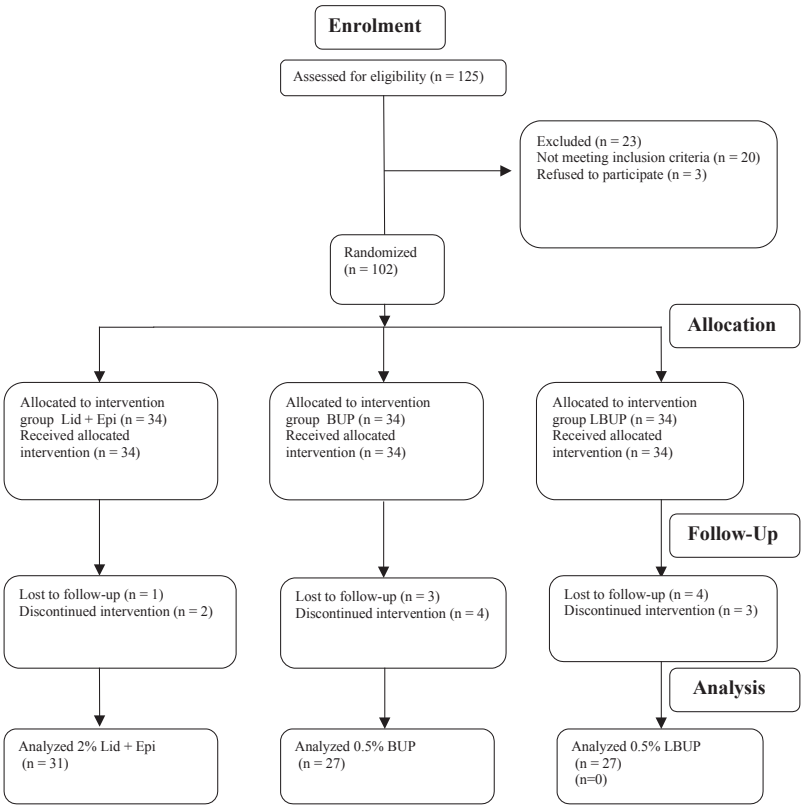

Fig. 1 – Flow diagram of randomization either 2% lidocaine with epinephrine (1 : 100,000) (Lid + Epi), 0.5% bupivacaine (BUP) or 0.5% levobupivacaine (LBUP) for lower third molar surgery.

There were statistically significant differences in postoperative pain intensity among the three investigated groups over 4 to 48 hours. Significantly higher levels of postoperative pain were recorded in the Lid + Epi compared to the Bup and Lbup groups at each time point. The patients in the Bup and Lbup groups experienced similar postoperative pain intensities except during the sixth hour, when pain levels were significantly higher in the Bup cohort (Figure 2). In addition, significantly more patients experienced moderate to severe

Table 1

Patient's demographic and clinical data

Parameters	Lid + Epi	Bup	Lbup
Number of patients	30	27	27
Female/Male, n	19/11	18/9	19/8
Age (years), $\bar{x} \pm SD$	23.6 ± 4.0	23,9 ± 3,5	24,4 ± 5,1
Weight (kg), $\bar{x} \pm SD$	67 ± 13	65 ± 12	68 ± 15
Impacted third molars, n	30	27	27
Duration of operation (min), $\bar{x} \pm SD$	14.3 ± 4.2	13.3 ± 3.9	15.5 ± 4.5
Section of crown and roots (yes/no), n	20/10	19/8	18/9
Bone removal, n			
mesial	6	7	5
distal	16	18	19
oclusal	3	2	2
buccal	0	1	0
lingual			

Lid + Epi : 2% lidocaine with 1 : 100,000 epinephrine; Bup : 0.5% bupivacaine; Lbup : 0.5% levobupivacaine.

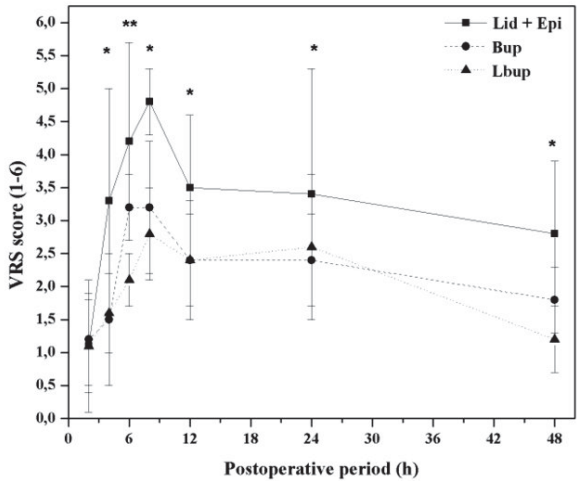

Fig. 2 – Pain intensity according to the verbal rating scale (VRS) after lower third molar surgery. Lid + Epi: 2% lidocaine with 1 : 100,000 epinephrine; Bup: 0.5% bupivacaine; Lbup: 0.5% levobupivacaine; VRS: verbal rating scale; *$p < 0.05$: Lid + Epi vs. 0.5% Bup, Lid + Epi vs. Lbup (Kruskall-Wallis test, Mann-Whitney U test); **$p < 0.05$: Bup vs. LBUP (Kruskall-Wallis test, Mann-Whitney U test).

postoperative pain (VRS ≥ 4) in the Lid + Epi group for all the measured time intervals (Table 2). A significant reduction in the need for rescue medication in the first 24 hours postoperatively was seen in both the Lbup and Bup groups (50% of patients required pain medication) as compared to the Lid + Epi patient sample where 80% of patients required pain medication (Table 3). A total analgesic consumption, measured after the first 24 hours till the seventh day following the surgical procedure was significantly less in the Lbup and Bup groups compared to the Lid + Epi group (Table 3).

Regarding the patient's satisfaction with the achieved postoperative analgesia, 60% (16/27) and 63% (17/27) of patients in the groups Bup and Lbup, respectively, declared achieved analgesia as excellent, compared to 10% (3/31) in the Lid + Epi group. This difference was statistically significant (Figure 3). The five-point verbal scale measurement showed that the mean score for the achieved analgesia was 3.00 ± 1.05, 4.52 ± 0.89 and 4.41 ± 0.91 in the Lid + Epi, Bup and Lbup group, respectively ($p < 0.05$; Kruskal-Wallis rank test), with a significant decrease in the Lid + Epi group compared to both the Lbup and Bup groups [($p < 0.05$, Mann-Whitney test); (data on patient's satisfaction with the

Table 2

Percentage of patients experiencing moderate-to-severe postoperative pain according to the verbal rating scale (VRS ≥ 4) over 48-hour period after 2% lidocaine with 1 : 100,000 epinephrine (Lid + Epi), 0.5% bupivacaine (Bup) and 0.5% levobupivacaine (Lbup)

Groups	2h	4h*	6h*	8h*	12h*	24h*	48h*
Lid + Epi	6	16	48	42	35	26	16
Bup	0	4	11	15	4	4	4
Lbup	0	4	7	11	7	4	6

***$p < 0,05$, χ^2 test.**

Table 3

Postoperative analgesic consumption after anesthesia with 2% lidocaine with 1:100,000 epinephrine (Lid+ Epi), 0.5% bupivacaine (Bup) and 0.5% levobupivacaine (Lbup)

Parameters	Lid + Epi	Bup	Lbup
N_1	25/30*	14/27	14/27
N_2	29/30	20/30	21/30
Pain medcation 24 h (mg), $\bar{x} \pm SD$	1280 ± 450**	630 ± 243	543 ± 277
Pain medication 7 days (mg), $\bar{x} \pm SD$	3430 ± 1633**	1788 ± 832	1640 ± 759

N_1 – number of patients requiring pain medication during 24 hours; N_2 – number of patients requiring pain medication during 7 days; *$p < 0.05$ (Chi-square test), **$p < 0.05$ – Lid + Epi vs. Bup; Lid+Epi vs Lbup (One-way ANOVA, *post hoc* Tukey test).

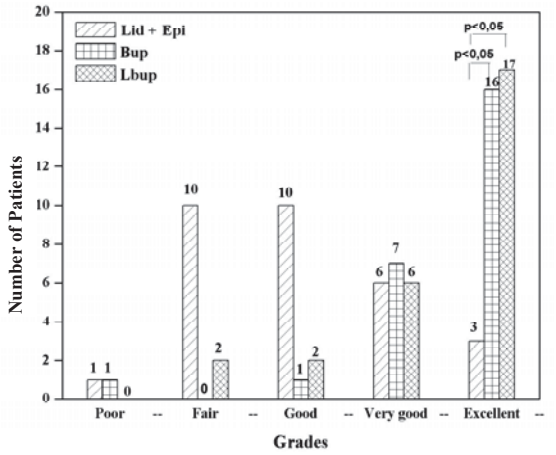

Fig. 3 – Subject's satisfaction with the achieved analgesia. Lid + Epi: 2% lidocaine with 1 : 100,000 epinephrine: Bup : 0.5% bupivacaine; Lbup: 0.5% levobupivacaine; *$p < 0.05$, χ^2 test.

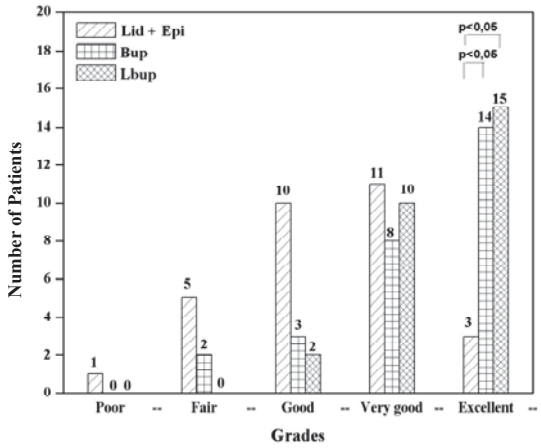

Fig 5 – Overall satisfaction with quality of the treatment. Lid + Epi: 2% lidocaine with 1 : 100,000 epinephrine: Bup : 0.5% bupivacaine; Lbup : 0.5% levobupivacaine; *$p < 0.05$, χ^2 test.

achieved postoperative analgesia are not presented)]. Regarding the patients' evaluation of the duration of anaesthesia, significantly more patients in the Lbup and Bup groups (40% in both groups) found local anaesthesia lasted too long in comparison to the Lid + Epi group (13%) (Figure 4). The patients' overall satisfaction was significantly lower in the Lid + Epi group (10% of patients declared an excellent level) than in the Lbup (56% excellent) and Bup (52% excellent) (Figure 5). The mean scores for overall satisfaction with the treatment quality were 3.22 ± 0.65, 4.26 ± 0.75 and 4.48 ± 0.82 for the Lid + Epi, Bup and Lbup groups, respectively ($p < 0.05$; Kruskal-Wallis rank test), with a significant decrease in the Lid + Epi group compared to the other two groups [($p < 0.05$, Mann-Whitney test); (data for overall satisfaction are not presented)].

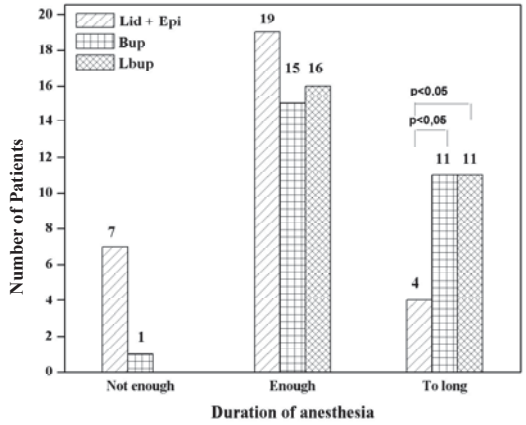

Fig. 4 – Subject's satisfaction with the duration of anesthesia. Lid + Epi: 2% lidocaine with 1 : 100,000 epinephrine; Bup: 0.5% bupivacaine; Lbup: 0.5% levobupivacaine; *$p < 0.05$, χ^2 test.

Discussion

The present, randomised, prospective, double-blind study demonstrated that 0.5% levobupivacaine, as a new long-acting local anaesthetic for use in oral surgery, was effective in achieving postoperative analgesia after lower third molar surgery, as it has been well known for 0.5% bupivacaine [6, 20]. On the other hand, intermediate anaesthetic, such as 2% lidocaine with epinephrine, did not show clinically relevant postoperative analgesic effects, because its duration of action duration did not cover the early postoperative period which is determined by a significant intensity of postoperative pain. Since postoperative pain after third molar surgery reaches its maximal intensity in the first 12 hours [21], and due to the high frequency of third molar surgery, it would be of great importance to use a local anaesthetic that provides prolonged analgesia and decreases patient discomfort. Furthermore, the reduction of postoperative pain improves quality of life, reduces morbidity and allows for the rapid return to daily activities [2].

Previously published results on the analgesic effect of levobupivacaine in third molar surgery may not be compared easily to our research, due to different concentrations of levobupivacaine used (0.75%) [22, 23], whilst in the study of Rood et al. [22], third molars were extracted under general anaesthesia and for postoperative pain relief either 0.75% levobupivacaine, 2% lignocerine with adrenaline 1 : 80,000, or placebo. However, at clinical concentrations of 0.5% and 0.75%, levobupivacaine does produce long-lasting block anaesthesia [22, 23]. This long-lasting effect of both levobupivacaine and bupivacaine can be attributed to the drugs' pharmacokinetic properties. Specifically, the protein-binding coefficient of lidocaine is 64%, which is much lower than the 96% of bupivacaine and levobupivacainen [24]. The high protein-binding coefficient of bupivacaine and levobupivacaine allows local anaesthetics' molecules to bond to tissue proteins and ensure increased concentrations of anaesthetic molecules at the site of injection which are responsible for prolonging the duration of anaesthesia [25, 26].

It is well-documented that surgical trauma and subsequent inflammation induce the sensitivity of peripheral nociceptors (primary hyperalgesia), a notion which has been clinically observed as increased postoperative pain emanating from the site of surgery [27]. Inadequate and short-lasting

nerve blocks may cause prolonged and enhanced postoperative pain, leading to central neural sensitisation [27, 28], which results in pain hypersensitivity beyond the area of surgery (secondary hyperalgesia) and the presence of pain after stimulus (allodynia)3. Juhl et al. [4, 28] showed that third molar surgery was followed by long-lasting mechanical, thermal and electrical sensitisation 30 days after intervention, even in the absence of spontaneous pain and consumption of postoperative analgesics. These findings suggest that anaesthetic blocks should last until inputs from peripheral surgical sites drop below the level that can maintain central sensitisation, especially in the hours immediately following lower third molar extraction. It is also recommended that long-acting local anaesthetics should be a part of the pre-emptive analgesia protocol, because it starts before surgery (anaesthetic injection before surgery) and lasts a good deal of time after surgery, in order to prevent postoperative pain and to reduce administration of postoperative analgesic therapy [29, 30]. Our results show that the analgesic efficacy of long-acting local anaesthetics is seen up to 48 hours postoperatively, long after local anaesthetic action has finished. In addition, the total amount of rescue analgesics is significantly lower with bupivacaine and levobupivacaine treatment over a seven-day period. These results could presents the indirect proof of the suppression of central sensitisation. Conversely, the use of lidocaine with epinephrine which is an intermediate local anaesthetic, does not provide sufficient blockage of postoperative neural hyperexcitability.

Regarding the patient's satisfaction with the overall treatment, significantly higher number of patients marked bupivacaine and levobupivacaine higher than lidocaine with epinephrine. It could be postulated that the overall patient's satisfaction is in strong correlation with satisfaction with the achieved analgesia, while prolonged analgesia seemed to favour the patients' choice of a better anaesthetic. Moreover, the quality of life after oral surgical interventions can have a major impact on a patient's future perception of pain and preoperative anxiety [31].

Conclusion

In our study, 0.5% levobupivacaine and 0.5% bupivacaine provided more pronounced postoperative analgesic effects in comparison to 2% lidocaine with epinephrine (1:80,000), due to the reduced levels of postoperative pain and the need for postoperative analgesic consumption. In addition, 0.5% levobupivacaine provided an analgesic effect similar to 0.5% bupivacaine after third molar surgery.

Acknowledgments

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CASE REPORTS

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Small bowel incarceration as a complication of port site drainage following laparoscopic hysterectomy

Ukleštenje tankog creva kao komplikacija drenaže nakon laparoskopske histerektomije

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Abstract

Introduction. Indication for surgical drainage may be prophylactic or therapeutic. However, surgical drains may cause complications. These complications can arise either following laparoscopic or open surgery. One of the rare complications resulting from drainage includes herniation of abdominal viscera at the drain site. The most common herniated abdominal organ is the small bowel. **Case report.** A 75-year-old woman underwent laparoscopic hysterectomy for atypical endometrial hyperplasia. After the operation, she developed small bowel herniation in the abdominal wall at the drain site, which was confirmed by multislice computed tomography. The patient underwent emergency relaparotomy that identified drain site incarceration of an ileal loop. Following resection of the incarcerated bowel, her postoperative recovery was uneventful. **Conclusion.** This case presents rare causative mechanism of intestinal obstruction. The possible occurrence of hernias following surgical drainage must be kept in mind.

Key words:
drainage; hysterectomy; laparoscopy; postoperative period; hernia; intestine, small; abdominal wall.

Apstrakt

Uvod. Indikacija za hiruršku drenažu može biti profilaktička ili terapijska. Međutim, hirurška drenaža može imati komplikacije, koje mogu pratiti bilo laparoskopsku ili otvorenu hirurgiju. Jedna od retkih komplikacija drenaže je visceralna hernijacija na defektu trbušnog zida nastalog stavljanjem drena. Među abdominalnim organima, tanko crevo najčešće podleže hernijaciji. **Prikaz bolesnika.** Bolesnici, staroj 75 godina, zbog atipične endometrijalne hiperplazije urađena je laparoskopska histerektomija. Nakon operacije došlo je do hernijacije tankog creva u zidu abdomena na mestu drena, što je potvrđeno kompjuterizovanom tomografijom abdomena. Kada je identifikovana inkarceracija vijuge tankog creva na mestu drena urađena je relaparotomija. Postoperativni tok protekao je uredno. **Zaključak.** Prikazan je redak uzročni mehanizam intestinalne opstrukcije. Mogućnost nastanka hernija nakon postoperativne drenaže mora se imati na umu.

Ključne reči:
drenaža; histerektomija; laparoskopija; postoperativni period; hernija; crevo, tanko; abdomen, zid.

