YU ISSN 0042-8450

ВОЈНОСАНИТЕТСКИ ПРЕГЛЕД

Часопис лекара и фармацеута Војске Србије

Military Medical and Pharmaceutical Journal of Serbia

Vojnosanitetski pregled

Vojnosanit Pregl 2009; January vol. 66 (No. 1): pp. 1-102.

YU ISSN 0042-8450 вол. 66, бр. 1, 2009.

ВОЈНОСАНИТЕТСКИ ПРЕГЛЕД

Први број *Војносанитетског прегледа* изашао је септембра месеца 1944. године

Часопис наставља традицију *Војно-санитетског гласника*, који је излазио од 1930. до 1941. године

ИЗДАВАЧ
Управа за здравство Сектора за материјалне ресурсе МО Србије

Адреса редакције: Војномедицинска академија, Институт за научне информације, Црнотравска 17, поштански фах 33–55, 11040 Београд, Србија. Телефони: главни и одговорни уредник 3609 311, технички секретар 3608 943, редакција 3609 902 и 3609 179, претплата 3608 997. Факс 2669 689. E-mail: **vmaini1@EUnet.yu** (главни и одговорни уредник) и **vmaini2@EUnet.yu** (редакција).

Радове објављене у „Војносанитетском прегледу“ индексирају: Science Citation Index Expended (SCIE), Journal Citation Reports/Science Edition, Index Medicus (Medline), Excerpta Medica (EMBASE), EBSCO, Biomedicina Serbica. Садржаје објављују Giornale di Medicine Militare и Revista de Medicina Militara. Приказе оригиналних радова и извода из садржаја објављује International Review of the Armed Forces Medical Services.

Часопис излази дванаест пута годишње. Претплате: жиро рачун код Управе за јавна плаћања у Београду бр. 840-941621-02 – ВМА (за Војносанитетски преглед), ПИБ 102116082, или на девизни рачун код Народне банке број: 54104-ознака валуте-549. Годишња претплата: 4 000 динара за грађане Србије, 8 000 динара за установе из Србије и 150 € (у динарској противвредности на дан уплате) за претплатнике из иностранства. Копију уплатнице доставити на горњу адресу.

Штампа Војна штампарија, Београд, Ресавска 40 б.

YU ISSN 0042-8450 vol. 66 No. 1, 2009

VOJNOSANITETSKI PREGLED

The first issue of *Vojnosanitetski pregled* was published in September 1944
The Journal continues the tradition of *Vojno-sanitetski glasnik* which was published between 1930 and 1941

PUBLISHER

Health Department, Sector for Material Resources, Ministry of Defence, Serbia

Editorial Office: Military Medical Academy, INI; Crnotravska 17, PO Box 33–55, 11040 Belgrade, Serbia. Tel: +381–11–3609–179; +381–11–3609–902, subscription 3608–997; Fax: +381–11–2669–689; E-mail: **vmaini1@EUnet.yu** and **vmaini2@EUnet.yu**

Papers published in the Vojnosanitetski pregled are indexed in: Science Citation Index Expended (SCIE) Journal Citation Reports/Science Edition, Index Medicus (Medline), Excerpta Medica (EMBASE), EBSCO, Biomedicina Serbica. Contents are published in Giornale di Medicine Militare and Revista de Medicina Militara. Reviews of original papers and abstracts of contents are published in International Review of the Armed Forces Medical Services.
The Journal is published monthly. Subscription: account with Uprava za javna plaćanja in Belgrade. Giro Account No. 840-941621-02 – VMA (za Vojnosanitetski pregled), PIB 102116082 to the foreign currency account with Narodna banka No: 54104-currency-549. Subscription prices per year: individuals 4 000.00 Din, and institutions 8 000,00 Din in Serbia, and foreign subscribers 150€.

Printed by: Vojna štamparija, Beograd, Resavska 40 b.

S A D R Ž A J / C O N T E N T S

Kosovka devojka – čuvena slika Uroša Predića (Orlovat, 17.12.1857 – Beograd, 11.02.1953), jednog od najvećih slikara srpskog realizma. Slika prikazuje devojku koja pomaže ranjenom junaku posle bitke na Kosovu polju, која se odigrala na Vidovdan, 28. juna 1389. godine, između srpske i turske vojske.

Kosovo Maiden – a famous painting of Uroš Predić (Orlovat, December 7, 1857 – Belgrade, February 11, 1953), one of the greatest Serbian Realist painters. The painting shows a young girl which helps a wounded hero after the Battle of Kosovo that was fought on St Vitus' Day in 1389 (June 28 by Gregorian calendar) between the Serbian Empire and the Otoman Empire.

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

U susret jubilejima

To go to jubilees

Silva Dobrić

Vojnomedicinska akademija, Institut za naučne informacije, **Beograd**

Nova 2009. godina obeležiće dva, za vojni sanitet, izuzetno značajna jubileja: 2. marta proslaviće se 165 godina od potpisivanja Ukaza Njegovog Knjaževskog Visočanstva Aleksandra Karađorđevića o osnivanju Centralnog vojnog špitalja, datum koji Vojnomedicinska akademija u Beogradu slavi kao svoj rođendan, dok će septembar mesec biti u znaku proslave 65. rođendana Vojnosanitetskog pregleda (VSP), časopisa lekara i farmaceuta Vojske Srbije.

Prvi broj VSP izišao je u septembru 1944. godine u Bariju, Italija, jer je u to vreme na prostorima bivše Jugoslavije još plamteo oganj Drugog svetskog rata. Od tada naovamo, časopis je, kao i naša zemlja, uostalom, imao uspone i padove, ali je uspeo da održi kontinuitet izlaženja i zadovoljavajući kvantitet i kvalitet radova. Do 1975. godine VSP je povremeno izlazio sa 12 brojeva godišnje, potom redovno sa šest brojeva i sa retkim dodacima (*supplements*), a u protekle tri godine (od 2005), zbog povećanog priliva radova, ponovo je uspostavljena jednomesečna dinamika izlaženja (VSP je trenutno jedini biomedicinski časopis u Srbiji koji izlazi mesečno).

Trend porasta broja pristiglih radova u Redakciju VSP nastavljen je i u protekloj godini. Dok je u periodu 2005-2007. taj broj iznosio 225-235 radova godišnje, prošle godine već je prešao 300. Ovo je najverovatnije posledica ulaska časopisa u sistem citiranja čuvene baze naučne publicistike *Science Citation Index Expended* (SCIE) koja prati najuticajnije naučne časopise sveta, zbog čega se smatra prestižnim objaviti rad u časopisu sa tzv. SCI liste. Trend povećanog priliva radova, potencijalnih kandidata za objavljivanje u VSP, biće sigurno nastavljen i u 2009. godini, o čemu svedoči podatak da je samo u poslednjih 20 dana decembra meseca u Redakciju časopisa stiglo preko 20 novih radova.

Kao i prethodnih godina i u 2008. odbijeno je oko 30% pristiglih radova, a od onih koji su dobili pozitivnu ocenu recenzenta, u 12 brojeva objavljena su 152 rada, što sa šest prikaza knjiga i dva izveštaja sa stručnih skupova, čini ukupno 160 različitih članaka (tabela 1).

Tabela 1

Struktura radova objavljenih u VSP u 2008. godini

Kategorija rada	Broj radova	%
Uvodnici	12	7,5
Originalni članci	81	50,6
Opšti pregledi	4	2,5
Aktuelne teme	16	10,0
Seminari praktičnog lekara	5	3,1
Kazuistika	28	17,5
Istorija medicine	4	2,5
Pisma uredniku	2	1,3
Ostalo (prikazi knjiga, izveštaji sa stručnog skupa)	8	5,0
Ukupno	160	100,0

Dok su u 2006.[1] i 2007. godini [2] na stranicama VSP dominirali radovi autora iz civilnih zdravstvenih i akademskih institucija, u 2008. godini došlo je do njihovog izjednačavanja sa brojem radova iz tzv. „vojnog sektora“ (tabela 2). Nadajmo se da će se ovaj odnos održati i ubuduće jer do sada nebrojeno puta je potvrđeno da stručnjaci iz vojnosanitetskih ustanova Srbije imaju mnogo toga da pokažu domaćoj i svetskoj stručnoj i naučnoj javnosti.