Introduction

An indication for surgical drainage may be prophylactic (preventing fluid accumulation or detecting anastomotic leakage) or therapeutic (to evacuate existing collection of fluid) [1, 2]. Although surgical drainage is useful, it can also cause serious complications such as severe tissue reactions, leaving behind a foreign body, hemorrhage, leakage from bowel anastomoses and the induction of infection, while drain site visceral herniation is a rare complication [1, 3]. Commonly these hernias occur several months to several years following surgery. The most common herniated abdominal organs are small bowel loop and appendix, but unusual contents of drain site hernia such as Fallopian tube or gallbladder are also described [1–4].

The main reason for postoperative bowel obstruction is adhesion formation, but it can also arise because of an incision hernia [5]. These hernias may follow both laparoscopic and open surgery, on the incision, drain or port site. Infrequently, they appear in the immediate postoperative period, following drain removal and presenting as a surgical emergency due to intestinal obstruction.

The aim of this report was to raise awareness of this complication, as too liberal use of prophylactic drainage following laparoscopic surgery can jeopardize the basic idea

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of minimally invasive surgery, causing a complication that requires an additional surgical procedure.

Case report

A 75-year-old woman was referred to our hospital for hysterectomy due to atypical endometrial hyperplasia. The patient's medical history revealed cardiovascular disease, as well as breast cancer. The patient underwent left radical mastectomy two years before, and was treated with tamoxifen.

A total laparoscopic hysterectomy and bilateral salpingo-oophorectomy were performed without difficulties. There were no pathological findings within peritoneal cavity during the operation. An open silicone 5-mm soft drain was placed in the abdominal cavity through the left lateral laparoscopic port for prophylactic reasons. The drain-tube was taken out on the second postoperative day, without any registered complications and the patient had regular bowel sounds. The patient had an uneventful postoperative recovery until the fourth postoperative day, when she suffered vomiting and abdominal pain. On the fifth postoperative day a bulging, nondeductible, tender mass with 20 × 30 mm diameter, protruding just above the drain site incision was detected. The ultrasonography revealed a mass with 23 × 32 × 20 mm and low echogenicity located in the left abdominal wall. The diagnosis of abdominal wall hematoma was considered. There were no clear signs of acute abdomen. Radiographic examination did not reveale the presence of air – fluid levels. The patient continued vomiting, bowel sounds became absent and repeated radiographic examination on the sixth postoperative day showed intestinal air – fluid levels. The surgeon was consulted and he ordered abdominal multislice computed tomography. Computed tomography of the abdomen showed herniated loop of the small bowel in the left lateral abdominal wall (Figure 1). The patient underwent emergency repeated laparotomy that identified drain site incarceration of an ileal loop (Figure 2). The wall of herniated intestinal loop was damaged because of multi-day incarceration (Figure 3). During the surgery, a residual peritoneal opening at drain site was visible (Figure 4). A 5 cm long small-bowel segment was resected and end-to-end anastomosis performed. The abdominal wall defect was sutured. The patient's further recovery was excellent, and the patient was discharged 13 days after the second surgery. At present, 13 months after the operation, the patient did not experience any recurrence of hernia.

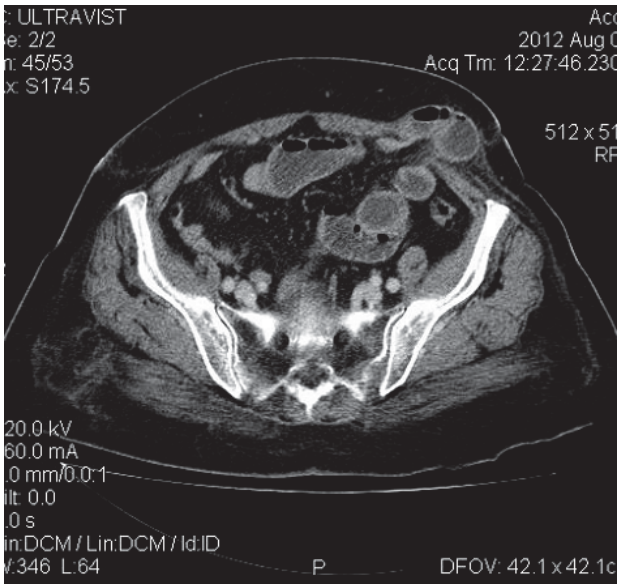

Fig. 1 – Multislice computed tomography image of the abdomen shows a herniated loop of the small bowel in the left lateral abdominal wall.

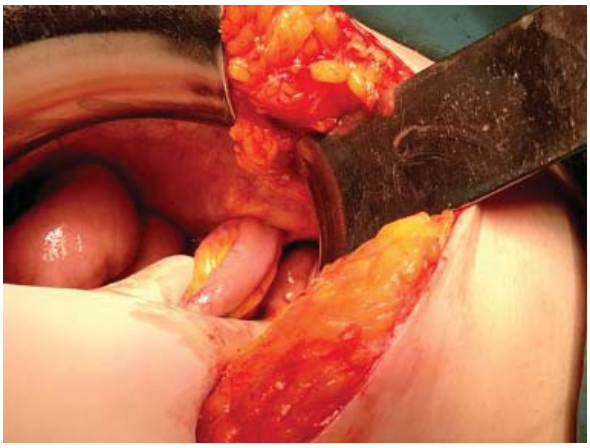

Fig. 2 – Drain site incarceration of an ileal loop.

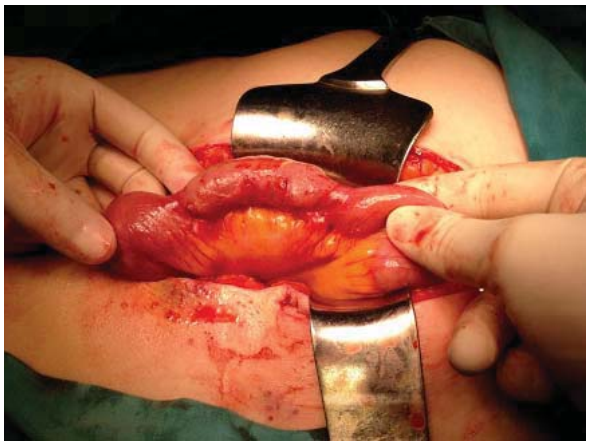

Fig. 3 – Herniated ileal loop with altered wall morphology as a consequence of multi-day incarceration.

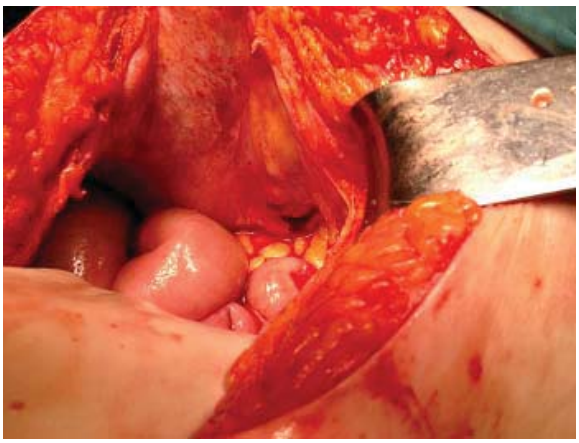

Fig. 4 – Residual peritoneal opening at abdominal drain site.

Discussion

There is a debate considering drainage in surgical practice. Drainage following abdominal surgery is used to detect intra-abdominal fluid, such as inflammatory or hemorrhagic, or content of anastomotic leak [1, 2]. On the other hand, complications of drainage described in the literature are numerous [1, 3]. Therefore some investigators advocate that indications for prophylactic drainage should be minimized, and suggest not to use drains in uncomplicated operations [6]. However, therapeutic drain usage is very important especially for surgical operations involving major bacterial contamination [2].

Port site hernias are uncommon complication of laparoscopic surgery, causing significant morbidity. Review of the literature revealed numerous reports of incisionalal hernias on trocar port sites after laparoscopy [5–9]. They are promoted by pneumoperitoneum during this kind of surgery. There are also reports about incisional hernias following similar defects of abdominal wall after drainage procedures in open surgery [1, 10, 11]. Most of the reported cases refer to the drains with diameter larger than 10 mm [11]. Predisposing factors for incisional hernias are thinness and malnutrition, obesity, preexisting morbidity such as diabetes mellitus, corticosteroids therapy, increased intraabdominal pressure (vomiting, coughing), advanced age, prolonged surgery and wound infection [12]. The literature provides several recommendations considering drainage: asymmetrical method of drain insertion which causes peritoneal stretching, gradual removal of the drain, drain site inspection after drain removal, usage of smaller drains in elderly and thin patients (diameter less than 10 mm), purse string closure of fascia defect after removing drains whenever the defect measures 10 mm or more in size [3, 7, 11].

Herniation rarely occurs with drains smaller than 10 mm, as in our patient. The most probable mechanism in the presented case was manipulation at the port site causing the enlargement of the abdominal wall defect and drain insertion through the port site. Nevertheless, we cannot rule out the possibility of pulling intestinal loop into the abdominal wall defect during drain removal. General weakness of the abdominal wall muscle caused by advanced age probably facilitated this complication in the presented patient.

Conclusion

Drains should be used sparingly and careful insertion and management is necessary. One must never forget that drain placement creates an iatrogenic defect of the abdominal wall located at the wound incision, and that these defects are large enough to create a risk of hernia formation. It is important to make a diagnosis of this potential complication in time because it will significantly reduce further morbidity. Therefore, the possible occurrence of hernias following removal of a drainage tube must be kept in mind.

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CASE REPORT

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Penile fracture: A rare case of simultaneous rupture of the one *corpus cavernosum* and complete urethral rupture

Fraktura penisa: redak slučaj istovremene rupture jednog korpusa kavernozuma i kompletne rupture uretre

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Abstract

Introduction. Penile fracture is a traumatic rupture of *tunica albuginea* and the tumescent *corpora cavernosa* due to the nonphysiological bending of the penile shaft, presenting with or without rupture of *corpus spongiosum* and urethra. The incidence of concomitant injury of the urethra is 0–38%. Complete urethral rupture is rare, but it is almost always associated with bilateral corporeal injury. **Case report.** We presented a patient with complete urethral rupture, and rupture of the right cavernous body. According to the available literature, this case is extremely rare. **Conclusion.** Fracture of the penis is relatively uncommon and is considered a urologic emergency. Prompt surgical exploration and repair can preserve erectile and voiding function.

Key words:
penis; coitus; wounds and injuries; urologic surgical procedures.

Apstrakt

Uvod. Fraktura penisa je traumatska ruptura tunike albugineje i tumescentnih kavernoznih tela zbog nefiziološkog savijanja tela penisa, sa ili bez rupture spongioznog tela i uretre. Učestalost konkomitantne povrede uretre je 0–38%. Kompletna uretralna ruptura je retka, ali je skoro uvek udružena sa bilateralnom korporalnom povredom. **Prikaz slučaja.** Prikazali smo i bolesnika sa kompletnom rupturom uretre i rupturom desnog kavernoznog tela. Prema raspoloživoj literaturi, ovo je izuzetno retka pojava. **Zaključak.** Fraktura penisa je retka, ali se smatra hitnom urološkom povredom. Blagovremena hirurška eksploracija i rekonstrukcija mogu da sačuvaju erektilnu funkciju i funkciju voljnog mokrenja.

Ključne reči:
polni organi, muški; polni odnos; povrede; hirurgija, urološka, procedure.

Introduction

Penile fracture belongs to the group of blunt injuries of the penis. The reason for so rare incidence of penile injuries is the mobility of the penis and its topography. Topographically, the penis is well-protected organ. Penile fracture is unusual, but not rare [1]. In erectile condition, the penis is much more vulnerable to injury due to high intracavernous pressure during erection [1–3]. Traumatic rupture of the *corpus cavernosum* or penile fracture occurs as the consequence of direct blunt trauma of the erectile or semi-erectile penis. Rupture is caused by overextension of *t. albuginea* induced by abrupt increase of intracorporeal pressure [2]. *T. albuginea* tissue is physiologically thinnest in erection, i.e. about 0.25–0.5 mm [3, 4]. In flaccid penis, the thickness of *t. albuginea* ranges from 2 to 3 mm depending upon the region of measurement [4]. The most frequent cause of penile fracture is sexual intercourse, although it may happen during masturbation, manipulation or any other situation of blunt force action [1, 5].

The exact incidence of penile fracture is not known, because many cases remain unrecorded or many patients do not present to doctor's office because of shame and feeling uncomfortable.

Most cases of penile fracture are without urethral injury and voiding difficulties. Occasionally, due to the effect of mass of edematous tissue and hematoma, the compression of urethra and difficulty with miction may occur. Concurrent urethral injury is present in 0–38% of cases [2, 6]. Complete urethral rupture is rare, but it is almost always associated with bilateral corporeal injury [6]. The presented case showed complete rupture of the urethra, and rupture of the right cavernous body.

Case report

A presented patient was 32 years old. The injury occurred during sexual intercourse in classical position when his spouse was lying on her back with her legs pushed apart

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and bent knees, and he was on top. During sexual intercourse, the penis slipped out from the vagina and the patient tried again forced penetration ("he wanted to reenter with all his efforts"), but in misdirection and his penis hit against the pubic symphysis. He heard "as something cracked", had severe pain and sudden loss of erection. Next, the penis became swollen and blue. He noticed the blood at the meatus. He got scared and immediately presented to emergency urological outpatient department. The patient did not have desire to void. Severe pain aggravated by trying to void, but he could not void.

Physical examination revealed a large hematoma involving the whole penis and angulation of the penis to the left (Figure 1). Diffuse painless hematoma most prominent on the right lateral side and at the base could be palpated. In this area, hematoma appeared as soft, elastic tumefaction, painful and in size of big strawberry. Upon deeper palpation, soft and extremely painful defect was detected in *t. albuginea*. During physical examination, there was no blood at the meatus.

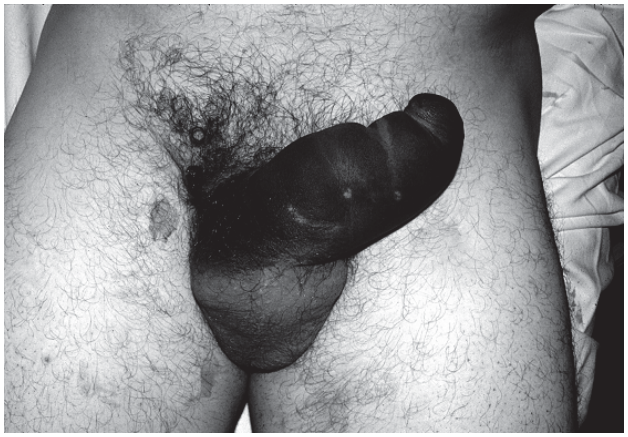

Fig. 1 – Presentation of dexter penile fracture with large edema and hematoma of the penile body. The penis angulates to the opposite side of the site of injury.

Using the straight 7.5 MHz probe, ultrasonographic examination was detected anechogenic change on the right side of the *corpus cavernosum*. Low pressure retrograde urethrogram showed complete disruption at the proximal third of the urethra. Cavernosography was performed using 50% nonionic contrast and showed the location of extravasation of contrast and the site of rupture of *t. albuginea* on the right lateral base of the penis. In the same area, a large hematoma filled with contrast was visible (Figure 2).

The surgical approach was through peripenile longitudinal anterior incision on the side of hematoma (rupture). After evacuation of hematoma, the laceration of *t. albuginea* was reached, with vital cavernous tissue underneath. *T. albuginea* rupture was transversal in relation to longitudinal axis of the penis with distinct edges (Figure 3).

On the same location, the complete rupture of penile urethra, transversal one with "worn-out" edges could be seen (Figure 4). *T. albuginea* was sutured with 3–0 Vicryl using continuous suture while primary anastomosis of the urethra was performed *via* catheter using PDS 5–0 interrupted suture with previous urethral spatulation. The operation was completed by vacuum drainage. A broad spectrum antibiotic and low molecular heparin were given during the hospital stay. On the day 12 the catheter was removed.

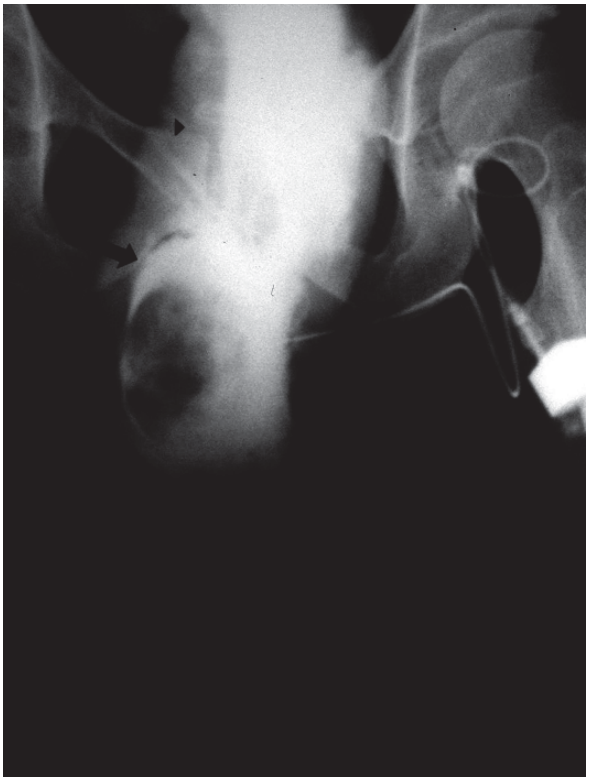

Fig. 2 – Preoperative cavernosography: Hematoma filled with contrast visualized at the right base side of the penis on the site of rupture (black arrows).

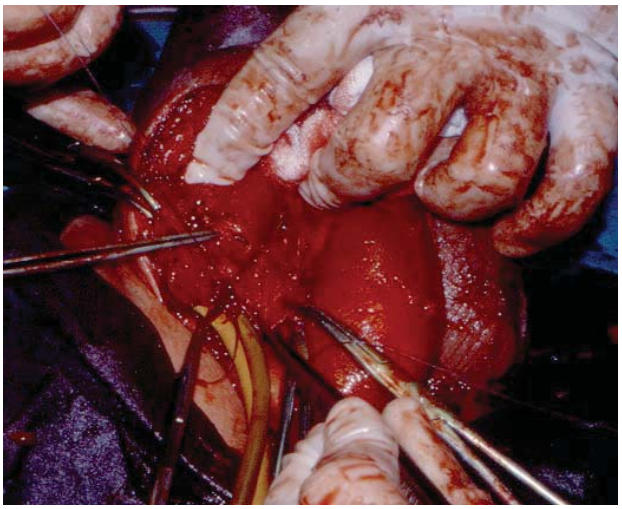

Fig. 3 – The site of rupture of *tunica albuginea*. Evacuation of hematoma reveals transversal *t. albuginea* laceration of the right *corpus cavernosum*, spreading from 10–11 hours to 6 hours, not extending to the left *corpus cavernosum*. The rupture has well-defined edges like knife incision.