U protekloj godini nešto je opao broj radova iz inostranstva, ali očekujemo da će zahvaljujući ulasku VSP na SCI listu porasti zainteresovanost autora iz inostranstva da rezultate svojih istraživanja objave na njegovim stranicama.

Correspondence to: Silva Dobrić, Vojnomedicinska akademija, Institut za naučne informacije, Crnotravska 17, 11 040 Beograd, Srbija. Tel.: +381 11 26 69 689. E-mail: vmaini2@hotmail.com

Tabela 2

Podela radova objavljenih u VSP u 2008. godini prema instituciji autora rada

Institucija autora radova	Broj radova	%
Vojnomedicinska akademija (VMA)	57	35,6
Vojna bolnica Niš	12	7,5
VMA + civilne institucije	14	8,8
VMA + inostrane institucije	3	1,9
Civilne institucije u Srbiji	70	43,7
Inostrane institucije	4	2,5
Ukupno	160	100,00

Broj radova u VSP na engleskom jeziku povećava se iz godine u godinu. Tako je u 2007. godini svaki peti rad objavljen na strancima VSP bio na engleskom jeziku [2], a prošle godine svaki četvrti. Uredništvo VSP podržava ovakav trend jer veruje da će na taj način radovi objavljeni u časopisu biti „vidljiviji“ na međunarodnoj sceni što povećava izglede za njihovu veću citiranost, a, time, i za bolji impakt faktor samog časopisa.

Prošle godine, posle dužeg vremena, uz redovne brojeve VSP štampan je i jedan suplement u kojem su objavljeni radovi sa naučnog skupa „Srpski vojni sanitet 1917-1918“ koji je održan na Vojnomedicinskoj akademiji 31. oktobra 2008. Skup su organizovali Vojnomedicinska akademija i Akademija medicinskih nauka Srpskog lekarskog društva povodom 90. godišnjice proboja Solunskog fronta i oslobođenja Srbije u Prvom svetskom ratu. U suplementu je, kroz 13 radova, sveobuhvatno sagledana organizacija saniteta srpske vojske u završnim borbama za oslobođenje otadžbine, a mnogi podaci izneseni u ovim radovima, po prvi put su stavljeni na uvid stručnoj i široj javnosti.

U ovoj, za VSP jubilarnoj, godini Uredništvo časopisa učiniće sve da i ubuduće obezbedi objavljivanje samo visokokvalitetnih radova koji će po svim segmentima ispunjavati stroge kriterijume savremene naučne publicistike. U tome, kao i do sada, veliku pomoć očekujemo od naših recenzenata, eminentnih stručnjaka iz različitih oblasti medicine, stomatologije i farmacije, kojih je u protekloj godini bilo gotovo 140, i kojima, ovom prilikom, izražavamo veliku zahvalnost za trud koji su uložili u podizanju kvaliteta radova objavljenih u VSP.

Recenzenti Vojnosanitetskog pregleda u 2008. godini

Ameno Kiyoshi
Aleksandar Nedok
Anđelka Ristić-Anđelkov

Biljana Đorđević
Boris Ajdinović
Borisav Janković
Boško Ranković
Branislav Đurović
Branislav Popović
Branislava Glišić
Branislava Miljković
Branka Đurović
Branka Nikolić
Branka Roganović
Budimir Pavlović

Danilo Vojvodić
Darko Nožić
Dino Tarabar
Dragan Jovanović
Dragan Mikić
Dragan Nikolić
Dragan Tavčioski
Dragana Obradović
Dragana Stamatović
Dragica Pešut
Dragutin Tričković
Dušan Jovanović
Dušan Pavlica
Dušan Stefanović
Dušica Risović

Elijana Garalejić
Elizabeta Ristanović
Evica Dinčić

Genka Petrova
Goran Brajušković
Goran Plavec
Goran Rađen
Gordana Dedić
Gordana Žunić

Ilija Tomić
Ivana Novaković
Ivanka Gajić

Jasna Jović
Jefta Kozarski
Jovan Nikolić

Lidija Kandolf Sekulović

Ljiljana Petrović-Rackov
Ljiljana Radojčić
Ljiljana Tukić
Ljiljana Živanović
Ljubica Đorđević
Ljubica Konstantinović
Ljubo Marković

Marjan Novaković
Milanko Čabarkapa
Mile Ignjatović
Milica Berisavac
Milica Ninković
Milica Prostran
Milomir Todorić
Milotka Fabri
Mirjana Pavlović
Mirko Rosić
Miroljub Trkuljić
Miroslav Vukosavljević

Nada Dobrota
Nada Kovačević
Nada Kuljić-Kapulica
Nadežda Dimić
Nataša Vučković
Nebojša Stanković
Nenad Arsović
Nenad Baletić
Nenad Perišić
Nenad Ugrešić
Nikola Filipović
Novak Milović

Petar Aleksić
Philip O Wilson
Predrag Peško
Predrag Romić

Rada Ješić
Radoje Ilić
Radoš Zečević
Radovan Čekanac
Rajko Hrvačević
Ružica Kozomara

Sašo Rafajlovski
Sava Mićić
Sidor Mišović
Slavica Rađen
Slavica Ušaj
Slavica Vučinić
Slaviša Đurđević
Slobodan Apostolski
Slobodan Ilić
Slobodan Janković
Slobodan Marjanović
Slobodan Obradović
Slobodan Slavković
Smiljana Matić
Snežana Rakić
Snežana Šušnjar
Sonja Radaković
Srboljub Stošić
Srđan Lazić
Srđan Stepanović
Svetislav Pervulov
Svetislav Tatić
Svetlana Stošić Divjak

Svetozar Damjanović
Svjetlana Matković

Tihomir Ilić

Vladimir Jakovljević
Veljko Mirović
Vena Selaković – Mićunović

Vesna Bjegović
Vesna Kilibarda
Vesna Šuljagić
Vidosava Radonjić
Viktorija Dragojević-Simić
Vinka Maletić-Vukotić
Vladan Radosavljević
Vojkan Stanić

Zdravko Mijailović
Zlata Brkić
Zoran Anđelković
Zoran Hajduković
Zoran Janković
Zoran Kovačević
Zoran Mijušković
Zoran Popović

Zoran Šegrt
Zoran Vukašinović
Zorica Đurić
Zvonko Magić

Žarko Vučinić
Željka Tatomirović

L I T E R A T U R A

1. *Dobrić S*. A New Year – the „old“ wishes. Vojnosanit Pregl 2006; 64(1): 5–6. (Serbian)
2. *Dobrić S*. A reason for optimism. Vojnosanit Pregl 2008; 65(1): 5–6. (Serbian)

ВОЈНОСАНИТЕТСКИ ПРЕГЛЕД
ВОЈНОМЕДИЦИНСКА АКАДЕМИЈА
Црнотравска 17, 11040 **Београд, Србија**
Тел/факс: +381 11 2669689
vmaini2@hotmail.com
vmaini2@eunet.yu

Приступ чланцима публикованим у часопису Војносанитетски преглед у *pdf* формату

По узору на велике издавачке куће у свету које публикују и часописе из области биомедицине као и раширену праксу *on line* доступности медицинске периодике и чланака преко *Interneta* у *pdf* формату (програм *Adobe Reader*) и Војносанитетски преглед, пратећи савремене трендове издаваштва и доступности у електронској форми, нуди свим заинтересованима чланке у *pdf* формату публиковане од 2002. године до данас. Од 2002. године часопис је доступан преко *EBSCO* базе података у *pdf* формату, али је мали број установа у Србији претплаћен на ову медицинску научноинформацијску базу.

Сви заинтересовани могу преузети жељени чланак у *pdf* формату, из часописа који је доступан преко сајта ВМА: http://www.vma.mod.gov.yu

ORIGINAL ARTICLES UDC: 616.316–003.7–009–08

Botulinum toxin in the treatment of sialorrhea

Botulinski toksin u lečenju sijaloreje

Marina Svetel*, Milan Vasić†, Nataša Dragašević*, Tatjana Pekmezović‡, Igor Petrović*, Vladimir Kostić*

Clinical Centre of Serbia, *Institute of Neurology, **Belgrade;** Clinical Center "Zvezdara"
†Institute of Otorhynolaryngology, **Belgrade; School of Medicine, University of Belgrade,**
‡Institute of Epidemiology, **Belgrade, Serbia**

Abstract

Background/Aim. Botulinum toxin-A (BTX-A) is known to block the release of acetylcholine from motor and autonomic nerve terminals and may significantly decrease saliva production when injected intraglandulary. The aim of this study was to evaluate effects of BTX-A injections in the treatment of disabling sialorrhea in various neurological disorders. **Methods.** This study included 19 consecutive patients with significant sialorrhea associated with various neurological disorders. Out of them 13 patients were with Parkinson's disease, two with pantothenate kinase-associated neurodegeneration, two with multiple system atrophy, one with Wilson's disease, and one patient with postoperative sialorrhea. Botulinum toxin-A (Dysport®, Ipsen Pharma) was injected into the parotid glands with (n = 7 patients) or without (n = 12 patients) ultrasound guidance. All the patients were scored before and after the treatment and in weekly intervals thereafter using the salivation item of the part II (Activities of Daily Living) of the Unified Parkinson's Disease Rating Scale (UPDRS). **Results.** Thirteen patients (68%) reported beneficial effect of BTX-A injection, while 6 of them (32%) had no response at all. The sialorrhea scores before and after the treatment were 3.1 ± 0.1 (range 2–4) and 1.8 ± 0.1 (range 0–3), respectively ($t = 5.636$; $p < 0.001$). There was no difference in the magnitude of response between the groups with ($t = 4.500$; $p = 0.004$) and without ($t = 3.674$; $p = 0.005$) ultrasound control of injection sites. Adverse effects were registered in 5 patients (26%). **Conclusions.** Botulinum toxin-A injections to easily accessible parotid glands, without necessity for ultrasound guidance, are safe and efficaceous treatment for sialorrhea in different neurological disorders.

Key words:
sialorrhea; parkinson disease; neurodegenerative diseases; botulinum toxins.

Apstrakt

Uvod/Cilj. Botulinski toksin A (BTX-A) blokira oslobađanje acetilholina iz motornih i autonomnih nervnih završetaka, te može znatno da umanji stvaranje pljuvačke kada se ordinira intraglandularno. Cilj ove studije bio je da se utvrde efekti primene BTX-A u lečenju sijaloreje kod raznih neuroloških poremećaja. **Metode.** Ovom studijom bilo je obuhvaćeno 19 konsekutivnih bolesnika sa značajnom sijalorejom izazvanom različitim neurološkim bolestima. Od tog broja 13 bolesnika je bilo sa Parkinsonovom bolesti, dva sa pantotenat kinaza-udruženom neurodegeneracijom, dva sa multiplom sistemskom atrofijom, jedan sa Wilson-ovom bolesti i jedan bolesnik sa postoperativnom sijalorejom. Botulinski toksin A (Dysport®, Ipsen Pharma) injektovan je u parotidne žlezde kod bolesnika sa (n = 7) i bez (n = 12) ultrazvučnog navođenja. Svi bolesnici ocenjivani su pre i posle tretmana u nedeljnim intervalima uz primenu dela UPDRS skale koji se odnosi na hipersalivaciju (*Unified Parkinson's Disease Rating Scale* – UPDRS, *Part II Activity of Daily Living*). **Rezultati.** Ukupno 13 bolesnika (68%) saopštilo je povoljno dejstvo injektovanja BTX-A, dok je šest bolesnika (32%) ostalo bez ikakve reakcije. Ocene stepena sijaloreje pre i posle tretmana bile su 3,1 ± 0,1 (opseg 2–4) i 1,8 ± 0,1 (opseg 0–3), respektivno ($t = 5,636$; $p < 0,001$). Nije bilo razlike u magnitudi reakcije između grupa sa ($t = 4,500$; $p = 0,004$) i bez ($t = 3,674$; $p = 0,005$) ultrazvučnog upravljanja mestima injektovanja. Neželjeni efekti zabeleženi su kod pet bolesnika (26%). **Zaključak.** Injektiranje botulinskog toksina A u lako pristupačne parotidne žlezde, bez potrebe za ultrazvučnim navođenjem, bezbedno je i efikasno u lečenju sijaloreje kod različitih neuroloških bolesti.

Ključne reči:
sijaloreja; parkinsonova bolest; neurodegenerativne bolesti; botulinski toksini.

Correspondence to: Vladimir S. Kostić, Clinical Centre of Serbia, Institute of Neurology, Dr Subotića 6, 11000 Belgrade, Serbia. Phone: +381 11 268 55 96. E-mail: vkostic@sbb.co.yu

Introduction

Sialorrhea, defined as an overflow of saliva from the mouth (drooling), negatively affects both patient's quality of life and social interactions [1, 2]. Its etiology includes acute and chronic neurological disorders (Parkinson's disease, Wilson's disease, motor neuron disease, multiple system atrophy, pantothenate kinase-associated neurodegeneration, bulbar and pseudobulbar palsy, etc.), hypersecretion (inflammatory processes in oral cavity), adverse effects of some drugs, or anatomic abnormalities affecting oral cavity [3].

Mild cases of sialorrhea may be treated pharmacologically (i.e. anticholinergics, although their use is often restricted by side effects), while more severe cases of drooling are eventually referred to surgery [4].

Kerner [5] noted severe dryness of mouth in patients with botulism, and was the first to suggest possibility that botulinum toxin might be used to treat sialorrhea. Botulinum toxin-A (BTX-A) blocks the release of acetylcholine from motor and autonomic nerve terminals, and, when injected intraglandulary, it may significantly decrease saliva production and can be beneficial in excessive sialorrhea [6-8]. However, a number of issues (doses, sites of injections, method of application) is still open.

The aim of this study was to evaluate the effects of BTX-A injections to the parotid glands in the treatment of disabling sialorrhea in various neurological disorders.

Methods

The study comprised 19 consecutive patients with sialorrhea associated with various neurological disorders (Table 1), who were treated with BTX-A injections at the Institute of Neurology, Belgrade from January 2006 to January 2007. All the patients rated their sialorrhea with score ≥ 2 according to the salivation item of the part II (Activities of Daily Living) of the Unified Parkinson's Disease Rating Scale (UPDRS) [9]. None of them had problems with swallowing of solid food. The study was approved by the Ethical Committee of the Clinical Center of Serbia. The patients were included in the study after giving informed and written consent.