In one year follow-up the patient presented with normal erectile and voiding function.

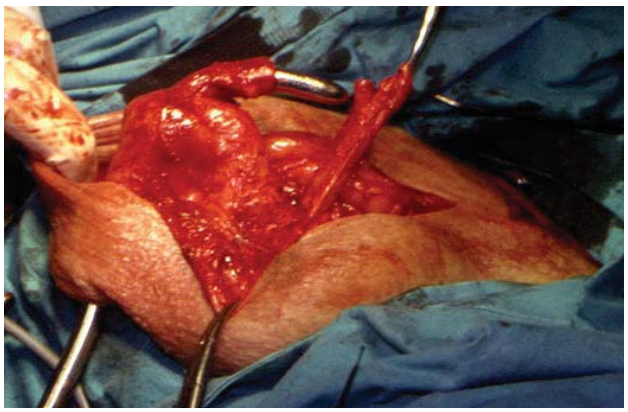

Fig. 4 – Complete rupture of the penile urethra. The distal end of urethra with refreshed margins, resected remnants are found on Béniqué. The proximal part of the urethra elevated by the forceps. Note the edges of the urethra – worn-out with fringes.

Discussion

Adequate management of penile fracture in view of surgical or conservative treatment has been the issue of controversy [7]. Randomized prospective studies on conservative treatment of penile fractures reported significant immediate and late complications. The frequency of complications of conservative treatment is between 10% and 53% [8, 9]. Conservative (nonsurgical) treatment may cause complications, such as penile curvature, pain during erection, fibrotic penile lesions, arteriovenous fistula, infection, and erectile dysfunction curvature of the penis, erectile dysfunction [9, 10].

Currently, early surgical treatment is believed to yield excellent results, short hospitalization, low morbidity and early restoration to normal sexual activity [3, 9, 10].

Vigorous sexual intercourse was the cause of penile fracture with complete urethral rupture in this case report. Transversal tear of *t. albuginea* was noted in operated patient, in relation to longitudinal axis of the penis. During erection, there is a five-fold reduction of *t. albuginea* thicknes. It is very vulnerable to traumatic rupture [2–4]. Also, the tunica of the erect penis, the firmly engorged *corpora cavernosa* under strain of buckling can generate pressures in excess of 1500 mmHg and exceed the limit of the thinned tunica [9].

Urethral rupture is associated in up to 38% of penile fracture due to high energy trauma [6, 10]. Voiding difficulties, hematuria and blood at the meatus are usual signs of urethral injury, but the abscence of these features does not exlude the possibility of urethral injury [10]. Evidence of bilateral corporal rupture should also be prompt investigation for a potential urethral injury, because bilateral corporal rupture have a higher of urethral disruption compared with unilateral fractures [9, 10]. Based on the available literature, urethral rupture is usually partial, rarely complete.

Conclusion

Fracture of the penis is relatively uncommon and is considered as urologic emergency. Prompt surgical exploration and repair can preserve erectile and voiding function.

Concomitant complete urethral rupture is rare, but it is almost always associated with bilateral corporeal injury. However, complete rupture of the urethra may be associated with rupture of one corpus cavernous only.

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CASE REPORT

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Specificities of transplantation of kidneys procured from donors with *situs inversus totalis* – A case report and review of the literature

Specifičnosti transplantacije bubrega dobijenih od donora sa *situs inversus totalis* – prikaz bolesnika i pregled literature

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Abstract

Introduction. *Situs inversus totalis* (SIT) represents a total vertical transposition of the thoracic and abdominal organs which are arranged in a mirror image reversal of the normal positioning [1]. We presented a successful pre-dialysis kidney transplantation from a living sibling donor with SIT and the longest donor follow-up period, along with analysis of the reviewed literature. **Case report.** The pair for pre-dialysis kidney transplantation included a 68-year-old mother and 34-year-old daughter at low immunological risk. Comorbidities evidenced in kidney donors with previously diagnosed SIT, included moderate arterial hypertension and borderline blood glucose level. Explantation of the left donor kidney and its placement into the right iliac fossa of the recipient were performed in the course of the surgical procedure. A month after nephrectomy, second degree renal failure was noticed in the donor. A 20-month follow-up of the donor's kidney and graft in the recipient proved that their functions were excellent. **Conclusion.** In donors with previously diagnosed SIT the multidisciplinary approach, preoperative evaluation of the patient and detection of possible vascular anomalies are required to provide maximum safety for the donor.

Key words:
situs inversus; kidney transplantation; tissue donors.

Apstrakt

Uvod. *Situs inversus totalis* (SIT) predstavlja potpunu vertikalnu transpoziciju torakalnih i abdominalnih organa koji se u odnosu na normalan raspored preslikavaju kao u ogledalu. U radu je prikazana uspešno izvršena predijalizna transplantacija bubrega dobijenog od živog srodnog donora sa SIT i najdužim periodom praćenja, uz analizu do sada objavljenih sličnih slučajeva. **Prikaz bolesnika.** Par pripreman za predijaliznu transplantaciju bubrega činile su živi donor – majka, stara 68 godina, i primalac – kćerka, stara 34 godine, sa niskim imunološkim rizikom. Kod donora je ranije dijagnostikovan SIT, a od komorbiditeta bila je prisutna arterijska hipertenzija regulisana terapijom uz granične vrednosti glikemije. Eksplantacija levog bubrega donora i njegova transplantacija u desnu ilijačnu jamu primaoca izvedeni su otvorenim hirurškim pristupom. Mesec dana nakon operacije kod donora je uočena renalna insuficijencija drugog stepena. Dvadeset meseci nakon transplantacije stanje bubrega donora i grafta kod primaoca bili su uredni. **Zaključak.** Multidisciplinarni pristup, preoperativna procena bolesnika i otkrivanje mogućih vaskularnih anomalija neophodni su kod donora sa ranije dijagnostikovanim SIT, u cilju obezbeđivanja maksimalne bezbednosti za donora u intraoperativnom i postoperativnom periodu.

Ključne reči:
situs inversus; transplantacija bubrega; tkivo, davaoci.

Introduction

Situs inversus totalis (SIT) represents a total vertical transposition of the thoracic and abdominal organs which are arranged in a mirror image reversal of the normal positioning [1]. The incidence of SIT ranges between 1 : 8,000 and 1 : 20,000 individuals [1, 2]. SIT may be the consequence of sporadic genetic mutation and it is rarely hereditary. SIT is discovered incidentally, upon clinical examinations and radiological procedures. In case of SIT, the heart is located on the right side (dextrocardia), the lung with three lobes on the left side, the liver on the left side, the spleen in the right, while small and large intestines are

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in reverse position. When all organs change their positions, the connections and communication between them remain undisturbed, and thus SIT patients are mostly asymptomatic and have normal lifespan [1–7].

SIT was an absolute contraindication for organ donation, particularly for donation of the liver and heart, having in mind associated anomalies of blood vessels appearing in more than 40% of cases [8]. Our paper presented a SIT patient as a living kidney donor as well as our previous experiences with kidney transplantations involving donors with SIT.

Case report

Pre-transplantation evaluation of the kidney donor – the recipient's 68-year-old mother, was commenced after initial examination performed in transplantation outpatient unit, revealing no immunological complications (the same blood group A Rh D, 5/9 HLA match and negative crossover match according to complement-dependent cytotoxicity (CDC). As for the comorbidities, the donor had arterial hypertension corrected by angiotensin-converting enzyme inhibitor (ACE) and borderline blood glucose levels. Physical examination performed on admission evidenced body mass index (BMI) 29.1 kg/m^2, with normal findings according to organ systems. The obtained results of laboratory tests were within reference values, kidney function was normal as well as virological tests, including hepatitis and HIV markers (Table 1).

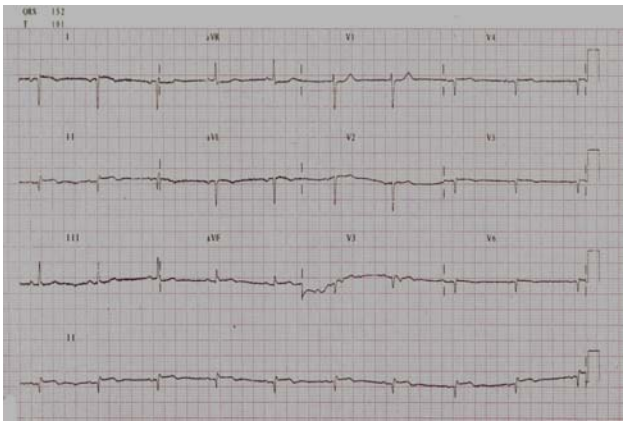

Fig. 2 – Electrocardiogram-dextrogram.

echocardiography. Abdominal ultrasonography (US) revealed the spleen below the right costal arch and the liver below the left costal arch, as well as the kidneys of normal size and echogenicity, without hydronephrosis and calculosis. Renal and pelvic multislice computed tomography (MSCT) angiography evidenced two arteries of the right kidney with ostial stenosis of the lower pole artery. The left kidney was vascularized by a single artery. One renal vein was present on each side. Pelvic blood vessels were free of any anomalies (Figure 3). Dynamic scintigraphy of the kidneys with separate creatinine clearance evi-

Table 1

Kidney donor parameters before and after donor nephrectomy

Parameters	Before nephrectomy	One month after nephrectomy	One year after nephrectomy
Serum creatinine [μmol/L]	62	82	103
Serum urea [mmol/L]	5.9		
GFR MDRD [mL/min/1.73 m^2]	85.3	64.2	62.3
24-hours proteinuria [g]	0.032		
Microalbuminuria [mg/mL]	10		

GFR MDRD – glomerular filtration rate according to modification of diet in renal disease

The diagnosis of SIT was confirmed by heart and lung radiography (Figure 1), electrocardiography (Figure 2) and

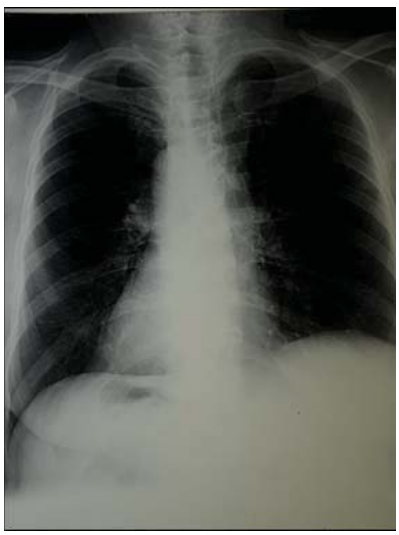

Fig. 1 – Chest radiography: dextrocardia.

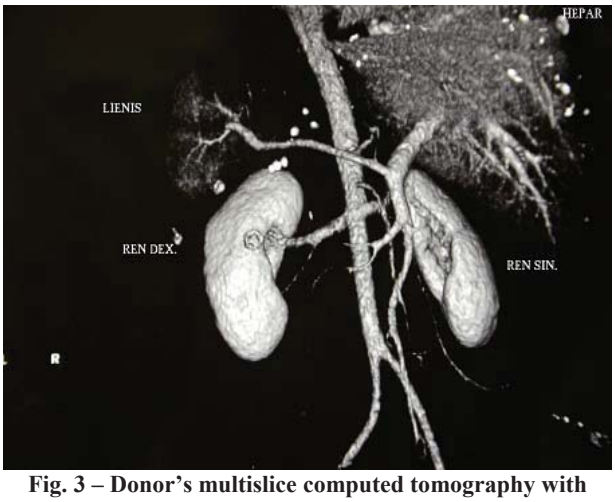

Fig. 3 – Donor's multislice computed tomography with angiography.

denced a homogenous distribution of renal flow: separate kidney clearance 47.6% on the left side and 52.4% on the right one with of 82.36 mL/min/1.73 m^2.

The kidney recipient was a 34-year-old female patient with preterminal renal failure resulting from chronic glomerulonephritis [serum creatinine 508 μmol/L, urea 32mmol/L, glomelular filtration rate (GFR) according to modification of diet in renal disease (GFR MDRD) 12.6 mL/min/L.73m^2].

On the pre-transplantation meeting it was decided to explant the left kidney of the donor and implant it in the right iliac fossa of the recipient. Standard explantation of the left kidney was performed and it was perfused with 1000 mL of Euro-Collins solution. Warm ischemia lasted for 2 minutes, while cold ischemia and rewarm time lasted 20 minutes. The kidney was positioned in the recipient's right iliac fossa using the standard surgical procedure: end-to-end anastomosis of the renal and hypogastric arteries, end-to-side anastomosis of the renal vein and external iliac vein and ureterocystoneostomy performed using the method of two parallel incisions along with "JJ" probe placement.

Postoperatively, the donor was in good general condition, with daily diuresis of 2,000 mL, normotensive with regular antihypertensive therapy, without complaints. Laboratory tests performed in early postoperative period on day 0 revealed the serum creatinine value of 58 μmol/L, being 118 μmol/L on the postoperative day 14 – on discharge. A month after the nephrectomy, second degree renal failure was noticed (Table 1). Abdominal ultrasound examination revealed normal solitary kidney and other organ findings. Regular nephrologic follow-up examinations did not evidence deterioration of the renal function within 1-year period after donor nephrectomy (Table 1). Follow-up US examination performed after one year revealed the following: the remaining right kidney was sized 11.3 × 4.8 cm, with 1.7 cm thick parenchyma, normal echogenicity, without stasis or calculosis.

Postoperative recipient's diuresis was 16,500 mL on the day of transplantation to be gradually decreased and maintained at 4,600 ml at the average, over the 2-week postoperative period. In the 14-day posttransplantation period, during hospitalization, serum creatinine values ranged between 102 μmol/L and maximal 176 μmol/L, without any signs of acute transplant rejection. Acute exacerbation of the chronic renal failure with transient increase in the serum creatinine coincided with an episode of urinary infection caused by *Klebsiella* species that was managed by susceptibility test-based antibiotic therapy, i.e. carbapenem in a total dose of 15 grams.

Quadruple immunosuppressive therapy was applied for prevention of rejection. Induction was performed by intraoperative administration of antithymocyte globulin (ATG) in the dose of 8 mg/kg, along with the triple therapy according to immunosuppression protocol: glucocorticoids, tacrolimus and mycophenolate mofetil. Ultrasound examination of the transplanted kidney (graft) performed on discharge, on the postoperative day 14, revealed normal findings (Figure 4). The kidney was sized 11.6 × 4.4 cm, with homogenous 1.7 cm thick parenchyma, without hydronephrosis or calculosis. Vasculature was well-defined up to the smallest branches on the periphery, with the resistive index (RI) in the interlobar and iliac arteries of 0.66.

Laboratory tests, indicative of renal function parameters performed by the end of the first year confirmed the optimal graft function (serum creatinine 114 μmol/L, GFR MDRD 61.29 mL/min/1.73 m^2, Biuret 0.115 g/24h/ proteinuria). Ultrasound examination of the transplanted kidney/graft evidenced identical parameters to those obtained upon the previous examination with somewhat less pronounced arterial circulation which was normally tracked up to the level of Malpighian pyramids, and more difficultly peripherally, with refractive index at the level of interlobar arteries of 0.72, considered to be normal finding for transplanted kidney (Figure 5). Stasis was not evidenced in the excretory system.

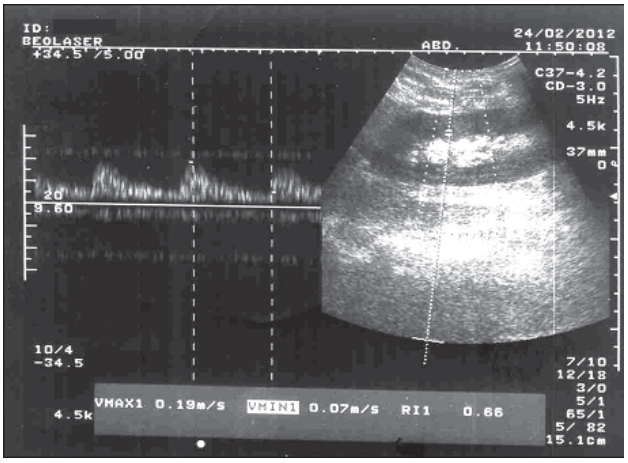

Fig. 4 – Graft Doppler ultrasonography after transplantation.

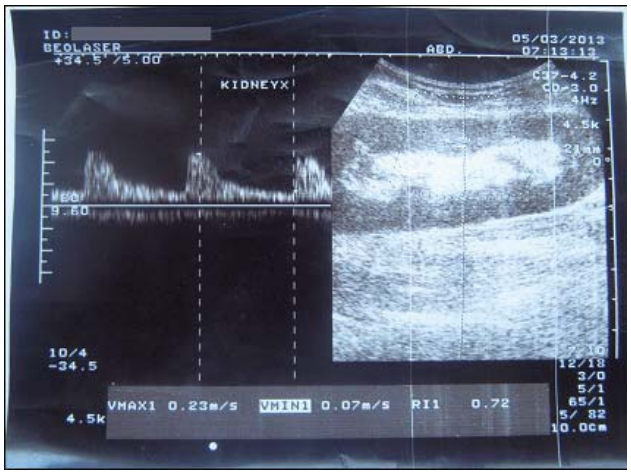

Fig. 5 – Graft Doppler ultrasonography one year after transplantation.

Discussion

SIT was one of the absolute contraindications for organ donation till 1988 [8]. SIT is a rare, congenital anomaly that may be associated with vascular and visceral abnormalities and intestinal malformations [6, 9, 10]. It is also associated with other anomalies such as polysplenia, Ivemark-Kartagener syndrome and biliary atresia [11–14]. Due to a possible onset of complications within the associated anomalies, a particular attention was also paid to it in other surgical interventions, particularly in abdominal surgery [15–23]. However, the attitude has been changed over the last several years. Few case reports on patients with *situs inversus* who had underwent cholecystectomy, distal gastrectomy

due to the gastric carcinoma using the laparoscopic method, gastrectomy with cholecystectomy, liver resection, splenectomy and lung tumor have been published so far [17–24].

In transplantation medicine, SIT represents a potential risk for possible complications, particularly in case of liver and heart transplantations. In 1988 Raynor et al. [25] described liver transplantation in a patient with *situs inversus*. Thereafter, other successful liver transplantations were described as well [25, 26]. In 1990 Doty et al. [27] described cardiac transplantation in a patient with SIT, while Rabago et al. [28] described in 1996 heart-lung transplantation in a patient with SIT.