Botulinum toxin-A (Dysport®; Ipsen Pharma) was injected (final concentration 10U/0.1ml; 1 ml syringe using a 22-gauge needle penetrating to a depth of 1 cm) into preauricular portion of parotid glands, behind the angle of the ascending mandibular rami, and then into the inferoposterior portion of the parotid gland lying just before the mastoid processes. In order to avoid chewing difficulties, injections were applied after clinical detection of the masseter muscle (palpation). Botulinum toxin-A was applied with and without ultrasound guidance in 7 and 12 patients, respectively. All the patients were scored before and after the treatment, using the UPDRS salivation item and clinically followed in weekly intervals (0 = normal; 1 = slight but definite excess of saliva in mouth, may have night-time drooling; 2 = moderately excessive saliva, may have minimal drooling; 3 = marked excess of saliva with some drooling; 4 = marked drooling, requires constant tissue or handkerchief)

Results

Six patients (32%) did not respond at all, while 13 patients (68%) reported beneficial effect of BTX-A injection (change in drooling score ≥ 1 point). The sialorrhea scores before and after the treatment were 3.1 ± 0.1 (range 2-4) and 1.8 ± 0.1 (range 0-3), respectively ($t = 5.636$; $p < 0.001$). There was no difference in the magnitude of response between the groups with ($t = 4.500$; $p = 0.004$) and without ($t = 3.674$; $p = 0.005$) ultrasound control of injection sites (Table 2).

Table 1

Clinical and demographic characteristics of patients with sialorrhea

Number of patients	19
Male to female ratio	14:5
Age (years); ($\bar{x}$ ± SD)	62 ± 17 (24–77)
Diagnosis of patients with sialorrhea	
Parkinson's disease (n)	13
Pantothenate kinase-associated neurodegeneration (n)	2
Multiple system atrophy (n)	2
Wilson's disease (n)	1
Post-operative sialorrhea (endarterectomy) (n)	1

Table 2

Response to botulinum toxin A (BTX-A) injections in parotid glands in patients with sialorrhea

Patients	Responders : non-responders		*p*
	Before the treatment	After the treatment	
All patients (n = 19)	–	13 : 6	
With ultrasound control (n = 7)	–	5 : 2	
Without ultrasound control (n = 12)	–	8 : 4	
Scores on UPDRS ADL drooling item			
All patients (n = 19)*	3.1 ± 0.1 (2-4)	1.8 ± 0.1 (0-3)	< 0.001
With ultrasound control (n = 7)*	2.9 ± 0.9 (2-4)	1.6 ± 0.9 (0-3)	0.004
Without ultrasound control (n = 12)*	3.2 ± 0.4 (3-4)	2.0 ± 0.8 (0-3)	0.005

UPDRS ADL – Unified Parkinson's Disease Rating Scale Activities of Daily Living; *values present means ± SDs with ranges in parentheses.

The mean dose of BTX-A per session was 104 ± 28 U (range: 64-140 U). In 13 patients who had beneficial response, it lasted approximately 3 months (2.9 ± 1.1 months; range 1–5 months). The time of the appearance of clinically relevant response was 7.9 ± 5.5 days (range 1–21 days).

Adverse effects were registered in 5 patients (26%) with dry mouth and mild swallowing difficulties being the most frequent.

Discussion

Although we did not use a very sensitive scale, we found beneficial effect of BTX-A injections on sialorrhea in approximately two thirds of the patients (68%), which is in accordance with the estimates of 69%–90% of responders in the previous studies [10–12]. Lim et al. [3] analyzed studies that included > 16 patients and identified 4 controlled studies, three of them being double blind, and only two of them randomized [6–8, 10]. Two studies reported significant improvement of drooling after BTX-A injections, one study found significant improvement in physical appearance and ease of caring for subjects, and one found no improvement in either frequency or severity of drooling [6, 8, 12, 13]. Lagalla et al. [14] described good response in 88% of BTX-A treated patients in comparison with 31% of those receiving placebo. Time to beneficial effect (between one and 21 days) and mean duration of the effect in our study (2.9 months) were similar as in other studies [11, 15].

Some authors suggested that therapeutic success might be achieved by injecting only submandibular glands, while other authors preferred combined administration to submandibular and parotid glands [8, 10, 12]. However, no study compared efficacy when different targets were injected. In our study we exclusively injected BTX-A to easily approached parotid glands in order to preserve adequate submandibular production of saliva which was necessary for dental caries prevention [16].

Lipp et al. [6] conducted double-blind, placebo controlled study on the efficacy of 3 different doses of BTX-A (Botox®; Allergan) and recommended a dose of 75 U, which proved to be more efficaceous than the smaller doses (37.5 U and 18.75 U). Lagalla et al. [14] administered 50 U of Botox® in every parotid gland, similar to Ellies et al. [16] The doses of Dysport® we used per session (104 U) were comparatively lower. It has been suggested that the usage of higher doses might result in better and longer-lasting response, but methodological differences between studies (including differences in injection sites) made it impossible to recommend the optimal mode of BTX-A application for sialorrhea with certainty [6].

The response in the patients who were injected with ultrasound guidance and those who were not sonographically guided was not different in our study, which contrasted Shetty at al. [17] who were giving low doses of Botox® (15 U) in each submandibular gland and recommended application only under ultrasound guidance. This difference may reflect an easiness to access the parotid glands.

Different studies used different subjective (visual analogue scales, quality of life questionnaries) and objective measures (salivatory gland scintigraphy, weight change of dental rolls after 5 minutes discontinuation of swallowing) that were used to assess BTX-A efficacy in sialorrhea [6, 8, 14]. However, Lipp et al. [6] reported discrepancy between the objective decrease of saliva production or reduction of drooling and changes in the quality of life measures. Therefore, in this study we decided to use the simple salivation item of the UPDRS part II (Activities of Daily Living).

The main limitation of our study was its open-labelled design. However, we believe that our results are still valuable considering: a rather large number of patients with different neurological disorders associated with sialorrhea; response achieved by injecting only parotid glands, data suggesting no necessity for ultrasound guidance in such apporach.

Conclusion

According to the results obtained, we suggest that BTX-A injections to easily accessible parotid glands are safe and efficaceous treatment for sialorrhea in different neurological disorders.

Acknowledgments: This work was funded by the Ministry of Science, Republic of Serbia (Project no. 145057Đ).

REFERENCES

1. *Bateson MC, Gibberd FB, Wilson RS.* Salivary symptoms in Parkinson s disease. *Arch Neurol* 1973; 29(4): 274–5.
2. *Verma A, Steele J.* Botulinum toxin improves sialorrhea and quality of living in bulbar amyotrophic lateral sclerosis. Muscle Nerve 2006; 34(2): 235–7.
3. *Lim M, Mace A, Nouraei SA, Sandhu G.* Botulinum toxin in the management of sialorrhoea: a systematic review. Clin Otolaryngol 2006; 31(4): 267–72.
4. *Hockstein NG, Samadi DS, Gendron K, Handler SD.* Sialorrhoea: a management challenge. Am Fam Phys 2004; 69(11): 2628–34.
5. *Bushara KO.* Sialorrhea in amyotrophic lateral sclerosis: a hypothesis of a new treatment-botulinum toxin A injections of the parotid glands. Med Hypotheses 1997; 48(4): 337–9.
6. *Lipp A, Trottenberg T, Schink T, Kupsch A, Arnold G.* A randomized trial of botulinum toxin A for treatment of drooling. Neurology 2003; 61(9): 1279–81.
7. *Mancini F, Zangaglia R, Cristina S, Sommaruga MG, Martignoni E, Nappi G,* et al. Double-blind, placebo-controlled study to evaluate the efficacy and safety of botulinum toxin type A in the treatment of drooling in parkinsonism. Mov Disord 2003; 18(6): 685–8.
8. *Ondo WG, Hunter C, Moore W.* A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. Neurology 2004; 62(1): 37–40.
9. *Fahn S, Elton R.* Unified Parkinson's Disease Rating Scale. *In: Fahn S, Marsden C, Goldstein M, Calne D,* eds. Recent Developments in Parkinson's disease, vol 12. Florham Park:

New York MacMillan Healthcare Information 1987; 11: 153–163.

10. *Jongerius PH, Rotteveel JJ, van Limbeek J, Gabreëls FJ, van Hulst K, van den Hoogen FJ.* Botulinum toxin effect on salivary flow rate in children with cerebral palsy. Neurology 2004; 63(8): 1371–5.
11. *Porta M, Gamba M, Bertacchi G, Vaj P.* Treatment of sialorrhoea with ultrasound guided botulinum toxin type A injection in patients with neurological disorders. J Neurol Neurosurg Psychiatry 2001; 70(4): 538–40.
12. *Suskind DL, Tilton A.* Clinical study of botulinum-A toxin in the treatment of sialorrhea in children with cerebral palsy. Laryngoscope 2002; 112(1): 73–81.
13. *Hassin-Baer S, Scheuer E, Buchman AS, Jacobson I, Ben-Zeev B.* Botulinum toxin injections for children with excessive drooling. J Child Neurol 2005; 20(2): 120–3.
14. *Lagalla G, Millevolte M, Capecci M, Provinciali L, Ceravolo MG.* Botulinum toxin type A for drooling in Parkinson's disease: a double-blind, randomized, placebo-controlled study. Mov Disord 2006; 21(5): 704–7.
15. *Vaile L, Finlay F.* Is injection of botulinum toxin type A effective in the treatment of drooling in children with cerebral palsy? Arch Dis Child 2006; 91(10): 862–3.
16. *Ellies M, Laskawi R, Rohrbach-Volland S, Arglebe C, Beuche W.* Botulinum toxin to reduce saliva flow: selected indications for ultrasound-guided toxin application into salivary glands. Laryngoscope 2002; 112(1): 82–6.
17. *Shetty S, Daves P, Ruske D, Al-Qudah M, Lyons B.* Botulinum toxin type-A (Botox-A) injections for treatment of sialorrhea in adults: a New Zealand study. *N Z Med J* 2006; 119(1240): U2129.

The paper received on February 21, 2008.

ORIGINAL ARTICLE UDC: 616.89–008.441.9:159.944.4

Predicting violence in veterans with posttraumatic stress disorder

Predviđanje nasilnog ponašanja veterana sa posttraumatskim stresnim poremećajem

Aleksandar A. Jovanović*, Dušica Lečić Toševski†, Maja Ivković*, Aleksandar Damjanović*, Miroslava Jašović Gašić*

Clinical Centre of Serbia, *Institute of Psychiatry, **Belgrade;**
†Institute of Mental Health, Belgrade

Abstract

Background/Aim. Frequent expression of negative affects, hostility and violent behavior in individuals suffering from posttraumatic stress disorder (PTSD) were recognized long ago, and have been retrospectively well documented in war veterans with PTSD who were shown to have an elevated risk for violent behavior when compared to both veterans without PTSD and other psychiatric patients. The aim of this study was to evaluate the accuracy of clinical prediction of violence in combat veterans suffering from PTSD. **Methods.** The subjects of this study, 104 male combat veterans with PTSD were assessed with the Historical, Clinical and Risk Management 20 (HCR-20), a 20-item clinician-rated instrument for assessing the risks for violence, and their acts of violence during one-year follow-up period were registered based on bimonthly check-up interviews. **Results.** Our findings showed that the HCR-20, as an actuarial measure, had good internal consistency reliability (α = 0.82), excellent interrater reliability (Interaclass Correlation ICC = 0.85), as well as excellent predictive validity for acts of any violence, non-physical violence or physical violence in the follow-up period (AUC = 0.82–0.86). The HCR-20 also had good interrater reliability (Cohen's kappa = 0.74), and acceptable predictive accuracy for each outcome criterion (AUC = 0.73–0.79). **Conclusion.** The results of this research confirm that the HCR-20 may also be applied in prediction of violent behavior in the population of patients suffering from PTSD with reliability and validity comparable with the results of previous studies where this instrument was administered to other populations of psychiatric patients.

Key words:
stress disorders, post-traumatic; risk assessment; veterans; predictive value of tests; aggression.

Apstrakt

Uvod/Cilj. Često ispoljavanje negativnog afekta, neprijateljskog i nasilnog ponašanja kod osoba sa posttraumatskim stresnim poremećajem (PTSP) odavno je uočeno i posebno dobro dokumentovano kod ratnih veterana kod kojih je uočen povišen rizik od nasilnog ponašanja u odnosu na veterane bez PTSP i druge psihijatrijske bolesnike. Cilj ove sudije bio je da se izvrši klinička procena rizika od nasilnog ponašanja kod učesnika rata sa PTSP. **Metode.** Ispitanici ove studije, 104 veterana muškog pola sa PTSP procenjivani su instrumentom strukturisane kliničke procene rizika od nasilnog ponašanja *Historical, Clinical and Risk Management* 20 (HCR-20), a ispoljavanje nasilnog ponašanja praćeno je tokom jednogodišnjeg perioda, u okviru kontrolnih pregleda na svaka dva meseca. **Rezultati.** Sa stanovišta aktuarijalne procene, HCR-20 je imao dobru internu konzistenciju (α = 0,82), odličnu saglasnost između ispitivača (ICC = 0,85), kao i odličnu prediktivnu vrednost u pogledu ispoljavanja nasilnog ponašanja (fizičko ili nefizičko nasilje) u toku jednogodišnjeg perioda praćenja (AUC = 0,82–0,86), što je u skladu sa psihometrijskim svojstvima ustanovljenim u drugim studijama. Sa stanovišta strukturisane kliničke procene rizika (nizak, srednji ili visok), saglasnost među ispitivačima u pogledu HCR-20 bila je dobra (*Kohen*ov kapa koeficijent = 0,74), a prediktivna tačnost prihvatljiva (AUC = 0,73–0,79). **Zaključak.** Rezultati istraživanja potvrđuju da se HCR-20 može koristiti za predviđanje nasilnog ponašanja kod populacije obolelih od PTSP sa pouzdanošću i vrednošću koju je imao u ranijim studijama, kada je primenjivan na drugim populacijama psihijatrijskih bolesnika.

Ključne reči:
stresni poremećaji, posttraumatski; rizik, procena; veterani, ratni; testovi, prognostička vrednost; agresivnost.

Introduction

Though clinicians have traditionally assessed violence risk on an individual basis, using unstructured or unaided clinical judgment (which has frequently been criticized for being impressionistic and subjective), the prediction of violence has substantially improved over the last decades thanks to the development of various systematic violence risk assessment schemes such as the Dangerous Behavior Rating Scale (DBRS), the Psychopathy Checklist-Revised (PCL-R),

Correspondence to: Dušica Lečić Toševski, Institute of Mental Health, Palmotićeva 37, 11 000 Belgrade, Serbia. Tel.:+381 11 32 38 160. E-mail: dusica.lecictosevski@eunet.rs

the Violence Risk Appraisal Guide, the Historical, Clinical and Risk Management 20 (HCR-20), and the Classification of Violence Risk (COVR) [1–6]. These divergent approaches have resulted in different views to the relative contribution of clinical items in risk prediction scales as well as in debate over the merits of clinical vs. actuarial approaches and their relevance to risk prediction [7].

The actuarial prediction procedure has been described as a formal or algorithmic method that uses an equation, a formula, or an actuarial table to arrive at a probability, or expected value, of some outcome [8]. While this approach has generally improved the reliability and validity of risk assessment, its clinical application has certain limitations because it tends to ignore individual variations in risk, overfocuses on relatively static (demographic) variables (in large, frequently heterogeneous populations), fails to consider clinically relevant variables and minimizes the importance of clinical assessment [9]. On the other hand, a model of decision making called the "structured professional judgment model" or "structured clinical judgment model" of risk assessment has emerged in recent years and has produced a number of assessment schemas well as comprehensive reviews [10–15]. This model is based on empirical knowledge and clinical expertise, and defines the levels of risk for violence such as risk judgments of low, moderate, and high risk after a systematic consideration of a standard set of operationally defined risk factors.