A review of the reference literature indicated that the total of 6 transplantations were performed with the kidney procured from donors with SIT [8, 29–31] (Table 2). The first case of kidney transplantation from a donor with SIT was published in 2003 [29]. Four transplantations were performed with kidneys obtained from living donors with SIT while two were performed with organs procured from cadaveric donors with SIT (Table 2). Polak et al. [8] in 2006 reported a case of successful kidney transplantation from the cadaveric donor with SIT.

In all cases successful kidneys transplantation from donors with SIT was described owing to good preoperative evaluation aimed at timely detection of blood vessel anomalies present in these donors [8]. Surgical approach may include open nephrectomy, hand-assisted laparoscopic donor nephrectomy and laparoscopic nephrectomy [29–32]. Most of the authors failed to indicate the duration of the donor and recipient follow-up period, except for two authors who reported follow-up periods of 6 and 12 months, respectively [31, 32]. It may be observed that greater experience of surgeons leads to higher number of laparoscopic donor nephrectomies [29, 31, 32]. We reported a case of successful predialysis kidney transplantation from a donor with SIT without major associated blood vessel anomalies or associated syndromes appearing in 20–25% of SIT cases [8, 33]. Second degree renal failure was evidenced in our donor, which is not unusual after nephrectomy, but was not previously reported [34]. At the time of writing this report, renal function was satisfactory in both donor and recipient for 20 months.

A large disproportion between the available organs for transplantation and long waiting lists oblige us to increase the number of transplantations by careful selection and evaluation of patients previously considered unsuitable candidates for organ donation. Since donor's safety is the utmost priority, based on the review of the reported cases, it is clear that each individual case necessitates multidisciplinary approach to patients with SIT. Careful preoperative evaluation which includes the methods of visualization of organs and their vascularization may reveal possible abnormalities relevant for the surgeon [30]. Since these cases are rare, recommendations are necessery for the transplantation experts to do appropriate preoperative evaluation and postoperative follow-up of donors with SIT.

Table 2

Published cases of *situs inversus* donor nephrectomies

Authors	Number of kidneys procured	Outcome	Characteristics	Follow-up period
Polak WG et al.[8]	2	Successful	Cadaveric donor - 2 recipients	Unknown
Black PC et al. [29]	1	Successful	Living donor Hand assisted laparoscopic Right donor nephrectomy	Unknown
Hoffmann D et al.[30]	1	Successful	Living donor Open nephrectomy	1 year
Berber I et al. [31]	1	Successful	Living donor Laparoscopic nephrectomy	6 months
van Dellen et al. [32]	1	Successful	Living donor Hand assisted laparoscopic Left sided IVC Longer right renal vein Right donor nephrectomy	Unknown

IVC – inferior vena cava

Conclusion

This case report on a donor with *situs inversus* and a successful kidney transplantation indicates that it is not an absolute contraindication for organ donation any more. This rare case also confirms the necessity of the multidisciplinary approach and team work (nephrologist, vascular surgeon, urologist, radiologist and anesthesiologist) in order to achieve satisfying results, and maximum safety for the donor.

Acknowledgments

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CASE REPORT

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Challenges in treatment of postinfarction ventricular septal defect and heart failure

Izazovi u lečenju postinfarktnog septalnog defekta i srčane slabosti

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Abstract

Introduction. Acquired ventricular septal defect (VSD) is uncommon, but serious mechanical complication of acute myocardial infarction with poor outcome and high mortality rate in surgically or medically treated patients. **Case report**. We report a 58-year-old male patient admitted to our hospital six days following acute inferior myocardial infarction complicated by ventricular septal rupture with signs of heart failure. Coronary angiography revealed 3-vessel disease, with proximally occluded dominant right coronary artery. Transthoracic echo exam revealed aneurysm of a very thin inferior septum and the basal portion of the inferior left ventricular wall, with septal wall rupture. One of the VSD dimensions was 15 mm and left- to right shunt was calculated 2 : 1. Since the patient was at too high risk for surgical closure, transcatheter closure of VSD was chosen as a better option. Under short intravenous sedation, 24 mm Amplatzer device was implanted percutaneously with transesophageal echo guidance. The post-procedural result revealed a small residual shunt, but it was followed by significant improvement of the patient's clinical status. A 24h Holter ECG monitoring did not show cardiac rhythm or conduction disturbances. Coronary angiography was repeated ten days following the procedure, after hemodynamic stabilization of the patient, with direct stenting of the circumflex artery and the intermediate artery. Ostial left descending artery lesion was left for further functional significance assessment. **Conclusion:** Percutaneous closure with a septal occluder device can be definitive primary treatment for anatomically suitable patients or it can serve as a bridge to surgical treatment.

Key words:
myocardial infarction; heart, septal defects, ventricular; heart failure; heart catheterization; treatment outcome.

Apstrakt

Uvod. Stečeni ventrikularni septalni defekt (VSD) je retka ali ozbiljna mehanička komplikacija akutnog infarkta miokarda sa lošom prognozom i visokom stopom mortaliteta kod bolesnika lečenih hirurškim putem ili konzervativno. **Prikaz bolesnika.** U radu je prikazan bolesnik, star 58 godina, koji je primljen u našu instituciju šest dana nakon akutnog infarkta miokarda, komplikovanim rupturom inferoseptalnog dela septuma i znacima srčane insuficijencije. Koronarografija urađena u regionalnoj bolnici pokazala je trosudovnu koronarnu bolest sa proksimalno okludiranom, dominantnom, desnom koronarnom arterijom. Transtorakalnim ehokardiografskim pregledom ustanovljena je aneurizma vrlo istanjenog inferiornog septuma i bazalnog dela inferiornog zida leve komore, sa rupturom septuma. Jedna od dimenzija defekta bila je 15 mm, sa izračunatim Qp: Qs odnosom od 2 : 1. S obzirom na to da je bolesnik bio pod jako visokim rizikom od hirurške korekcije defekta, odlučeno je da se pristupi transkateterskom zatvaranju VSD, kao boljoj opciji za bolesnika. Pod kratkom intravenskom sedacijom, postavljen je Amplatzer okluder 24 mm, uz neprekidnu transezofagealnu ehokardiografiju. Postproceduralnim ehokardiografskim pregledom ustanovljeno je prisustvo malog rezidualnog šanta, ali uz značajno poboljšanje hemodinamskog statusa. Na bolesnikovom 24-časovnom Holter elektrokardiogramu nisu registrovani poremećaji srčanog ritma. Deset dana nakon intervencije, urađena je ponovna koronarografija i stentiranje cirkumflekne arterije i ramus intermedijusa. Ostijalna lezija na prednjoj descedentnoj arteriji ostavljena je za dalju funckionalnu dijagnostiku. **Zaključak.** Transkatetersko zatvaranje ventrikularnog septalnog defekta septalnim okluderom može biti definitivni način lečenja bolesnika sa anatomski pogodnim defektima, ali i poslužiti za premošćavanje do hirurškog lečenja.

Ključne reči:
infarkt miokarda; srce, ventrikulski septumski defekti; srce, insuficijencija; kateterizacija srca; lečenje ishod.

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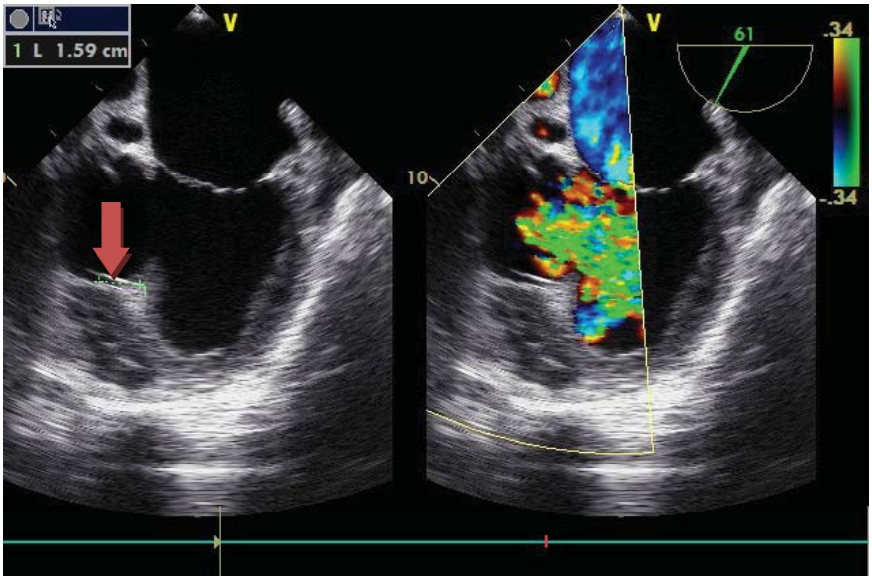
Introduction

Acquired ventricular septal rupture (VSD) is uncommon, but a serious mechanical complication of acute myocardial infarction (AMI) with the prevalence of 0.2–0.34% [1] and mortality rate up to 90% in medically treated patients [1]. It occurs mostly within the first week after acute myocardial infarction [1]. The American College of Cardiology/American Heart Association guidelines recommend urgent surgery repair of post infarction VSD (PIVSD) and coronary artery bypass grafting (CABG), even in hemodynamically stable patients [2]. But despite advances in surgical care, the operative mortality remains 25–87% [3, 4] especially if associated with major risk factors such as cardiogenic shock (88% mortality *vs* 29% in those without cardiogenic shock) [5], renal failure or other comorbidities. Mantovani et al. [6] reported that posterior defect have higher mortality rate (50% *vs* 25% for anterior defect). Major residual shunt after surgery is also reported by Deja et al. [7] in up to 40%. Since 1988 alternative treatment has been accepted as the option of choice in anatomically suitable patients with a high risk for surgical closure – transcatheter closure.

Case report

We reported our first transcatheter closure of PIVSD in a 58-year-old male patient with no previous chest pain history and due to pain in epigastrium first admitted to the regional gastroenterology department and the same day transfferd to cardiology department under the diagnosis of inferior AMI. Angiography was done in the regional hospital revealing 3-vessel coronary disease with occlusion of the right coronary artery (RCA). On the day 2 postinfarction the patient deteriorated with new harsh holosystolic murmur – ultrasound confirmed ventricular septum rupture (VSR). The patient was admitted to our hospital six days following AMI with VSR and sign of heart failure. New York Heart Association (NYHA) functional class was III. The patient was dyspnoic without chest pain, with the increased heart rate and blood pressure of 90/60 mmHg. Electrocardiogram (ECG) on admission showed sinus rhythm, with the heart rate of 95/min, Q- and negative T-wave in diaphragmal leads. Physical examination also revealed harsh pansystolic murmur along the left sternal border and rales over the lung fields, distended jugular veins. Transthoracic echo exam confirmed aneurysm of the inferior septum and basal segment of the inferior wall with VSR, one of dimensions being 15 mm (Figure 1a and b). Left-to-right shunt (Qp/Qs) was calculated as 2 : 1, and left ventricle ejection fraction was estimated as 45%. The patient was not supported with the intra-aortic balloon pump since it was not available in the regional hospital. Upon admission to our hospital, the heart team was consulted, but cardiac surgeons refused to do combined CABG and VSR closure surgery, because of the high perioperative risk due to recent myocardial infarction, large and anatomically complex VSR and hemodinamic instability of the patient (Euroscore II 10.54%). Transcather closure (TCC) was chosen as a better option. After the necessary equipment became available, the procedure was performed 14 days after acute myocardial infarction under sedation and transesophageal echo guidance, which was used for detailed assesment of the size and localization of VSR. Access was obtained from the right femoral vein and the right and left femoral artery. A left ventriculography was done in the left anterior oblique view with cranial angulation and aneurysm of the very thin inferior septum with septal rupture was confirmed (Figure 2a). The Amplatzer wire was advanced throught VSR into the pulmonary artery (PA) and then snared in the PA with a Lasso catheter and exteriorized through the right femoral vein, forming arteriovenous loop (Figure 2B). An appropriate size delivery sheath was advanced with VSD 24 occluder accross the defect into the left ventricle. After the device had been deployed (Figure 2c, d



a) **b)**

Fig. 1 – Transesophageal exam (stop frame) without (a) and with color Doppler (b) showing aneurysm of the inferior septum and basal segment of the inferior wall with ventricular septal rupture (arrow).

and e) left ventriculography and transesophageal echo were perfomed confirming a small residual shunt (Figure 3). Peri-procedural, the patient got acetylsalicylic acid, clopidogrel, unfractionated heparin.

Post-procedural monitoring showed improvement of the hemodynamical and clinical status of the patient. 24-h Holter ECG did not show any cardiac rhythm or conduction disturbances. Ten days after the procedure, coronary angiography

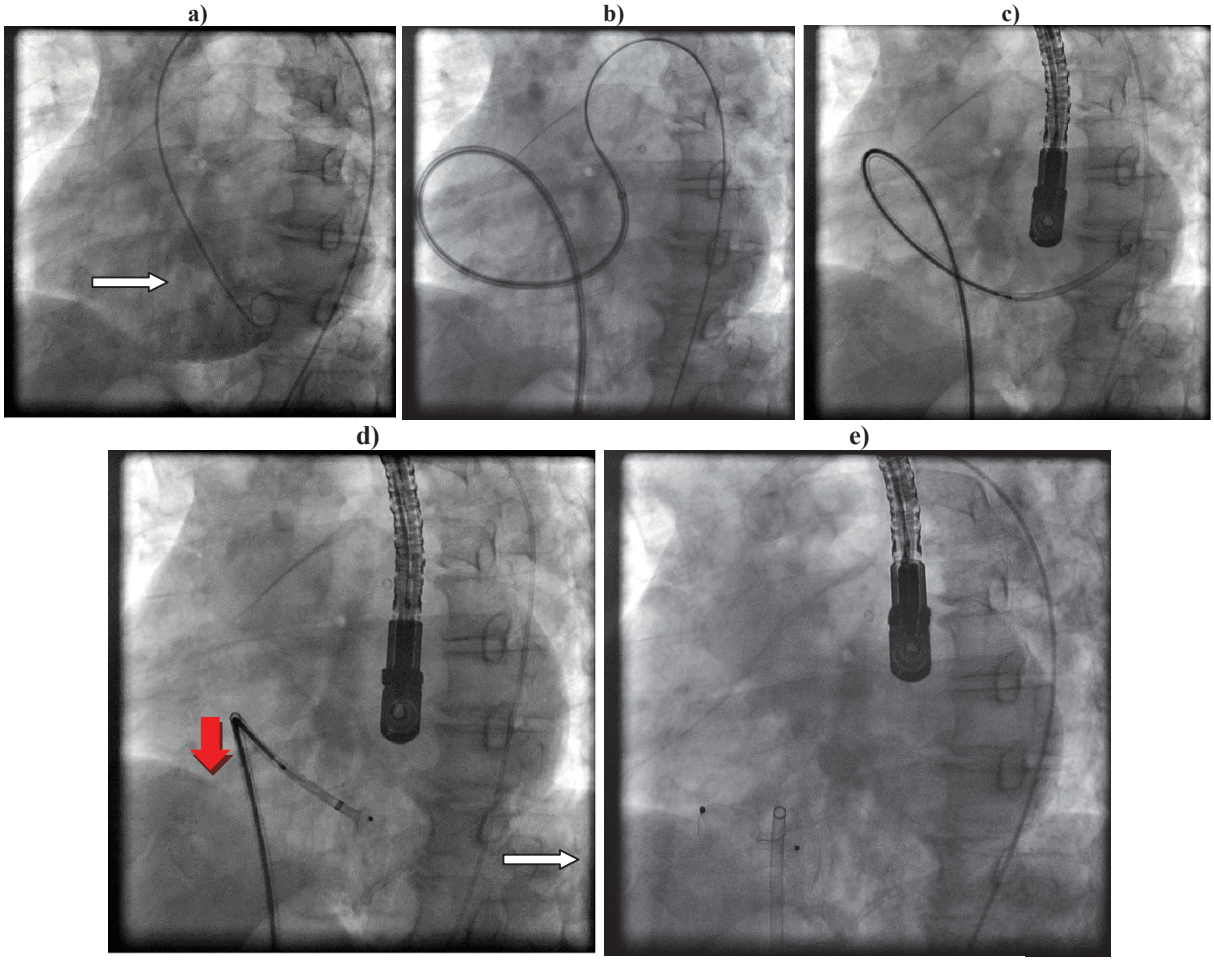


Fig. 2 – Angiographic steps in closure of muscular ventricular septal defect (VSD):
a) Left ventricle angiogram demonstrates the presence of a basal-septal VSD (white arrow); b) An Amplatzer wire was advanced throught a VSD into the pulmonary artery and with a Lasso catheter exteriorized through the right femoral vein, forming arteriovenous loop; c) The wire goes across the VSD from the left ventricle with a delivery sheath in the left ventricle where the device advances; d) The left sided disc advances into the left ventricle (red arrow); e) After the right sided disk has been deployed into the correct position, the device is released from the delivery cable.

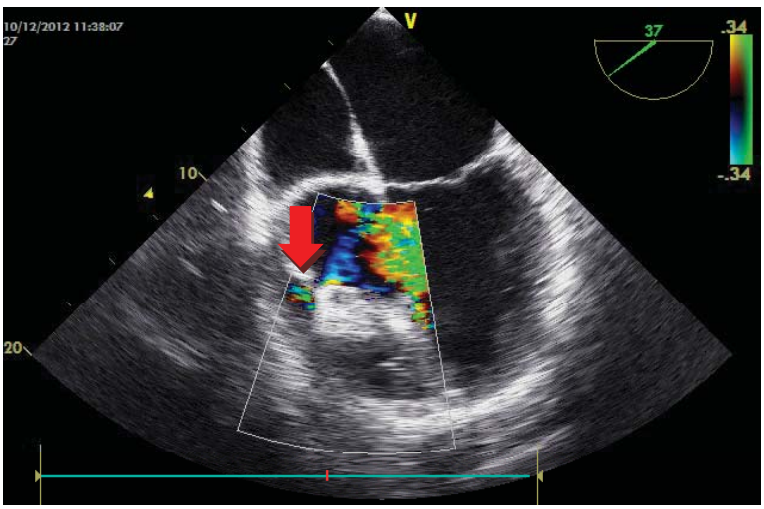


Fig. 3 – Transesophageal exam images of Amplatzer muscular ventricular septal defect (VSD) device after VSD closure with a small residual shunt.

was repeated with direct stenting of the intermediate artery and circumflex artery. The ostial left anterior descending coronary artery assessed as with < 50% stenosis was left for futher functional assessment. After a month the patient was discharged in the NYHA II class with recommended therapy ASA, clopidogrel, ACE inhibitors, beta blocker, statin and spironolactone.