A significant step in bridging the gap between clinical and actuarial measures was the development of the HCR-20, which adopted a combined approach and recognized the importance of both static actuarial variables and the clinical/risk management items that clinicians normally take into account in risk assessments of individuals. The studies of reliability and validity of the HCR-20 have covered large samples of forensic psychiatric patients, involuntarily hospitalized civil psychiatric patients, correctional settings, and mixed samples of correctional offenders and forensic patients [16–26]. Hence, the important issue of extending practical application of the HCR-20 to the domain of other psychiatry populations, such as voluntarily hospitalized patients or outpatients where clinical picture may also present with affect dysregulation and hostility, still requires further research [27].

Affect dysregulation is possibly the most far-reaching effect of psychological trauma underlying significant impairment in the regulation of anger, anxiety and sexual impulses of people with severe psychotraumas [28, 29]. Frequent expression of negative affects, hostility and violent behavior in individuals suffering from posttraumatic stress disorder (PTSD) were recognized long ago, and have been retrospectively well documented in war veterans, who were shown to have an elevated risk for violent behavior when compared to both veterans without PTSD and other psychiatric patients [30–39]. Given that a prospective research on predicting violent behavior in PTSD survivors with a systematic violence risk assessment scheme is undoubtedly relevant yet underresearched topic, the primary objective of our study was to assess the accuracy of violence prediction based on the HCR-20 in a treatment seeking sample of veterans suffering from PTSD, a population which has not yet been specifically examined with this instrument.

Methods

The sample consisted of 104 male veterans engaged previously in reserve forces of the former Yugoslav Army during armed conflicts in ex-Yugoslavia (after 1990). The subjects of this study were consecutively recruited at the Institute of Psychiatry and Institute of Mental Health, Belgrade in the period 1998 – 2002 among outpatients who were suffering from combat-related chronic PTSD and willing to participate in the study. The subjects were diagnosed according to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Axis I Disorders (SCID-I) [40], and the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) [41]. Written informed consent was obtained from all the subjects, and the results obtained were kept confidential.

All the subjects were assessed with the HCR-20, a 20-item clinician-rated instrument for assessing the risks for violence. The HCR-20 was developed from a detailed consideration of the previous studies concerning factors related to violence. It contains 20 items, each scored "0" (*no/absent*), "1" (*partially/possibly present*), or "2" (*yes/definitely present*) and divided into three subscales - Historical, Clinical and Risk Management. The ten Historical items (*Previous Violence, Young Age at First Violent Incident, Relationship Instability, Substance Use Problems, Major Mental Illness, Psychopathy, Early Maladjustment, Personality Disorder, Prior Supervision Failure*) correspond to risk factors for violence in the past. The five Clinical items (*Lack of Insight, Negative Attitudes, Active Symptoms of Major Mental Illness, Impulsivity, Unresponsive to Treatment*) reflect current correlates of violence. The five Risk Management items (*Plans Lack Feasibility, Exposure to Destabilizers, Lack of Personal Support, Noncompliance with Remediation Attempts, and Stress*) focus attention on situational factors that may influence risk for violence in the future. For each of the items the HCR-20 manual provides both a precise definition and detailed information on scoring procedure based on a semistructured interview. For research purposes, it is possible to use the HCR-20 as an actuarial scale and simply sum the numeric item codes to obtain total and subscale scores. For clinical purposes, the authors of the HCR-20 recommend that assessors make a "final risk judgment", i.e. final decision regarding risk for violence using a 3-point scale. Here, "low" indicates that the assessor believe that individual is at no risk, or very low risk, for violence; "moderate" indicates that the assessor believes the individual is at somewhat elevated risk for violence; and "high" indicates that the assessor believes the individual is at high or very elevated risk for violence.

The Screening Version of the Hare Psychopathy Checklist-Revised (PCL:SV), a 12-item symptom-construct rating scale based on a semistructured interview, was also completed for all the subjects in order to code the seventh item on the Historical subscale of the HCR-20 which refers

to psychopathy [42]. The PCL: SV is divided into two parts (each comprising of six items and each scored using a 3-point ordinal scale). One section of the PCL: SV deals with affective/interpersonal symptoms of psychopathy and the other with social deviance symptoms.

For the purpose of this study, two raters, specialists in neuropsychiatry completed research protocols for 104 subjects containing anamnestic data, psychiatric diagnoses, and the assessment with the HCR-20 and the PCL: SV. Each rater completed 78 protocols randomly assigned with an overlap of 50% to permit interrater reliability analyses for the HCR-20 and PCL: SV. Acts of violence during one-year follow-up period were recorded based on bimonthly check-up interviews lasting 30-45 minutes (supplemented by clinical records from treating psychiatrists and when available by information from close persons, social workers and judicial files) made by assessors who were not informed about the results for the HCR-20 risk assessments. Violent acts in this study were defined as deliberate and nonconsensual acts of actual, attempted or threatened harm to other persons, and regardless of severity divided into categories of any violence, physical violence and non-physical violence, which is consistent with the approaches used in other risk assessment studies.

Reliability analyses of the HCR-20 and PCL:SV comprised the evaluation of internal consistency reliability and interrater reliability. In order to investigate the relationship between HCR-20 scores and violence, three different analyses are reported: (a) Receiver Operating Characteristic (ROC) analyses for all subscales and the total scale, (b) cross tabs for the HCR-20 "final risk judgment" (low/moderate/high) and (c) results of a logistic regression analysis with all the items of the HCR-20 as predictor variables. With respect to the HCR-20 and PCL: SV as actuarial measures, a reliability analysis comprised the evaluation of internal consistency reliability in terms of Cronbach Alpha and interrater reliability in terms of Intraclass Correlation (ICC) [43, 44]. A one-way random-effects model of the ICC was used for both the reliability of single-rater ratings (ICC1) and averaged ratings (ICC2).

Results

The mean age of the subjects was 35 years (SD = 10.2). They were mostly married, having children, completed secondary education, employed and possessed fire-arms which is shown in Table 1.

Anamnestic data on the subjects and psychiatric comorbidity where substance use disorder was the most frequent (30%) comorbid diagnosis are shown in Table 2.

Seventy (67%) subjects committed at least one violent act in the one-year follow-up period while 63 (61%) committed non-physical violence in a sense of threatening or fear-inducing behaviour, 58 (56%) perpetrated physical violence, and nine (8%) were charged with violent criminal offences. Among the subjects who possessed firearms, 25 (24%) manifested dangerous firearm-related behaviour (threatening with a gun) in the follow-up period.

The Table 3 presents the central tendencies, dispersions, internal consistency reliability and interrater reliability of the HCR–20 (and its respective subscales) and the PCL: SV.

Receiver Operating Characteristic Analysis was conducted to evaluate the accuracy of sum of raw scores on the HCR-20 and its subscales as well as the PCL: SV in predicting the three violence categories, i.e. any violence, non-physical violence, and physical violence (Table 4). Receiver Operating Characteristic analysis is independent of the criterion base rate and is graphically presented with an "area under curve" (AUC) produced by plotting sensitivity and specificity pairs for each possible cut-off score on a measure.

Table 1
Sociodemographic data of the subjects

Characteristics	Subjects	
	n	(%)
Married	74	71
Number with children	53	51
Secondary educated	69	66
Employed	80	77
Possession of firearms	64	61

Table 2
Anamnestic data and psychiatric comorbidity of the subjects

Characteristics	Subjects	
	n	(%)
Mental disorders in the family	26	25
Juvenile criminal record	2	2
Past violent charge	7	7
Past violent conviction	5	5
Adult psychiatric treatment before PTSD*	15	14
Previous inpatient treatment	43	41
Substance use disorder	31	30
Mood disorder	9	9
Organic disorder	8	7
Personality disorder	17	16

*Posttraumatic stress disorder

Table 3

Descriptive characteristics, internal consistency reliability and interrater reliability of the History, Clinical, and Risk Management 20 (HCR–20) and the Screening Version of the Hare Psychopathy Check list (PCL: SV)

Measure (range)	Mean	Standard error	Standard deviation	Alpha	ICC_1† (CI)‡	ICC_2§ (CI)
HCR-20 total score (0-40)	11.33	0.56	5.72	0.82	0.95 (0.92–0.97)	0.97 (0.96–0.98)
Historical subscale (0-20)	3.71	0.33	3.38	0.82	0.96 (0.93–0.98)	0.98 (0.96–0.99)
Clinical subscale (0-10)	4.89	0.16	1.60	0.53	0.75 (0.60–0.85)	0.85 (0.75–0.92)
Risk Management subscale (0-10)	2.72	0.20	2.05	0.50	0.88 (0.80–0.93)	0.93 (0.89–0.96)
PCL:SV total score (0-24)	6.60	0.55	5.65	0.88	0.88 (0.81–0.93)	0.94. (0.89–0.96)

* Cronbach Alpha coefficient of internal consistency reliability (for 104 subjects); †single-measure intraclass correlation coefficient (for 52 overlapping subjects); ‡95% confidence interval; §average-measure intraclass correlation coefficient (for 52 overlapping subjects)

Table 4

Area under the receiver operating characteristic curves (AUC) for the History, Clinical and Risk Management 20 (HCR-20) and The Screening Version of the Hare Psychopathy Cheeklist (PCL:SV) in 104 veterans with posttraumatic stress disorder

Measure	Any violence*			Non-physical violence†			Physical violence‡		
	Mean	SE§	CI‖	Mean	SE	CI	Mean	SE	CI
HCR-20 total score (0–40)	0.85	0.04	0.78–0.92	0.82	0.04	0.74–0.90	0.86	0.04	0.79–0.93
Historical subscale (0–20)	0.83	0.04	0.75–0.90	0.81	0.04	0.72–0.89	0.86	0.04	0.79–0.93
Clinical subscale (0–10)	0.70	0.05	0.60–0.80	0.70	0.05	0.60–0.80	0.73	0.05	0.63–0.82
Risk Management subscale (0–10)	0.71	0.05	0.61–0.81	0.69	0.05	0.58–0.78	0.69	0.05	0.59–0.79
PCL: SV	0.82	0.04	0.74–0.90	0.80	0.04	0.71–0.88	0.87	0.03	0.81–0.94

*The HCR-20 optimal cut-off score of ≥ 10 corresponds to 0.73 specificity, 0.82 sensitivity and 0.75 hit rate;
† The HCR-20 optimal cut-off score of ≥ 10 corresponds to 0.75 specificity, 0.76 sensitivity and 0.75 hit rate;
‡ The HCR-20 optimal cut-off score of ≥ 10 corresponds to 0.83 specificity, 0.80 sensitivity and 0.82 hit rate;
§ Standard error;
‖ 95% Confederence interval.

Subsequently, if the AUC is significantly different from 0.50, it represents an improvement over chance in the prediction of a given outcome. Theoretical value of the AUC could range from zero to one, and for the propensity scores for any reasonable predictive model or diagnostic test, the AUC does not assume values below 0.5. In general: 1) $0.5 < AUC < 0.7$ suggests poor discrimination; 2) $0.7 < AUC < 0.8$ suggests an acceptable discrimination; 3) $0.8 < AUC < 0.9$ suggests an excellent discrimination, and 4) $AUC > 0.9$ suggests outstanding discrimination. According to our research findings, AUC values were statistically significant for each outcome criterion (any violence, non-physical violence or physical violence) and ranged from 0.69 to 0.86, as shown in Table 4. The diagnostic efficiency of the HCR-20 total score in terms of specificity (probability of correctly predicting a case as violent), sensibility (probability of correctly identifying a case as not violent) and hit rate (probability of accurate prediction) across the three categories of violence are presented in Table 4.

Another approach to violence risk assessment in this study was based on a structured clinical judgment model. In that sense, the raters reviewed all relevant clinical data to determine the presence of specific risk factors as operationalized in the HCR-20 risk assessment manual. Overall judgments of risks were low, moderate, or high, according to raters' estimates of the likelihood of violent behavior. Agreement between raters for the violence risk judgments on the HCR-20 is summarized in Table 5. The two raters agreed in 46 (88%) of the 52 overlapping patients, and there were no low/high-risk errors. Cohen's kappa was 0.78 (Asymp. Std. Error = 0.10, $p = 0.00$) and Chance-corrected agreement (Intraclass Correlation, ICC1, or weighted kappa) was 0.88, ($p = 0.00$, 95% confidence interval = 0.78–0.93).

The frequencies and proportions of each type of violence across the HCR-20 Final Risk Judgment levels (low, moderate, and high risk) are shown in Table 6. According to ROC analysis, the AUC values for the HCR-20 Final Risk Judgment were statistically significant for each outcome criterion (any violence, non-physical violence or physical violence) and varied between 0.73 and 0.79, as can be seen in Table 6.

Table 5

Agreement between two rates for structured final violence risk judgements on the History, Clinical and Risk Management in 52 subjects

	Rater B			
Rater A	Low Risk	Moderate Risk	High Risk	$Total_A$
Low Risk	18	3	0	21
Moderate Risk	1	14	1	16
High Risk	0	4	11	15
$Total_B$	19	21	12	52

Table 6

Committed violence across levels of structured clinical risk judgments for 104 subjects based on the History Clinical and Risk Management 20 (HCR-20)

HCR-20 Final Risk Judgment		Any violence*			Non-physical violence†			Physical violence‡		
		No	Yes	Total	No	Yes	Total	No	Yes	Total
Low Risk	Count	26	18	44	27	17	44	31	13	44
	%	59	41	100	61	39	100	59	41	100
Moderate Risk	Count	7	26	33	11	22	33	11	22	33
	%	21	79	100	33	67	100	21	79	100
High Risk	Count	1	26	27	3	24	27	4	23	27
	%	4	96	100	11	89	100	15	85	100

*Receiver Operating Characteristic analysis for the HCR-20 Final Risk Judgment: area under curve = 0.79; 95% confidence interval = 0.70 – 0.88
† Receiver Operating Characteristic analysis for the HCR-20 Final Risk Judgment: area under curve = 0.73; 95% confidence interval = 0.64 – 0.83
‡ Receiver Operating Characteristic analysis for the HCR-20 Final Risk Judgment: area under curve = 0.76; 95% confidence interval = 0.66 – 0.85

For each of the three categories of violence (dependent variable) a logistic regression analysis (Table 7) was performed for identifying the HCR-20 items (independent variables), which proved significant predictors of violence. In logistic regression we estimated probability (Prob) of an event occurring which can be written as Prob = $1/(1+e^{-Z})$, where Z equals $B_0 + B_1X_1 + B_2X_2 + ...B_nX_n$. B_{0-n} are logistic coefficients estimated from the data. X1-n are independent variables, and e is the base of the natural logarithms (approximately 2.72). If the estimated probability of the event was greater than 0.5, we predicted that the event will occur, and if the probability is less than 0.5 that the event will not occur. One way to asses how our model fits is to compare our predictions to the observed outcomes. In that respect, for any violence the model correctly predicted 80% of cases. For non-physical violence it was 81% and for physical violence 80%. As can be seen from Table 7 (values of logistic coefficient B and ExpB), the first item (Previous Violence) on the HCR-20 was the one which was the most strongly associated with each of the three categories of violence.