Discussion

TCC can be a definitive treatment or a bridge to surgical or PCI procedure in unstable patients considering that patients with PIVSD usually have single- vessel coronary disease [8] (45% *vs* 21% for 3- vessel coronary disease). Timing of TCC of PIMVSD is one of the major determinants of outcome. When TCC is performed during an acute phase, Thiele et al. [9] reported high mortality up to 65% as in surgically treated patients, but when done in the subacute phase Bialkowski et al. [10] reported successful implantation in 73% and overall mortality of 26%. The size of the defect has influence on the outcome, since the available devices have a limitation regarding the size. Since the major residual shunt or device embolization are reported when the defect is > 15 mm [11], larger defects should undergo surgical treatment. Our procedure was done 14 days after myocardial infarction, and the size of the defect was 15 mm with a very thin wall. Amplatzer perimembranous VSD occluder was the option of choice, but due to technical problem, a VSD muscular occluder was used. After the procedure, Holzer et al. [12] reported a high percent of residual shunt but only 18% were moderate. In the patient presented residual shunt was noticed but it was not significant, with a reduction in Qp/Qs. Although malignant arrhythmias can appear during or after the procedure [10] cardiac rhythm and conduction disturbances were not present in the presented patient. Indication for percutaneous revascularization of the infarct-related artery with plain old balloon angioplasty (POBA) or stent after diagnostic angiography and before Amplatzer implantation was discussed but was not indicated beacuse at the time of admission to our center, myocardial infarction was in the subacute phase: the patient was without chest pain, and the aneurysm was already formed in the inferior septal myocardium, with significant VSD and dominant symptoms were those of heart failure and not of ischemia. It was the decision of heart team that percutaneous coronary intervention of the infarct-related artery would not improve the patient's clinical status nor it would solve the mechanical problem of the complication.

The presented patient was in stable condition 6 months after the procedure, in the NYHA functional class I-II. The plan for further treatment is clinical and echo control and noninvasive assessment of the potentially ischemic left anterior descending artery (LAD) area and the stent treated artery.

Conclusion

Thranscatheter closure should be considered more frequently as a treatment modality in suitable patients with post myocardial infarction ventricular septal defect. The development of hybrid procedures and more sophisticated devices will also improve the outcomes in patients with transcactheter closure of post myocardial infarction venticular septal defect.

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CASE REPORT

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Osteoporosis reversibility in a patient with celiac disease and primary autoimmune hypothyroidism on gluten free diet – A case report

Reverzibilnost koštanih promena kod bolesnice sa celijakijom i autoimunskim hipotireoidizmom

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Abstract

Introduction. Secondary osteoporosis occurs in many diseases. Celiac disease-induced osteoporosis is the consequence of secondary hyperparathyroidism. Biochemical bone markers show predominance of bone resorption, thus making the bisphosphonates the first line therapy option. Intestinal mucosal changes are reversible on gluten-free diet. Osteoporosis reversibility is also possible, provided postmenopausal osteoporosis risk factors independent from celiac disease are not present. **Case report.** We presented a postmenopausal woman with at least a 10-year history of celiac disease prior to diagnosis, which had overt secondary hyperparathyroidism with insufficient status of vitamin D and a significant bone mass reduction. At the time of diagnosis of celiac disease the patient was receiving 250 μg of levothyroxine daily without achieving optimal substitution. Three years after the initiation of gluten-free diet the patient was without any signs and symptoms of the disease. All laboratory findings were within normal range. It was decided to treat the underlying disease and to supplement calcium and vitamin D without the initiation of bisphosponate therapy. **Conclusion.** Osteoporosis regression justified this therapeutic approach. The presence of primary autoimmune hypothyroidism makes this case specific, since the inability for optimal substitution therapy with a high daily dose of levothyroxine provoked the suspicion of celiac disease.

Key words:
celiac disease; hypothyroidism; diet, gluten-free; treatment outcome.

Apstrakt

Uvod. Sekundarna osteoporoza može se javiti u brojnim oboljenjima. Osteoporoza u glutenskoj enteropatiji posledica je sekundarnog hiperparatireoidizma. Koštani biohemijski markeri pokazuju dominaciju koštane resorpcije, što upućuje na bisfosfonate kao terapijsku opciju. Promene na crevnoj sluzokoži postaju reverzibilne konzumiranjem hrane bez glutena. **Prikaz bolesnika.** Prikazana je žena u postmenopauzi kod koje je verovatno najmanje 10 godina bila prisutna glutenska eneteropatija pre nego što je postavljena dijagnoza jasnog sekundarnog hiperparatireoidizma, sa nedovoljnim statusom vitmina D i izraženom redukcijom koštane mase. U vreme dijagnoze, bolesnica je dobijala 250 μg levotiroksina dnevno, bez postizanja optimalne supstitucije. Zauzet je stav da se kod bolesnice preduzme samo lečenje osnovne bolesti, uz adekvatnu suplementaciju kalcijumom i vitaminom D, bez uvođenja bisfosfonatne terapije. Tri godine posle uvođenja dijete bez glutena, bolesnica je bez tegoba, sa normalnim laboratorijskim nalazima. **Zaključak.** Regresija osteoporoze u stabilnu osteopeniju pokazala je opravdanost primenjenog terapijskog stava. Specifičnost ovog slučaja je i istovremeno prisustvo primarnog autoimunskog hipotireoidizma i činjenica da je nemogućnost postizanja optimalne supstitucije visokom dnevnom dozom levotiroksina bila jedan od razloga da se sprovede dijagnostika u pravcu glutenske enteropatije.

Ključne reči:
celijakija; hipotireoidizam; dijeta bez glutena; lečenje, ishod.

Introduction

Celiac disease is a multisystem disorder on the grounds of inadequate immune response to even minimal quantities of gluten from food [1]. Impaired immune response leads to chronic inflammation of small intestine mucosa with lymphocytic infiltration of the epithelium and *lamina propria*, villi atrophy and cryptal hyperplasia resulting in malabsorption syndrome. This is genetically determined in individuals with HLA class II DQ2/DQ8 alleles [2]. It can

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occur at any age and it can be accompanied with other autoimmune diseases.

The characteristics of osteoporosis are the reduction of bone mineral density (BMD), impairment of bone microstructure and increased fracture risk. It is most common in postmenopausal women as primary multifactorial disease, although many diseases and disorders, such as celiac sprue, can cause secondary osteoporosis. Regardless of what caused the osteoporosis its significance is in increased risk for fractures (vertebral, radial, hip fractures). Gold standard for the diagnosis is dual-energy x-ray absorptiometry (DXA) on the hip and lumbar spine. The result is T- or Z- score i.e. the difference between the acctually measured BMD and the expected standard, expressed in standard deviation (SD). These results are interpreted in assembly with other risk factors in order to estimate the individual risk for fractures and decide upon the treatment.

Recommendations to obtain DXA in each patient with celiac disease are justified by the fact that 20–75% of individuals with newly diagnosed celiac disease already have reduction of BMD (osteopenia and osteoporosis) [3]. Osteoporosis in women under 50 years of age, especially in the childbearing age, should always initiate further diagnostics in order to find the cause of secondary osteoporosis, with celiac disease being one of the most common [4–6].

Celiac disease and osteoporosis are linked through malabsorption syndrome and secondary hyperparathyroidism. Receptor activator of nuclear factor kappa-B ligand (RANKL) osteoclastogenesis and bone resorption are stimulated by inflammatory cytokines which appear as the consequence of impaired immune response to gluten. About 20% of celiac disease patients have osteoprotegerine autoantibodies, with predomination of bone resorption over bone formation [7]. Thus, the relative fracture risk in celiac disease patients is increased – 1.4 for all fractures, 2.1 for hip fractures [8].

Proximal small intestine villi atrophy reverses on gluten free diet and serologic markers of this disease (endomysial and/or tissue transglutaminase antibodies) become undetectable [9]. Furthermore, malabsorption syndrome consequences gradually improve, so bone remodeling becomes normal with the increase of BMD, making osteoporosis reversible, too [10]. The question to be answered is how osteoporosis on the grounds of celiac disease should be treated.

Case report

We presented a 58-year-old female with a 12-year history of primary autoimmune hypothyroidism admitted to the Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Center of Novi Sad, Serbia, in June 2008. The patient's levotyroxine daily dose had been successively increased to up to 250 μg due to inability to achieve adequate substitution. The patient presented with swelling of face and lower extremities, muscle weakness in lower extremities and chronic fatigue. Her laboratory analysis showed anemia. The medical history revealed she had been anemic for 10–15 years. In the course of her childhood and adolescence she had had chronic diarrhea, but for the last several years her stool had been normal. Clinical findings revealed undernourishment (body mass index 16.98 kg/m^2), pale skin and mucosa, doughy swellings of face and lower extremities. Malabsorption syndrome was suspected. The initial laboratory findings are shown in Table 1. Endoscopic procedure with proximal small intestine mucosal biopsy was done. Histology showed loss of intestinal villi, reduction of intestinal glands with extensive lymphocytes, neutrophiles and plasma cells infiltration. The diagnosis of celiac disease was made. Since this was a postmenopausal woman, we did DXA. It showed osteoporosis with T-score -2.7 (SD) and -3.4 (SD) on lumbar spine and hip, respectively (Figure 1). Osteocalcine level was in normal range (29.3 ng/mL), while

Table 1

Laboratory parameters before and during the treatment of celiac disease

Parameter	Baseline	6 months	18 months	3 years	Normal range
RBC ($\times 10^{12}$/L)	3.08	4.35	3.76	3.82	3.9–6.0
Hgb (g/L)	91.7	127	118	124	120–160
Hct (%)	27.1	37	35.2	35.9	37–50
Fe (μmol/L)	3.7	11.4	14.8	21	10.7–32.2
Mg (mmol/L)	0.64	0.73	0.71	0.76	0.73–1.06
Ca (mmol/L)	2.03	2.38	2.52	2.54	2.20–2.70
P (mmol/L)	0.93	1.47	1.19	1.06	0.81–1.45
Albumin (g/L)	38.9	46.5	52.4	48.3	35–52
Vitamin D (nmol/L)	36.3	55	69	51	30–100
PTH (pg/mL)	83.1	84.2	40.9	47.9	15–65
β-Crosslaps (pg/mL)	1197	1273	162	160	162–436
Osteokalcin (ng/mL)	29.3	154.3	31	24.1	12–41
Alkaline phosphatase (U/L)	150	145	51	40	30–115
FreeT4 (pmol/L)	9.3	14.1	18.6	19.9	9.1–19.1
FreeT3 (pmol/L)	1.8	4.2	4.1	3.9	2.6–5.7
TSH (mIU/L)	45.18	0.27	1.67	2.27	0.35–4.94
AntiTPO antibodies (IU/mL)	> 1,000	/	> 1,000	> 1,000	< 5.6
Anti-transglutaminase antibodies	positive	/	negative	negative	negative

RBC – red blood cells; Hgb – hemoglobin; Hct – hematocriti; PTH – parathyroid hormone; TSH – thyroid-stimulating hormone; anti-TPO antibodies – anti-thyroid peroidase antibodies.

β-cross laps level was elevated (1197 pg/mL), implying the dominance of bone resorption over formation. The level of 25-hydroxy-vitamin D (25OHD) was 36.3 nmol/L. The patient was an active smoker and that was the only positive independent fracture risk factor.

The patient started with gluten-free diet, with supplementation of 3,000 IU of cholecalciferol daily and 250 μg of levothyroxine. Three months later thyroid-stimulating hormone (TSH) level was 0.001 mIU/L and the dose was reduced to 150 μg daily. Control laboratory analyses and DXA were done after 6 months of gluten-free diet and vitamin D supplementation. TSH values were in the lower part of normal range with normal levels of free T3 and free T4. Circulatory levels of albumine, magnesium, calcium and phosphorus were also normal. Level of 25OHD was 55 nmol/L-still below desirable value of 75 nmol/L with parathyroid hormone (PTH) still slightly elevated (84.2 pg/mL). Osteocalcine was rising (154.3 ng/mL), crosslaps remained elevated (1273 pg/mL). Iron-deficiency anemia was corrected. DXA showed positive trend of T score value (Figure 1). Iron-deficiency improvement of clinical finding was noted, too. The patient was suggested to maintain gluten-free diet, with a combined preparation of 1,000 mg of calcium and 800 IU of cholecalciferol. Levothyroxine was further reduced to 100 μg daily.

Next control exams were done after one year and after 18 months of gluten-free diet. The patient was feeling well and had no signs and symptoms of the disease. The disappearance of anti-tissue-transglutaminase antibodies was noted. Thyroid function tests, albumin, calcium, phosphorus and magnesium were normal. Level of 25OHD increased further to 69 nmol/L, PTH level was normal (40.9 pg/mL), as well as osteocalcine and crosslaps. DXA on the spine and the hip showed a significant improvement of T- score, implying opsteopenia (Figure 1). The patient was advised to stay on gluten-free diet with calcium and cholecalcipherole supplementation. Levothyroxine was reduced to 87.5 μg daily.

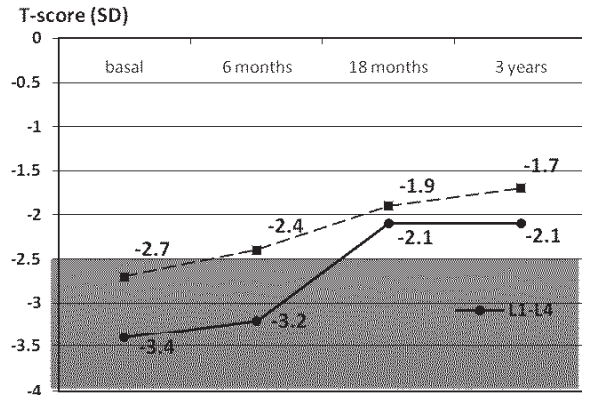

Fig. 1 – Lumbar (dashed line) and hip full line dual-energy x-ray absorptimetry before and during the treatment of celiac disease.

SD – standard deviation.

Three years after the initiation of gluten-free diet the patient was without any signs and symptoms of the disease. All laboratory findings were within normal range. DXA showed T-score -1.7 and 2.1 SD on the lumbar spine and the hip, respectively (Figure 1). During the follow-up period the patient did not have any fractures.

Discussion

Although genetically determined, celiac disease is often diagnosed in adulthood, most commonly between the fourth and sixth decade. Usually, those are the latent forms of the disease, while classical forms with diarrheal syndrome, abdominal pain, weight loss and rash are more often seen in children. Not surprisingly, the study on 1,612 celiac patients done in the USA showed that the duration of the disease prior to the diagnosis was 11 years and 15% of patients did not present with diarrhoea [11]. Anaemia, undernourishment and muscle weakness as manifestations of malabsorption dominate in the absence of typical clinical picture [12].

The presented patient was diagnosed with celiac disease at the age of 58. Immediate cause for the expanded diagnostics was the inability to achieve optimal hypothyroidism substitution, as well as a long history of iron-deficiency anaemia, oedema on lower extremities, undernourishment and muscle weakness. Symptoms of nutrient deficit dominated in the absence of diarrhoea and abdominal pain. According to anamnesis, we could assume it took ten years to make the diagnosis of celiac disease.

Celiac disease is frequently associated with other autoimmune disorders, most often with autoimmune hypothyroidism [13]. Considering the site of levothyroxine intestinal absorption, there is the need for unusually high levothyroxine daily dose with inability to reach optimal TSH feedback. This problem during treatment of primary hypothyroidism should provoke suspicion of malabsorption syndrome and celiac disease [14]. At the time of the diagnosis of celiac disease our patient was receiving 250 μg of levothyroxine daily without achieving optimal substitution. After the initiation of gluten-free diet levothyroxine dose declined to 87.5 μg with TSH in the reference range. Titre of anti-thyroidperoxidase (TPO) antibodies which remains high during the observation period proves the hypothyroidism to be autoimmune. Clinical presentation of celiac disease may be modified by joined autoimmune disorders. This was the case with our patient who had had the history of diarrhoea in adolescence but normal stools later on and presented with lower extremities swelling, chronic fatigue, depression all of which could be contributed to hypothyroidism.

Approximately 2–5% of patients with autoimmune thyroid disorder have celiac disease [15]. Up to 43% of patients with autoimmune thyroid disorder have typical markers of celiac disease in the sense of increased density of T-cell receptors carrying intraepitel lymphocytes with signs of mucosal T-cell activation [13]. This justifies screening for celiac disease in individuals with autoimmune thyroid disorder, especially if optimal substitution with levothyroxine is difficult to achieve as in our patient. Screening for autoimmune thyroid disorder in celiac disease should also be done, especially if clinical presentation is not fully improved by gluten-free diet [16].

The gold standard for the diagnosis of celiac disease is histological picture of proximal small intestine villi atrophy

that is fully reversible in the course of gluten-free diet. Antiendomysial and anti-transglutaminase (anti-t-TG) antibodies are serological markers of the disease. These markers become undetectable when the patient is put on the gluten-free diet, hence they can be used for monitoring of the effect of therapy and patient compliance [9]. Celiac disease diagnosis in our patient was made according to cotemporary standards. In the presence of signs and symptoms of malabsorption syndrome and positive anti-tissue-transglutaminase antibodies, diagnosis was confirmed with proximal small intestine mucosal biopsy. Decline of anti-tTG antibodies titre and later their negativisation showed patient adherence to dietary advice and consequent correction of immune response in the absence of gluten. Since all clinical and laboratory parameters suggested restitution, control mucosal biopsy was not done according to the current recommendations [17].

Small intestine mucosal atrophy in celiac disease leads to malabsorption of many nutrients: proteins, calcium, magnesium, vitamin K, iron, vitamin D, etc. Malabsorption of calcium and vitamin D results in hypocalcaemia, an secondary, regulative, hyperparathyroidism with increase of markers of bone resorption and remodelling (high turnover) [18]. Circulatory levels of 25OHD are usually in the reference range, over 30 but below 75 nmol/L. This level is not sufficiently high to maintain PTH and calcium within normal range [19]. This is the key mechanism for the reduction of BMD (osteoporosis and osteopenia) in celiac disease. Rarely, there is the apparent vitamin D deficit (below 30 nmol/L) which results in impairment of bone mineralisation and osteomalacia. In such a case, DXA method cannot differentiate osteoporosis and osteomalacia. Optimal vitamin D and calcium supplementation is important since in the milieu of gluten-free diet since it corrects hyperparathyroidism and suppresses bone resorption resulting in the increase of BMD. The significance of vitamin D status for muscular function and thus prevention of falls and fractures in terms of the reduction of BMD is a well-known fact.

At the time of the diagnosis of celiac disease our patient had a typical laboratory finding for regulatory hyperparathyroidism: hypocalcaemia, hypophosphatemia, low 25OHD and elevated PTH and bone resorption parameters. Regulatory hyperparathyroidism, a key factor for the occurrence of osteoporosis, vanished during the therapy for celiac disease. Vitamin D status was significantly improved after cholecalciferol substitution (calculated on the basis of the status of vitamin D and target values) and gluten-free diet were initiated. We achieved normal values of calcium, phosphorus, PTH and β-cross laps. Individualisation of daily dose and adequate intestinal absorption during gluten-free diet are preconditions for optimal substitution of vitamin D [20].

A common reduction in BMD in celiac disease patients justifies screening for osteoporosis. The degree of BMD reduction is particularly pronounced if celiac disease appears during skeletal growth and development and it is proportional to duration of untreated disease, *i.e.* to the duration of exposure to gluten [21]. Decision to screen for osteoporosis also depends on the presence of other risk factors for osteoporosis and fractures.

We diagnosed osteoporosis in the presented patient by DXA. We had both celiac disease dependent and independent reasons to carry out diagnostics of osteoporosis. Firstly, although it is impossible to be certain, we assumed our patient had a long history of celiac disease. Secondly, she reached menopause at the age of 46, had a low BMI and was an active smoker. Accelerated metabolic activity estimated by biochemical markers was considered as indicator of increased fracture risk independent of BMD [22]. DXA showed osteoporosis – T-score on lumbar spine and hip -2.7 SD and -3.4 SD respectively. According to the European guidance for the diagnosis and management of osteoporosis in postmenopausal women our patient was a candidate for initiation of medicamentous therapy with bisphosphonates [23].

However, gluten-free diet leads to correction of bone metabolism and vitamin D status, improvement of calcium absorption and increase of BMD within a year [24]. So, the question to be answered is how to treat osteoporosis in celiac disease and what does the treatment option depend on. The current recommendations state that during the first year osteoporosis should be treated only by treating celiac disease itself (gluten-free diet, supplementation of vitamin D and calcium) and by the correction of other independent risk factors and that achieved effect in that period is of prognostic value for at least the next three years [25]. If BMD remains low after a year, risk for fractures should be calculated [(the Fructure Risk Assessment Tool (FRAX) questionnaire)] and osteoporosis should be treated as in individuals who do not have celiac disease [26]. Medicamentous therapy of osteoporosis is initiated parallel with the start of celiac disease therapy if T-score is below -1.5 SD in the presence of other risk factors or previous small trauma fracture or if T-score is below -3.0 SD independently of the presence of other risk factors. Medicamentous therapy of osteoporosis implies bisphosphonates [27], selective estrogen receptor modulators, calcitonine, bone anabolic (teriparatide), strontium ranelate with adequate supplementation of vitamin D and calcium [28].

The presented patient was younger than 60 years, did not have small trauma fractures or family history of fractures, was undernourished and had accelerated bone metabolism because of celiac disease. On the basis of these facts, we decided upon a less aggressive treatment of osteoporosis, i.e. to treat it merely by treating celiac disease. Even more, bisphosphonates were contraindicated because of lesions of intestinal mucosa, hypocalcaemia and insufficient levels of vitamin D. The FRAX questionnaire was not used since there is still no its modification for Serbian population.

The patient was put on gluten-free diet and this resulted in significant corrections in any fields of this complex case in a few months. All signs and symptoms of the disease disappeared and weight gain was noticed. All parameters of calcium homeostasis and bone remodelling returned to normal. Brief elevation of biochemical bone markers coincided with short period of iatrogenous thyrotoxicosis before levothyroxine dose was reduced [29]. Disappearance of anti-tTG antibodies from circulation showed positive evolution of the disease together with good patient compliance to the given therapy.

Considering these results, DXA was done 6 months after the initiation of the therapy and it showed only positive

trend of BMD. After 18 months there was a significant improvement of osteoporosis, i.e. we found only osteopenia that was stable even after 36 months. In the meantime the patient had neither fall, nor small trauma fracture. This outcome justified our decision to treat osteoporosis merely by treating the underlying condition with supplementation of calcium and vitamin D. At the same time, osteoporosis reversibility showed that our postmenopausal patient had only secondary osteoporosis on the grounds of celiac disease.

Conclusion

Since celiac disease may be the cause of secondary osteoporosis with increased fracture risk, screening for osteoporosis should be performed in each patient with celiac disease. Proximal small intestinal mucosal changes in celiac disease patients are reversible on gluten-free diet, so the mechanism that leads to osteoporosis is reversible, too. Gluten-free diet and vitamin D supplementation make osteoporosis reversible.

The decision upon medicamentous treatment of osteoporosis in celiac disease depends on the degree of osteoporosis and on the presence of other independent fracture risk factors in postmenopausal women. Celiac disease is often accompanied by other autoimmune diseases, most commonly primary hypothyroidism. This complicates and modifies clinical manifestations of both diseases, making optimal substitution of hypothyroidism very difficult.

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Moral responsibility of healthcare personnel

Moralna odgovornost zaposlenih u zdravstvu

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Key words:
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Ključne reči:
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"In civilized life, law floats in a sea of ethics"
Earl Warren

Introduction

Without ethics, law could not exist. Right is a moral power in the same way as duty is moral need, wrote Leibniz. If moral norms are, for any reason, secretly and incomparably violated in one segment of society, this will some day result in the violation of those norms in other areas as well [1–3].

The most severe violations of ethics in everyday life are manifested as corruption, conflict of interest and mobbing. Therefore, in addition to legal responsibility, the effect of moral responsibility for such deviant behavior is particularly important to every society oriented towards progress and humanism.

Health care system is supposed to be the foundation of each humane society. The Public Health Law [4] of our country regulates the right in public interest by establishing conditions for the preservation and improvement of public health by comprehensive social activities.

Corruption affairs in a health care system certainly severely compromise the humane mission of this very important social activity. After all, the majority of physicians and other medical staff carry out their activities responsibly, professionally and honestly under extremely difficult working conditions. That healthy part of the system need to be preserved, encouraged and further strengthened. Moral norms are frequently neglected. Balzac used to say that society did not live on moral ideas only. However, the power of character is above intelligence.

Conflict of interest and public trust

The Constitution of the Republic of Serbia stipulates that no one can carry out a state or public function which is in conflict with their other functions, activities or private interests (Article 6, Paragraph 1) [5]. Also, everyone has the right to be truthfully, completely and timely informed about issues of public interest and the media are obligated to respect that right (Article 51, Paragraph 1) [5].

The Law on Preventing Conflict of Interest in Exercising Public Functions stipulates that a public officer shall carry out their function taking care neither to subordinate the public to the private interest nor to bring the two in conflict. The conflict of public and private interest occurs when a public officer's private interest affects or may affect the exercise of their function (Article 1) [6]. In line with that, a public officer must neither be in any relationship with persons who might affect their impartiality in performing the public function nor use the public function for gaining any sort of benefit for themselves or a related person [7]. According to this Law, a public officer shall immediately inform the authority that elected or appointed them and the Government Committee on any pressure or unforwarded influence they are exposed to in performing their function while the Government Committee shall make available to the public the data and documents on any pressure or unforwarded impact a functioner has been exposed to while performing their duty as well as on their functions in public companies, institutions or any other legal entities with partial state ownership and other businesses (Article 11, Paragraph 1 and Article 30, Paragraph 1) [6].

According to the Law on Free Access to Information of Public Interest, it is considered that justified public interest exists always when there is information available to public authority (in terms of this Law a public authority body is a legal entity established or financed in total or most part by a public authority) which is related to compromised and/or protection of public health and environment and, if there is other information available to public authority, it is considered that the justified interest of the public is to know about

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such interest, except if such public authority proves to the contrary. (Articles 3 and 4) [8]. Also, a confidential data is not the data indicated as secret in order to hide a criminal act, exceeded authority or abuse of official position or any other illegal act or action of a public authority (Article 3) [9].

Speaking about health care system, the countries in the Region are evealuated higher than we are. According to the Rulebook on Indices of Healthcare Quality, the quality indices include both those of healthcare facilities performance and those related to the perfomance of the Commission for the improvement of quality of work, acquiring and renewal of personnel knowledge and skills, keeping waiting lists, patient safety, user satisfaction with services of healthcare providers and personnel satisfaction (Article 2) [10]. For example, The Rulebook on the Continuing Education Requirements for Healthcare Professionals and Healthcare Associates [11] specifies the type, programs, method, procedure and duration of continuing education, facilities and associations that can conduct a continuing education course, criteria for accrediation of continuing education programs, and other important issues for conducting continuing education of healthcare professional and associates [12].

Unfortunately, in its reponse to the European Commission Questionnaire, the Government of the Republic of Serbia deliberated that healthcare system was in the first place by corruption (Chapter 23, question 36). The introduction, within the Ministry of Health, a separate organizational department for fighting corruption would certainly contribute to approaching the fight against corruption with much more responsibility.

Ethical principles in health care

A doctor's duty is to provide medical help equally to everyone irrespective of their age, gender, race, nationality, religion, social status, education, social background or any other personal characteristic. At that, the doctor must respect everyone's human rights and dignity (Article 4) [13]. A doctor applies their knowledge and skills in a responsible manner and according to the Etical Code principles. He/she must not cooperate with individuals and institutions and associations that abuse the public trust by advocating uncontrolled and profesionally unproven medicines and therapeutic procedures and must be aware of the fact that every thoughtless, dishonorable, humiliating and any other for a doctor inappropriate action will adversely affect other doctors and healthcare personnel, and the healthcare system as a whole. Any public authority and public resource abuse aiming at personal enrichment is also dishonorable for a doctor (Article 16, Paragraph 1 and Article 18, Paragraphs 2 and 3) [13]. Doctors perform their jobs in a professionally and ethically irreprochable manner and their professional relationship with patients must not be conditioned by any unethical reason (Article 41) [13]. The duty of the members of the Medical Association is to reject any professional act opposed to the professional ethical principles [14] of the Ethical Code or binding international documents. The Association shall assist them by its reputation and, as required, remedies, and undertake action against doctors who violate the provisions of the Ethical Code (Article 80 and Article 81) [13].

Ethical obligations and responsibilities of dental doctors

The ethical principles and rules of conduct set out in the Ethical Code of Dental Doctors [15] involve compliance with positive regulations, general and specific professional and ethical principles that specify the conduct of dental doctors towards: the patients, piers, associates and the Serbian Dental Association. This Code specifies the rules of conduct of dental doctors, the members of the Serbian Dental Association, irrespective if they work in the public of private sector, and dental doctors serving their mandatory internship, who perform their profession in the Republic of Serbia, intended to preserve the reputation and dignity of the dental healthcare activity. The Association is obligated to initiate a procedure before the Ethics Committee and Court of Honor against dental doctors who fail to comply with that Code (Article 1 and Article 2) [15].

The dental profession is neither an entrepreneur nor commercial activity since in conducting it, dental doctors are not primarily led by their material benefit but rather by the welfare of their patients, one of the main duties of dental doctors being the obligation to keep the reputation and dignity of the profession both in their dental work and private lives (Article 3, Paragraph 1 and Article 5, Paragraph 2) [15]. The violation of ethical principles and legal norms results in moral and legal accountability. Moral accountability is the issue to be decided on by the Ethics Committee of the Association, the Court of Honor of the Association, and by professional associations, and the violation of moral rights and principles leads to sanctions: from warning to the exclusion from the professional organization and ban on professional activity.

Ethical principles of pharmacists

The Ethical Code of Pharmacists of Serbia [16] promotes the principles of professional ethics in order to establish ethical conduct by the members of the Serbian Pharmaceutical Association (SPA) in the performance of their pharmaceutical healthcare activity. The foundation of the Code consists of the principles including the established ethical principles, fundamental ethical principles and ethical values applicable in healthcare in order to establish ethical conduct of the members of the Association. For example, a pharmacist neither participates in nor supports advertisment campaigns of medicines and/or medical devices which are non-compliant with legal regulations and which serve for spreading information that is misleading to the general public.

Responsibility of the members of Serbian Associations of Healthcare Professionals

The Association of Helathcare Professionals takes care of the reputation of its members and/or ensures that

healthcare activities are carried out in line with the Ethical Code, and provides assistance to the citizens in obtaining the rights to health care in case of unprofessional or unethical conduct of the Association members (Article 8) [17]. The Association of Helathcare Professionals is obligated to inform the public of all issues falling under its authority, and notify the Ministry of Interior, competent judicial authorities and the Ministry of Health on disciplinary procedurs taken against its members before the bodies of the Association, and on the procedures for issuing, renewal or withdrawal of licences if the given procedures give rise to a doubt that a criminal act has been committed (Article 35, Paragraph 1 and 2). A member of the Association shall be brought to the Court of Honor for disciplinary violation if, by acting or failing to act, that member violates their professional duty or the reputation of the Association (Article 39) in the event that they: act contrary to the provisions of the Healthcare Law and Health Insurance Law while providing health care to patients; violate the Ethical Code; perform their healthcare duty unprofessionally and/or contrary to the current developments in the medical, dental or pharmaceutical practice, or make a professional mistake; discredit the profession by their conduct towards patients, other members of the Association or third parties; abuse the health insurance resources while performing healthcare activities; fail to perform the obligations of a member of the Association set out by law, statute and other general acts of the Association. The Association Statute sets out other violations of professional duty or reputation of member of Association. The initiation of a procedure before the Court of Honor becomes obsolete one year after the violation of the professional duty and reputation of the member of Association set out in Article 40 of this Law, while the execution of the ordered measure set out in Article 43, items 1–4) of this Law becomes obsolete after six months from the date of validity of the decision on the ordered measure (Article 47, Paragraph 1 and 2) [17].

According to the Law on Associations of Healthcare Professionals, neither criminal or offence responsibility nor the responsibility as a member of the Association excludes disciplinary responsibility of the member of the Association (Article 40). The Court of Honor may order one of the following disciplinary measures for the above-mentioned violations of the professional duty or reputation of the member of the Association: public warning; fine of up to 20% of the average monthly salary in the Republic for the month preceding the month in which the fine is ordered, calculated according to the data of the competent statistical authority; temporary prohibition of independent conduct of certain health care activities; temporary prohibition of independent conduct of healthcare activity. Disciplinary measures set out in Article 43, items 1 and 2 of this Law are ordered for minor violations of professional duty and reputation of members of Association. The disciplinary measure set out in Article 43, item 2 of this Law can be ordered for the duration of one to six months. The disciplinary measures set out in Article 43, items 3 and 4 of this Law are ordered for severe violations of professional duty and reputation of members of Association. The disciplinary measures set out in Article 43, items 3 and 4 of this Law cannot be ordered for periods shorter than six months or longer than one year, exceptionally up to five years (Articles 43 and 44) [17].

Courage or obligation of whistleblower

A success of the fight against corruption is not possible without determinate and honorable people, whistleblowers who, despite threats, have sufficient civil courage to point to abuses and curruption in their working environment [18]. The task of whistleblowers is included in the Code of Professional Ethics of the Serbian Medical Association [13] in the provision setting out that a doctor is obligated to inform the Association about their observations and attitude related to unprofessional and criminogenic acts and activities in the domain of diagnostics and treatment and to request legal and social support (Article 16, Paragraph 2). A member of the Association has the right and obligation to inform on every violation of the Ethical Code provisions the Ethics Committee of the Association taking care of the enforcement of the Ethical Code pursuant to the law and Association's Statute. The member of the Association has also the right to file applications and proposals to the Ethics Committee of the Association related to issues in the jurisdiction of the Ethics Committee, and to be provided with the responses to them on request (Article 79). Also, a doctor is obliged to take the active part in anti-corruption activities in the healthcare system with the support and involvement of the Association and competent public and other authorities and organizations, as well as non-government entities (Article 17).

The Ethical Code of the Serbian Association of Nurses and Medical Technicians [19] specifies the basic ethical principles of the performance of professional duties of the members of the Association, the attitude of the members of the Association towards the patients, and inter-relationship of the members of the Association. The whistleblower rules are also contained in this Code in the provisions setting out that nurses and medical technicians who notice that their coleagues are violating the ethical principles of their profession should warn them and try to solve the problem in an informal way and that, if the obvious violation of this Code cannot be settled amicably, their duty is to notify the Ethics Committee of the Serbian Association of Nurses and Medical Technicians which will undertake certain action. Nurses and medical technicians must not submit notifications aiming at inflicting injury and humiliation of another but must strive to protect the profession; to that end, they must cooperate with the disciplinary authorities of the Serbian Association of Nurses and Medical Technicians.

Otherwise, the duty of a whistleblower to notify of a doubt of corruption is set out in the Public Officers Law [20]. Therefore, a public officer or employee shall inform their supervisor or manager in writing of any knowledge of a corruption act performed by a public official, public officer or employee of a public authority they work with, and shall enjoy the protection set out by law from the date of such written notification. (Article 23 a). As for the protection of whistleblowers, it is laid out in the Code of Conduct for

Public Officers [21] in Article 18 related to the preservation of the standard of conduct and mobbing prohibition. A public officer who thinks that they or any other public officer is requested to act in a way which is not in line with this Code, shall inform their manager of that in writing and shall, as a consequence of such information, neither be placed in an unfavorable position related to other public officers, nor harassed (mobbing) while performing their duty or exibiting their rights in the authority.

By the Decision of the Minister of Justice and Public Administration, issued in September 2013, a working group was established in order to prepare the draft law regulating the protection of whistleblowers, which working version is supposed to be generated by the end of the year.

Whistleblowers' courage and consistency sometimes result in the harassment at their workplaces. The Law on Prevention of Harassment at Workplace [22] prohibits any form of harassment at and related to workplace, and the abuse of the right to protection from harrassment (Article 5). An emplyee has the right to protection from harassement behavior (Article 10, Paragraph 2). According to the Rulebook on Employer and Employee Conduct for the Prevention and Protection from Harassment at Workplace [23] the harassor emplyee, and the employee who abuses the right to protection from harassment, is responsible for violation of work discipline and/or workplace duty, pursuant to the Law (Article 9).

The Labor Law of Montenegro [24] specifies the prohibition of mobbing by the prohibition of any form of harassment at workplace (mobbing) and/or any repeated behavior towards an employee or group of employees, which represents the violation of dignity, respect, personal and professional integrity, position of the employee creating fear or hostile, humiliating or offensive environment, aggravating working conditions or leading to employee isolating themselves or persuading them to cancel the work contract on their own initiative.

Public attention has been drawn to the case of a healthcare employee who pointed to a work irregularity in the institution she was employed with, who subsequently got a warning before the termination of her employment contract.

Conclusion

Justice only brings moral victories and should be the basis of any society. All users of health care need to have equal access to those services. Healthcare laws and ethics greatly overlap considering that the conduct of healthcare professionals should reflect the concern for welfare, dignity and health of any man. Our country also needs the business ethics for better future managers. But is the value of social power accompanied by responsibility? However, the best protection against corruption in healthcare consists of the proper and unbiased evaluation of work and work results of each employee.

Any concrete and efficient act of protection of whistleblowers would be a clear sign of the political will on the top level to fight corruption in Serbia. Today, efforts are obvious to improve the position of whistleblowers. What is missing? Unfortunately, the lack of legal protection is observed as well as the absence of material support in case of a whistleblower lossing job. Analysis of the model of whistleblower protection in other countries would also help as well as scientific gatherings dedicated to this topic that would be initiated by the public trustee. Adoption of the Law on whistleblower protection would be the most important step in terms of encouraging such persons to make their decision to report misconduct at work easier.

While Balsac considered perseverance the most needed of all virtues and the highest expression of strength in all human acts, indeed, according to Masaryk, the complete moral reform cannot be achieved without the light of education and careful upbringing. The ethical principle is to think good and to act in such manner everywhere and in any life and creation environment. This paper as well was driven by such wish.

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Osiguranje profesionalne odgovornosti lekara i ostalih zdravstvenih radnika

Professional liability insurance of physicians and other medical workers

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medical errors; liability, legal; insurance, liability; physicians; patients.

Uvod

Da bi se moglo govoriti o osiguranju profesionalne odgovornosti lekara i ostalih zdravstvenih radnika, moramo definisati odgovornost lekara i ostalih zdravstvenih radnika kao profesionalnu, zatim, sadržinu te odgovornosti, odnosno, lekarsku grešku, kao i oblik osiguranja od ove vrste odgovornosti. Činjenica je da osiguranje od profesionalne odgovornosti lekara i ostalih zdravstvenih radnika (u daljem tekstu ćemo upotrebljavati termin osiguranje od odgovornosti lekara, napominjući da ovom vrstom osiguranja treba da budu obuhvaćena sva lica koja pružaju bilo koju vrstu medicinske pomoći) predstavlja zaštitu ne samo pacijenata, već i zaštitu svih zdravstvenih radnika. Zbog toga, treba imati u vidu da ova vrsta osiguranja može predstavljati samo jedan od oblika zaštite, s obzirom na to da i sama država, odnosno, sistem zdravstva u njoj, mora definisati više efikasnih oblika zaštite, kao i da osiguranje od odgovornosti lekara mora biti regulisano na takav način da i ono bude jedan od navedenih oblika zaštite pacijenata i lekara. Problemi sa osiguranjem od odgovornosti lekara postoje, kako u našoj državi, tako i u zemljama u susedstvu, kao i u mnogo razvijenijim zemljama u svetu.

Pre izlaganja o napred navedenim institutima, treba pomenuti sisteme osiguranja u ovoj oblasti, s obzirom da se, do sada, mogu definisati tri sistema, koji se, manje ili više uspešno, primenjuju u državama različitih nivoa razvijenosti. Ta osiguranja su različita, ona se ne odnose samo na osiguranje od odgovornosti. Naime, sistemi o kojima je reč su sledeći: 1) klasični sistem (Radi se o sistemu, koji ima osnov u klasičnim načelima koji definišu naknadu štete. U ovom sistemu se definiše subjektivna odgovornost lekara. Odlike ovog sistema su dugotrajno vođenje postupka, visoki sudski troškovi, neophodnost definisanja određenog stepena krivice lekara, itd. U ovaj sistem spada i osiguranje od profesionalne odgovornosti lekara); 2) *"no-fault"* sistem (Kod ovog sistema se ne dokazuje krivica lekara. U ovom sistemu su odgovornost lekara ili drugog zdravstvenog radnika, sa jedne strane, i isplata štete, sa druge strane, dve odvojene stvari, koje se utvrđuju u dva nezavisna postupka [1]. Ovaj sistem vezujemo za skandinavske zemlje); 3) mešoviti sistem; (Ovaj sistem ima osnov u odgovornosti lekara po osnovu krivice, ali se kod određenih šteta, odnosno posledica pružanja medicinske usluge, uvodi i tzv. odgovornost bez krivice, tj. *"no fault"* sistem [2]. Ovaj sistem je karakterističan za Francusku).

Osnovno što nas interesuje odnosi se na „traženje“ najefikasnijeg sistema osiguranja. Naravno, taj sistem mora da prati određena zakonska regulativa. Osim toga, osiguravajuća društva moraju uzeti učešća u definisanju zakonskih odredbi, a uz to, moraju da definišu i opšte uslove osiguranja u ovoj oblasti. Naime, postavlja se pitanje da li opštim uslovima u ovoj oblasti treba obuhvatiti sva lica, sve stručnjake koji se, na bilo koji način, bave pružanjem medicinske pomoći, proizvodnjom i prodajom lekova i drugih lekovitih i pomoćnih lekovitih sredstava, odnosno, vršenjem različitih laboratorijskih analiza. Jasnije rečeno, da li se istim opštim uslovima mogu obuhvatiti lekari, stomatolozi, farmaceuti, itd. Treba analizirati opšte uslove jednog osiguravajućeg društva i videti da li je tako nešto uputno. Isto tako, treba se osvrnuti na funkcionisanje različitih sistema osiguranja u ovoj oblasti u različitim državama. Pre toga, potrebno je definisati lekarsku odgovornost kao profesionalnu, kao i sadržinu lekarske greške.

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Lekarska odgovornost kao profesionalna odgovornost

Definisati lekarsku odgovornost kao profesionalnu nije lako, imajući u vidu da je teško definisati i samu profesionalnu odgovornost. Naime, profesionalna odgovornost se uvek veže za vršenje neke profesije, neke stručne delatnosti. Profesionalna odgovornost nije precizno definisana, ali je povezana sa profesijama u kojima postoje kodeksi ponašanja, strukovna udruženja, itd. [2]. No, ne možemo profesionalnu odgovornost vezati ni za sve one koji vrše neku stručnu delatnost, već samo za one koje vrše intelektualnu profesiju. Intelektualni aspekt profesije, da bi se postavilo pitanje profesionalne odgovornosti, mora biti vezan i za stručnost, kao i za pružanje pojedine vrste usluga trećim licima, na čijem dobru može nastati šteta [3]. Lekari, advokati, notari, stečajni upravnici, arhitekte, kao i druga slična zanimanja su te profesije kod kojih se može definisati ova vrsta odgovornosti. Znači, intelektualna komponenta mora biti vezana i za stručnost i za pružanje usluga trećim licima [4]. Jedno od pitanja koje se postavlja odnosi se na obavezu koje lice, o čijoj profesionalnoj odgovornosti govorimo, mora preuzeti na sebe. Naime, radi se o obavezi da izabere određene mere, zatim da primeni određeni način preduzimanja tih mera, kao i sredstva, koja bi trebalo da dovedu do tog cilja. To znači da se pitanje profesionalne odgovornosti postavlja samo kod obaveze koja ne mora dovesti do rezultata [4] . Ako navedeno prenesemo na oblast lekarske greške, onda ćemo zaključiti da se odgovornost lekara može postaviti kod davanja dijagnoze, kao i kod primene određene terapije.

Znači, ako bi se moglo reći da je odgovornost lekara i drugih zdravstvenih radnika profesionalna odgovornost, onda je potrebno tu odgovornost bliže odrediti sa stanovišta prava, kako bi se mogle odrediti i posledice te odgovornosti, ako dođe do štete. Koji standard za utvrđivanje odgovornosti moramo definisati u ovoj oblasti? To je pažnja dobrog stručnjaka, odnosno, pažnja savesnog i razumnog lekara iste specijalizacije u istim ili sličnim uslovima. Jednog lekara ne može opravdati njegovo pozivanje na to da je pružio lekarsku uslugu prema svom najboljem znanju, ako se ustanovi da je njegovo znanje nedovoljno za pružanje takve lekarske usluge [5].

Lekarska greška

Lekarska greška se vezuje za sve faze u pružanju medicinske pomoći. Postoje različiti kriterijumi za razlikovanje više vrsta lekarskih grešaka. Neki autori razlikuju lekarsku grešku tehničke prirode i lekarsku grešku koja se sastoji u nepoštovanju prava pacijenata. Dalje, lekarska greška tehničke prirode odnosi se na grešku u dijagnozi ili na grešku u terapiji [6]. Sa druge strane, što se tiče lekarske greške koja je vezana za nepoštovanje prava pacijenata, ona je dosta široko, postavljena i može se odnositi na neke propuste u samoj zdravstvenoj ustanovi, ali može biti vezana i za sam sistem organizovanja pružanja medicinske pomoći u jednoj zemlji. Uže gledano, lekarska greška može nastati u vezi sa određivanjem dijagnoze i u vezi sa određivanjem terapije, odnosno, načina lečenja. Lekarsku grešku možemo vezati i sa pogrešnom ili nestručnom upotrebom medicinskih aparata, kao i sa nevođenjem ili neurednim vođenjem medicinske dokumentacije. Naravno, i ovi se slučajevi vezuju za navedeno razlikovanje lekarske greške.

Činjenica je da od definisanja lekarske greške, načina njenog nastanka, kao i od posledica koje ona može izazvati, zavisi i definisanje odgovornosti lekara, pa, samim tim, i osiguranja te odgovornosti.

Osiguranje od profesionalne odgovornosti lekara

Osiguranje od odgovornosti je specifična vrsta osiguranja. Naime, osiguranik se osigurava od odgovornosti da bi sebe obezbedio od eventualnih isticanja zahteva za naknadu štete od strane trećih, oštećenih, lica [7]. Osiguranik ovim osiguranjem štiti svoju imovinu od eventualnih slučajeva kada to lice načini drugom štetu i kada bi morao da tu štetu nadoknadi svojom imovinom. U tome je smisao osiguranja od odgovornosti, koje spada u imovinska osiguranja. Kad govorimo o osiguranju profesionalne odgovornosti, govorimo o osiguranju od odgovornosti u obavljanju određene stručne delatnosti.

Ako je lekarska odgovornost definisana kao profesionalna odgovornost treba videti šta je pokriveno osiguranjem od odgovornosti lekara, odnosno, kada će jedno osiguravajuće društvo platiti određeni iznos, ako dođe do propusta ili greške lekara, što zavisi od toga kako su definisani ovi instituti u zakonu i opštim uslovima osiguranja. Ako bi pošli od opšte definicije, koja se, na neki način, može primeniti i kod osiguranja od profesionalne odgovornosti koja se tiče drugih struka, onda bi rekli da osiguranje od lekarske odgovornosti obuhvata građansku odgovornost osiguranika za štete nastale usled smrti, povrede tela ili zdravlja, trećih lica koje su prouzrokovane lekarskom greškom. Definisanje građanske odgovornosti može biti dosta široko. U svakom slučaju, ovakvo definisanje ove vrste osiguranja štiti i lekara i pacijenta.

Kada će osiguravajuće društvo platiti štetu, odnosno, šta je pokriveno ovom vrstom osiguranja? I ovde se može dati opšta definicija. Naime, pokriveni su budući, neizvesni i od volje osiguranika nezavisni štetni događaji koji su nastali kao rezultat propusta lekara ili greške lekara, kao i nesavesnog ili nestručnog postupka lekara, kao i drugog medicinskog osoblja. Ta postupanja moraju biti učinjena protivno propisima i standardima medicinske struke, što za direktnu posledicu ima nepovoljan ishod lečenja i na osnovu kog bi treće lice moglo da zahteva naknadu štete [8].

Suma osiguranja predstavlja gornju granicu za naknadu štete po jednom štetnom događaju, odnosno, po jednom osiguranom slučaju. To je iznos do čije visine je jedno osiguravajuće društvo obavezno po osiguranom slučaju – štetnom događaju. Osim sume osiguranja po štetnom događaju, postoji i pojam agregatne sume osiguranja koja predstavlja ukupnu obavezu osiguravača za ceo period osiguranja i predmet je ugovaranja. Ovo je naročito bitno kod ove vrste osiguranja, pogotovo kad se zaključuje na nivou cele medicinske ustanove. Izbor adekvatne sume osiguranja je vrlo važan, jer predstavlja ujedno iznos do koga, po pretpostavci, mogu da idu odštetni zahtevi trećih lica. Visina premije osiguranja za-

visi od izbora limita pokrića, tj. sume osiguranja kako po štetnom događaju, tako i agregatne, zatim izvora opasnosti i ukupnog prihoda [8]. U SAD su činioci koji određuju premiju i sumu osiguranja vezani i za mesto gde se bolnica ili druga zdravstvena ustanova nalazi. Jedna od važnih karakteristika ovog oblika osiguranja odnosi se i na to da obaveza osiguravača nije samo u isplati štete, odnosno, sume osiguranja, već i u preduzimanju odbrane od neosnovanih i preteranih zahteva za naknadu štete, kao i u naknadi troškova sudskog postupka [9]. Ovo je, naročito, bitno kod sudskih postupaka, u slučaju kada su tuženi i osiguranik i osiguravač.

Činjenica je da svako osiguravajuće društvo definiše i isključenja iz osiguranja, odnosno, situacije, kada nije u obavezi da plati štetu, iako se ista dogodila. Tada se ne može reći da se dogodio osigurani slučaj, jer iz osiguranog slučaja proizlazi i obaveza na naknadu štete. Ovde je u pitanju postojanje okolnosti koja isključuje obavezu plaćanja iznosa štete. Kod osiguranja od profesionalne odgovornosti lekara, treba imati na umu i sprovođenje medicinskog veštačenja u slučajevima kada se pretpostavlja postojanje neke okolnosti koja predstavlja osnov za isključenje iz osiguranja. Znači, u vezi sa tim, mora se definisati i na koji način lekar mora da pruža medicinsku uslugu ili pomoć. On to mora činiti sa povećanom pažnjom, odnosno, po pravilima svoje struke. Nakon nastanka osiguranog slučaja, oštećeno lice ima pravo na naknadu štete, ali do ugovorene osigurane sume [10].

Da bi mogli da odredimo opšte uslove ove vrste osiguranja, moraju se tačno odrediti i elementi odgovornosti lekara. Ali, o tim elementima, odnosno, pretpostavkama ne možemo govoriti, ako se ne odredi vrsta odgovornosti koja će biti osigurana. Odgovornost postoji i kad postoji krivica lica koje je prouzrokovalo štetu i kad je ta šteta prouzrokovana, bez obzira na subjektivan odnos štetnika prema izazvanoj štetnoj posledici. Pretpostavke za utvrđivanje odgovornosti lekara su sledeće: a) postojanje subjekata štete – oštećeno i odgovorno lice; b) štetna radnja, c) protivpravnost, bez obzira na oblik i vrstu ; d) uzročna veza između radnje i štetne posledice; e) odgovornost štetnika; f) šteta, bez obzira da li je materijalna ili nematerijalna [11].

Okviri za regulisanje osiguranja od profesionalne odgovornosti lekara u Srbiji

U Srbiji nije zakonski regulisano osiguranje od odgovornosti lekara. To znači, da se lekari i drugi zdravstveni radnici osiguravaju na dobrovoljnoj osnovi, što ne može biti dobro u nekom dužem periodu. Time se dobrovoljno osiguranje ne stavlja u inferioran status u odnosu na obavezno osiguranje, ali je činjenica da se ova vrsta osiguranja mora regulisati kao obavezna. No, imajući u vidu teškoće vezane za celokupan zdravstveni sistem u našoj zemlji, potrebno je da se i država uključi u rešavanje ovog problema. To podrazumeva definisanje programa koji bi morao da odredi na koji način će država pomoći da se ostvari zaštita i pacijenata i lekara. Sa druge strane, osiguravajuća društva moraju definisati uslove za osiguranje od odgovornosti lekara i drugih zdravstvenih radnika, koja će poštovati sve specifičnosti struke, kao i sva pravila koja su prisutna kod ove vrste osiguranja. Znači, sa jedne strane, možemo govoriti i o zakonskom okviru, za koji bi morala da bude odgovorna država, zajedno sa svim subjektima koji čine sistem zdravstva u našoj zemlji, a, sa druge strane, mora se definisati i okvir koji će obezbediti efikasno osiguranje, za koji, pre svega, treba da budu odgovorni oni koji pružaju usluge osiguranja, ali će taj okvir zavisiti od zakonskog.

Osiguravajuća društva u Srbiji pružaju mogućnost zaključenja osiguranja od odgovornosti lekara. Predstavićemo osnovne karakteristike opštih uslova jednog osiguravajućeg društva u ovoj oblasti, a u pitanju je društvo čiji kapital ima strano poreklo. Opšti uslovi koji se primenjuju u Srbiji, primenjuju se i u zemlji gde se nalazi matično društvo. Interesantno je da se ti uslovi primenjuju i na osiguranje odgovornosti lekara, kao i odgovornost stomatologa, farmaceuta, kao i lica koja obavljaju biohemijsku delatnost. Već je rečeno da nije uputno da isti opšti uslovi obuhvataju osiguranje od odgovornosti svih navedenih struka.

Po Opštim uslovima ovog osiguravajućeg društva [12], predmet osiguranja predstavlja lekarska delatnost osigurana u skladu sa zakonom, a posebno lekarska delatnost koja je organizovana kao privatna praksa, poliklinika ili na drugi način u skladu sa zakonom, uključujući i obaveze naknade štete nastale pri pružanju prve pomoći. Isto tako, Opšti uslovi predviđaju mogućnost posebnog pismenog ugovaranja, kada mogu biti pokrivene i štete iz odgovornosti direktora bolnice ili rukovodioca bolničkog odeljenja ili lekara, koji, osim u svojoj ordinaciji, radi i na bolničkom odeljenju, nastale zbog radnog naloga koji je izdat lekarima bolnice, kao i iz odgovornosti nelekarskog medicinskog osoblja, koje mora po imenu biti navedeno u polisi osiguranja. Osigurani slučaj se, u ovom aktu, definiše kao događaj koji je prouzrokovan osiguranim rizikom, na osnovu koga treće oštećeno lice može zahtevati naknadu štete. Osiguravajuća zaštita obuhvata odbranu od neosnovanih i preteranih zahteva za naknadu štete, zatim naknadu štete, kao i naknadu troškova postupka. Gornja granica obaveze osiguravajućeg društva je ugovorena suma osiguranja, koja obuhvata sve vidove štete koji su navedeni. Ovo osiguranje pokriva imovinsku štetu pod kojom Opšti uslovi smatraju uništenje stvari, izgubljenu zaradu, izmaklu korist, kao i troškove lečenja i sahrane. Pod imovinskom štetom se ne smatra uništena ili umanjena mogućnost daljeg razvoja i napredovanja i osiguravajuće društvo ovakve štete neće isplatiti.

Ukoliko dođe do promenjenih okolnosti, odnosno, ako se proširi rizik u vezi sa obavljanjem lekarske delatnosti, tada je osiguranik obavezan da obavesti osiguravajuće društvo o tim okolnostima, kako bi osiguranjem bilo obuhvaćeno povećanje rizika, ali, samo ako osiguravajuće društvo ne raskine ugovor o osiguranju. Spomenućemo još neke odredbe Opštih uslova koje se odnose na ovu vrstu ugovora o osiguranju, kao što su: trajanje ugovora je jedna godina, osim ako nije drugačije određeno, pravo ugovarača osiguranja da raskine ugovor nakon nastanka osiguranog slučaja, ukoliko osiguravajuće društvo nije u potpunosti ili delimično platilo štetu; primena Zakona o obligacionim odnosima; - izmena Opštih uslova i tarifa premija za vreme trajanja ugovora o osiguranju; itd.

Mora se reći da su odredbe Opštih uslova prilično opšte određene, što znači da se većina odredaba može primenjivati i na osiguranja drugih vrsta profesionalnih delatnosti.

Različiti oblici osiguranja lekara u drugim zemljama

Napred su pomenuta tri osnovna sistema osiguranja u ovoj oblasti. U nastavku će biti dat kratak prikaz nekih od tih sistema, odnosno, oblika osiguranja u pojedinim zemljama, uz isticanje nekih od problema koje su pojedine države imale u sprovođenju osiguranja u ovoj oblasti, kao i činjenicu da je država morala da adekvatno reaguje, kako bi se ostvarila zaštita i lekara i pacijenata. Osiguranja koja će biti predstavljena spadaju u osiguranje od odgovornosti, zatim, u osiguranje lica, kao i u osiguranje od nezgode, ali neka od njih predstavljaju i kombinacije ovih oblika osiguranja.

Osiguranje od odgovornosti lekara u Sloveniji

Slovenija je interesantna sa stanovišta naše zemlje, ne samo zato što je bila republika u okviru SFRJ, već i zato što je osiguranje od odgovornosti lekara u ovoj zemlji obavezno. Dva zakonska akta regulišu osiguranje od odgovornosti lekara u Slovenijii. Zakon o zdravstvenoj službi Republike Slovenije [13] predviđa obavezno osiguranje lekara za eventualnu grešku i štetu koju on može napraviti u pružanju lekarskih usluga. Uobičajena visina osigurane sume je oko 13.000 evra u slovenačkim tolarima (SIT). Ali, u praksi, lekari se osiguravaju na mnogo veće sume. Sa druge strane, Zakon o lekovima Republike Slovenije [14] određuje obavezno osiguranje lica koje predlaže testiranje leka. Međutim, ovaj Zakon ne predviđa ni osiguranu sumu za navedeno osiguranje, kao ni ko će tu sumu odrediti. Jedno od pitanja koje se u Sloveniji postavlja u ovoj oblasti, jeste i pitanje uzajamnog osiguranja [15].

Samoosiguranje pacijenata – Skandinavski model

Samoosiguranje pacijenata u pojedinim evropskim zemljama ima svoje različite oblike. Ova vrsta zaštite pacijenata, ali i lekara, je deo opšteg zdravstvenog osiguranja [8]. Prvi oblik ovog osiguranja je osiguranje „bez greške“, gde se radi o obaveznom pokriću, kao što je to u Danskoj, Finskoj, Islandu ili Švedskoj. Inače, ovaj oblik se naziva i Skandinavski model osiguranja pacijenata i on je prvi put uveden u Švedskoj 1. januara 1997. godine. Ovo osiguranje se ne zasniva na principu krivice. Ali, problem postoji. Ne prihvata se oko 60% zahteva za naknadu štete zbog nemogućnosti dokazivanja uzročne veze. Osiguranje je ograničeno iznosima od 750.000 evra po oštećenom licu, odnosno, 3 900 000 evra po osiguranom slučaju. U Finskoj sistem *"no-fault"* osiguranja postoji još od sedamdesetih godina, a 1987. godine je donesen Zakon o ozledama pacijenata [16]. Osim toga, u ovoj zemlji postoje i slučajevi osnivanja grupe osiguravača. Broj odštetnih zahteva se u Finskoj kretao oko 7-8 hiljada u periodu od 1999. do 2003. godine [17]. U Finskoj, pacijenti imaju pravo na naknadu štete, ukoliko su je pretrpeli u toku medicinske intervencije i nege, zatim kod primene terapije, kao i kod naučnih ispitivanja i doniranja organa. Ovim osiguranjem su pokriveni svi zdravstveni radnici, bez obzira da li rade u državnim ili privatnim zdravstvenim ustanovama, kao i same zdravstvene ustanove i bolnice. Za rešavanje sporova, u vezi naknade štete, formiran je poseban organ - Udruženje za osiguranje pacijenta, koje ima pravo uvida u sve nalaze i u ceo tok bolesti pacijenta. Postupak za utvrđivanje nastale štete se vodi na zahtev lekara, pacijenta ili ombudsmana [18].

„Mešoviti“ sistem u Francuskoj

Napred je već spomenuto da je u Francuskoj prihvaćen „mešoviti“ sistem u ovoj oblasti. Naime, sistem samoosiguranja pacijenata je prihvatila Francuska, u kojoj je 2002. godine osnovan poseban nacionalni fond koji funkcioniše po osnovu kolektivne odštete uz obavezno osiguranje lekara i zdravstvenih ustanova [19]. Interesantan je način regulisanja naknade štete po ovoj vrsti osiguranja. Naime, radi se o jednoj vrsti poravnanja. Znači, optuženi bi trebalo da plate štetu, odnosno, pacijenti treba da prihvate njihovu ponudu, ako im odgovara. Time se ublažavaju posledice samog parničnog postupka [20].

Osiguranja od lekarske odgovornosti u okviru zdravstvenog osiguranja u SAD

U SAD, pitanje lekarske odgovornosti nije važno samo sa stanovišta premijskog osiguranja, već i zdravstvenog osiguranja. U ovoj državi ova vrsta osiguranja ima veliki značaj i ono je obavezno. Lekari su prinuđeni da plaćaju visoke iznose premija osiguranja. Premija za ovu vrstu osiguranja se određuje na osnovu vrste lekarske greške, zatim specijalnosti lekara, mesta gde lekar obavlja posao, broja sati koji provede na radnom mestu, itd. Ali, najvažnija činjenica kod određivanja premijske stope je iskustvo bolnice, a, takođe, uzima se u obzir i mesto njenog nalaženja [21]. Međutim, u pojedinim državama SAD, kao npr. u Floridi, ne postoji obaveza zaključenja osiguranja od lekarske odgovornosti. No, i kad postoji obaveznost osiguranja od ove vrste odgovornosti, može se dogoditi da polisa ne pokriva rizik za ceo period osiguranja. Tada su lekari u obavezi da zaključe tzv. *"tail coverage"*, kako bi bili pokriveni zahtevi za naknadu štete i obaveze po odlukama sudova. Neki lekari plaćaju i više od 100000 dolara na ime zaključenja osiguranja. Mora se reći, a to je i logično, da lekari specijalisti u oblasti neurohirurgije, ortopedije, akušerstva, ginekologije i sl., plaćaju najviše premije, s obzirom da oni obavljaju praksu koja u sebi sadrži više rizika i mogućnosti za nastanak komplikacija.

Ono što je interesantno, jeste da se ova vrsta osiguranja može zaključiti i na nivou bolnice, odnosno, bilo koje zdravstvene ustanove. Naime, ako lekari rade u bolnici, odnosno, ako pružaju medicinsku pomoć pacijentima u njihovim stanovima i kućama, tada oni imaju pravo na određene beneficije koje se odnose na plaćanje premije. To dovodi do šireg pokrića, imajući u vidu da će i sami lekari biti više zainteresovani za zaključenje osiguranja od sopstvene odgovornosti, ako mogu da dobiju bolje uslove u smislu niže premije i načina plaćanja iste. Međutim, postoje pojedine države u SAD koje nisu sprovele reforme u oblasti regulisanja ovih vrsta delikata, u kojima osiguranje od odgovornosti nije dostupno. Mnogi lekari zbog toga odlaze da vrše lekarsku praksu u one države, u kojima imaju mogućnost da se osiguraju. No, sa druge strane, neki od njih prestaju da obavljaju lekarsku pra-

ksu, imajući u vidu opasnost koja im preti. Kriza u ovoj oblasti traje duži niz godina u SAD, a najveća je u državama Konektikat, Florida, Ilinois, Nju Džerzi, i Pensilvanija [22].

U reformama koje se u zdravstvu sprovode u SAD, jedan od ciljeva je da se osiguranje od lekarske odgovornosti, kao i druge vrste osiguranja u zdravstvu, usmere ka stvaranju jednog profesionalnog, poslovnog i regulatornog okvira za bolje finansiranje zdravstvene zaštite, uopšte. Zato se funkcionisanje osiguranja od lekarske odgovornosti povezuje sa funkcionisanjem celokupne zdravstvene zaštite [23].

"No-fault" sistem osiguranja na Novom Zelandu

Pre više od trideset godina na Novom Zelandu je uvedeno opšte osiguranje od nesrećnog slučaja, u okviru kojeg je definisan i *"no fault"* sistem. U tom sistemu osiguranja, stavlja se akcenat na nesreće koje se dese na radnom mestu ili u saobraćaju, kao i u sportu, ali među svim tim slučajevima, nalaze se i nesreće i povrede nastale u medicinskim ustanovama. To su tzv. „medicinski nesrećni slučajevi", za koje je predviđeno obeštećenje pacijentima, a u te slučajeve spadaju: 1) pozitivne lekarske radnje ili pozitivne lekarske greške koje su uzrokovane nedovoljno visokim i očekivanim stepenom pažnje; 2) nastupanje teških, neočekivanih, kao i nepoželjnih i štetnih po zdravlje pojava koje su proizašle iz postupka lečenja; i 3) medicinski nesrećni slučajevi nastali kvarenjem medicinskih aparata [24]. Ako nastupi osigurani slučaj, pacijentu će se isplatiti naknada štete iz posebnog fonda za njihovo osiguranje, a potraživanje naknade štete preko suda ili preko same medicinske ustanove nije dozvoljeno. U ovom sistemu, pacijenti primaju naknadu za običnu štetu i izgubljenu dobit u vidu gubitka zarade u iznosu od 80% prosečnog primanja u jednoj radnoj nedelji, u vreme nastanka medicinske nesreće, a što iznosi oko 340 USD. Isto tako, nadoknađuju se i troškovi medicinskog tretmana kao i naknada zbog trajne nesposobnosti za rad, zatim naknada zbog nemogućnosti izdržavanja bračnog druga i ostalih lica koje je oštećeni bio dužan da izdržava. Celim sistemom rukovodi Državna komisija za obeštećenje kojoj se i podnosi zahtev za naknadu štete. Oštećeni ima obavezu da navedenoj Komisiji podnese zahtev u roku od jedne godine od dana nastanka štete. Najviše zahteva za naknadu štete se podnosi u oblasti hirurgije. Podnosi se, prosečno, 2 000 zahteva za naknadu štete godišnje, odnosno, 50 zahteva na 100 000 stanovnika (Novi Zeland ima oko 3 800 000 stanovnika). Najviši dosuđeni zahtevi su u oblasti šteta nastalih usled neuroloških povreda dece [25]. Premije osiguranja su, u ovoj zemlji, znatno niže nego u zemljama u kojima je prisutan klasični sistem osiguranja od odštetne odgovornosti.

Problemi vezani za osiguranje od profesionalne odgovornosti lekara

U Srbiji, praktično, još nije u potpunosti „zaživelo" zaključenje osiguranja od profesionalne odgovornosti lekara, a u drugim zemljama pojavljuju se veliki problemi u vezi sa ovom vrstom osiguranja. Zbog svih karakteristika osiguranja od odgovornosti, uopšte, kao i u domenu, kada se radi o osiguranju od odgovornosti profesija, tj. lekara, povećava se broj parničnih postupaka povodom sporova proizašlih iz navedenih ugovora o osiguranju. U tim postupcima dosuđuju se veliki iznosi, što predstavlja teret ne samo za medicinske ustanove i osiguravajuća društva u jednoj državi, već i za samu državu. Zbog toga, osiguravajuća društva ne žele da se bave ovom vrstom osiguranja, a isto tako, ni pojedine medicinske ustanove ne žele da pružaju pojedine medicinske usluge, koje, na bilo koji način, predstavljaju rizik za život i zdravlje pacijenta. U zemljama, u kojima je prihvaćen tzv. *"no-fault"* ili skandinavski model osiguranja, osigurava se pacijent. U Švedskoj se ne sprovodi parnični, već administrativni postupak, u kome se ne utvrđuje krivica lekara, kao ni nepažnja. Međutim, utvrđuje se greška lekara koja je dovela do ugrožavanja zdravlja pacijenta ili bilo koje druge posledice. Administrativni postupak ne isključuje mogućnost da pacijent podnese tužbu protiv lekara. Ovaj model osiguranja ima jedan nedostatak, koji se sastoji u tome što se može primenjivati samo u razvijenim zemljama. Drugi nedostatak se tiče sume osiguranja, koja je unapred utvrđena, odnosno, isplaćuje se ono što je predviđeno ugovorom o osiguranju. Ipak, ako je pacijent nezadovoljan iznosom, on može, kao što smo rekli, podneti tužbu, kako bi ostvario veću naknadu štete. Dobre strane ovog modela odnose se na brzinu naknade štete, izbegavanje dugih sudskih postupaka, kao i otklanjanje psihološkog pritiska na lekara, s obzirom da se ne utvrđuje njegova krivica, ako dođe do štete [26].

Da li bi ovaj model mogao biti uveden u Srbiji? Teško je na to pitanje odgovoriti, kada postoje veliki nedostaci i u regulisanju „klasičnog" osiguranja od profesionalne odgovornosti lekara. Sigurno je da će se broj grešaka u ovoj delatnosti povećati, a, isto tako, i broj sudskih postupaka. Da li bi osiguravajuća društva bila u stanju da izdrže pritisak koji štete u ovoj oblasti mogu da proizvedu. Sigurno je da bi ovu vrstu osiguranja trebalo zakonski regulisati kao obavezno i time postići više puta navedeni dvostruki cilj – zaštitu i pacijenata i lekara. Međutim, treba videti da li bi sva osiguravajuća društva mogla da se bave ovom vrstom osiguranja i da li bi trebalo povećati početni fond sigurnosti za osiguravajuća društva koja žele da se bave i ovim osiguranjem, odnosno, odrediti obavezno povećanje rezervi za ta društva. Osim toga, trebalo bi rešiti i druga pitanja koja se tiču samog zaključenja ugovora o osiguranju. Naime, ko bi zaključivao taj ugovor, lekari pojedinačno (kao i drugo medicinsko osoblje) ili medicinska ustanova za sve lekare i druge zdravstvene radnike koji rade u toj ustanovi. Zatim, da li bi premiju osiguranja plaćali lekari iz svojih prihoda ili bi se našli drugi izvori (fond same ustanove, fond koji bi država ustanovila). Tada bi se postavilo pitanje i sredstava zdravstvenog osiguranja. Sledeće, trebalo bi regulisati da lica koja vrše lekarsku profesiju mogu izgubiti licencu za obavljanje svog rada, ako ne zaključe ugovor o osiguranju. Naravno, ovde se može postaviti i niz drugih pitanja.

Pravilno regulisanje ove materije je jako bitno za zdravstveni sistem jedne zemlje. Da je to tako, govori i praksa u zemljama Evropske unije, gde je u svakom desetom lekarskom, odnosno, medicinskom postupku, utvrđena greška lekara ili drugog zdravstvenog radnika koja ima posledice za pacijenta. To je sadržano u izveštaju evropske komisije [27].

Zaključak

Na osnovu svega navedenog, može se zaključiti da osiguranje od profesionalne odgovornosti lekara i drugih zdravstvenih radnika treba regulisati kao obavezno, da bi se ostvarila zaštita i pacijenata i lekara. U definisanju modela ove vrste osiguranja moraju da učestvuju, kako zdravstvene ustanove, tako i osiguravajuća društva, zajedno sa nadležnim državnim organima. Mora se imati u vidu sledeće: mogućnost izdvajanja sredstava iz dela budžeta (predviđenog za zdravstvo) za plaćanje premije osiguranja; mogućnost izdvajanja jednog dela doprinosa koji se uplaćuju na ime zaposlenja, odnosno radnog staža lekara ili drugog zdravstvenog radnika za plaćanje premije osiguranja; mogućnost preventivnog ponašanja u ovoj oblasti, kako bi se smanjio broj zahteva za naknadu štete. Ako bi osiguranje od profesionalne odgovornosti lekara bilo predviđeno kao obavezno, onda bi bilo potrebno utvrditi da li bi se ono zaključivalo kao kolektivno osiguranje ili kao individualno. Možda bi trebalo predvideti mogućnost zaključenja i jednog i drugog osiguranja. Osiguravajuća društva bi morala, opštim uslovima, da predvide da li će i na koji način rizik uticati na formu zaključenja, kao i na sumu osiguranja. Sigurno je da bi trebalo predvideti mogućnost da lekari koji pružaju komplikovanije lekarske usluge, kao što su hirurzi, neurohirurzi, ginekolozi i ostali, zaključuju ugovor o osiguranju na veću sumu osiguranja za svako osigurano lice.

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Results should be presented in logical sequence in the text, tables and illustrations. Emphasize or summarize only important observations.

Discussion is to emphasize the new and significant aspects of the study and the conclusions that result from them. Relate the observations to other relevant studies. Link the conclusions with the goals of the study, but avoid unqualified statements and conclusions not completely supported by your data.

References

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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.

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Primeri referenci:

Đurović BM. Endothelial trauma in the surgery of cataract. Vojnosanit Pregl 2004; 61(5): 491–7. (Serbian)

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)

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