Discussion

Our findings regarding the internal consistency reliability, interrater reliability and predictive validity of the HCR-20, as an actuarial measure for predicting violence among veterans suffering from PTSD, indicate solid psychometric properties of this instrument which are comparable to the results of previous studies where this instrument was administered to populations of psychiatric patients such as forensic psychiatric patients discharged from security units, involuntarily hospitalized civil psychiatric patients, correctional offenders and mixed samples of correctional offenders and forensic patients mainly suffering from psychotic disorders, substance use disorders and personality disorders. The Cronbach Alpha, ICC and AUC for the HCR-20 subscales have shown that the H subscale proved far better than Clinical and Risk Menagement subscales, which is in accordance with other findings showing that previous history of violence is the best single predictor of future violence. Though the ICC_2 was used to show the potential reliability of averaged ratings,

Table 7

Parameter estimates in logistic regression analyses (at the final step) for identifying the History, Clinical and Risk Management (HCR-20) items those proved significant predictors of violence in 104 male veterans

Variables in the equation for any violence	B*	SE†	Wald‡	df§	*p*‖	Exp(B)¶
Lack of personal support the third item on the Risk Management subscale R of the HCR-20	0.871	0.361	5.816	1	0.016	2.389
Previous violence the first item on the Historical/subscale of the HCR-20 (H1)	3.654	1.097	11.103	1	0.001	38.642
Stress (fifth item on the R)	0.954	0.400	5.686	1	0.017	2.597
Constant	–1.331	0.482	7.608	1	0.006	0.264
Variables in the equation for nonphysical violence	B*	SE†	Wald‡	df§	*p*‖	Exp(B)¶
Lock of personal support (third item on the R)	0.984	0.349	7.943	1	0.005	2.676
Previous violence (H1)	2.557	0.644	15.769	1	0.000	12.898
Unresponsive to treatment (fifth item on the Clinical subscale of the HCR-20)	0.780	0.381	4.198	1	0.040	2.182
Constant	–1.249	0.386	10.447	1	0.001	0.287
Variables in the equation for physical violence	B*	SE†	Wald‡	df§	*p*‖	Exp(B)¶
Lack of insight (the first item on the Clinical subscale of the HCR-20)	1.348	0.467	8.348	1	0.004	3.851
Previous violence (H1)	2.342	0.628	13.923	1	0.000	10.398
Stress (fifth item on the R)	0.865	0.395	4.788	1	0.029	2.374
Constant	–2.102	0.557	14.223	1	0.000	0.122

*logistic coefficient; †standard error of B; ‡Wald statistics; §degree of freedom; ‖significance of B; ¶the change in odds of a violence occurring associated with one-unit change in the independent variable.

the ICC_1 was considered the primary index of reliability for two reasons. Firstly, all findings on the HCR-20 (apart from those regarding interrater reliability) reported here are exclusively based on ratings made by a single rater. Secondly, the application of the HCR-20 in clinical settings will most likely only use single raters and not the average score from several independent raters. Therefore, only the single-rater ICC appears relevant for this measure at all and the naturally higher averaged ratings ICC might be misleading.

The most important type of information needed to evaluate the predictive efficiency of the HCR-20 as an actuarial measure was about its sensitivity, specificity and overall hit rate. However, a consideration of these results led us to a less optimistic evaluation of the measure. Here, only for physical violence it was possible to specify a cutoff score (Table 3) that would maintain every aspect of predictive efficiency above 0.8.

The AUC values in the scope of this study simply show probability that a violent person will receive a higher score on the predictor variable (HCR-20, PCL: SV) than a non-violent person. Here, it may be useful to include information about discrimination levels for the AUC [45, 46].

With regard to the structured clinical judgment model, both the agreement of raters for final risk judgments and the predictive validity of the HCR-20 for each of the three types of violence proved to be acceptable. Though the results for the final risk judgment reported in Table 5 indicate that the measure has acceptable predictive accuracy (AUC ranged from 0.73 to 0.79) and a high specificity (i.e. a large majority of individuals categorized as "high risk" showed violent events in the future), the sensitivity appears to be poor (i.e. 41% of the subjects classified as "low risk" committed any violence in the follow-up interval). This unfavorable feature of the instrument obviously needs to be improved, which may be accomplished with a structured interview that could lead to a more reliable formulation of final risk judgment levels.

Although psychopathy is a vital component of any violence risk assessment, it is considered to occur less frequently out of correctional or forensic psychiatric settings. Actually, we did not focus attention on psychopathy as a violence predictor, and PCL: SV was not considered a risk assessment measure but rather a screening test for the diagnosis of psychopathy as one of the violence risk factors assessed with the HCR–20. Still, psychopathy, as measured by the he PCL: SV total score was found to have the predictive validity that could be compare with that of the HCR–20 total score. This might suggest a possible direction for future research with a more comprehensive assessment instrument such as PCL-R.

The final goal of accurate and reliable assessment of risk factors is to establish the best interventions likely to ameliorate the risk of violent behaviour and its negative consequences [47]. As Monahan et al.[6] emphasised, "for a successful management of violence multiple targets for intervention would exist, and they will differ from person to person". In this respect, our findings concerning relative contribution of specific factors in assessing violence risk in veterans with PTSD have several clinical implications. As expected, "Previous Violence" (the first of Historical factors) was the most strongly associated with each of the three categories of violence detected in the veterans with PTSD in the follow-up period. Rather than causal, this factor is referred to as a violence risk marker with a strong predictive power due to a high correlation with other causal risk factors [48]. The first item on Historical subscale can change in time only for the worse, i.e. when someone previously non-violent commits an act of violence or escalates it. Consequently, management decisions based on the presence of this factor need to be made only after careful consideration of the nature of previous violence and seriousness of any recidivism. Our finding of a high frequency of firearms possession (61%) and consequent firearm-related impulsive behavior (24%) in the follow-up period is in accordance with earlier studies pointing to high levels of aggression, impulsive weapon use, and weapon availability as significant factors in gun-related violence in veterans with PTSD. The possession of firearms in our subjects was six times higher than in adult population in Serbia where, according to official information of the Ministry of Internal Affairs, firearms are in legal possessions of 11% of adult citizens. On the other hand, according to the recent findings of Fontana and Rosenheck [49], veterans of the Iraq and Afghanistan wars when compared with veterans who served in the Persian Gulf war and in the Vietnam war manifested significantly more violent behavior which implies a substantial need for violence risk assessment in developing treatment interventions that focus on the preservation of social assets in veterans of contemporary wars.

According to our findings, "Lack of Insight" (the first item on the Clinical subscale) and "Unresponsive to Treatment" fifth item on the Clinical subscale of the Clinical scale, as well as "Lack of Personal Support" (the third) and "Stress" (fifth item of the Risk Management subscale on the HCR-20), also proved to be closely related to future violent behavior in the subjects. Contrary to the Historical items, the Clinical and Risk Management items on the HCR-20 are usually referred to as dynamic violence risk factors because they not only relate to violence, but also may significantly fluctuate with time and circumstances and hence be targeted for violence reducing strategies [50].

A lack of insight generally refers to a lack of person's self-perception of being dangerous and incapacity to understand the importance of doing something about it [51]. Our subjects had difficulties to overcome discrepancies between military and civilian reality, which resulted in overlooking the inadequacy and dangerousness of their military skills in civilian context [52, 53]. On several occasions, we could hear them say that aggression was "what they were taught in order to survive", that civilians were "just a collateral damage", and that "ordinary people without war experience can't understand them", or even, that others may be classified into "people and civilians". Therefore, developing insight in psychotherapy with veterans seems to be an important hence delicate clinical issue, which refers to both the therapeutic relationship and patient's motivation to develop awareness and readiness to change [54, 55]. On the other

hand, the "Unresponsive to Treatment" deals with the extent to which an individual responds to interventions and programs and there are varieties of factors that have an effect on this multidimensional concept [56, 57]. Most of our subjects were treated with a combination of medication (mostly combination of selective serotonin reuptake inhibitors antidepressants and benzodiazepines) and psychotherapy (mostly individual cognitive-behavior therapy and less frequently family therapy). We would like to stress that frequent comorbid disorders in veterans such as major depression, organic impairment, severe intoxication with substances or alcohol, or profound personality pathology interfered with psychotherapeutic and behavioral interventions. In general, once the violence risk is established, the efficiency of interventions that might ameliorate outcome should always be most seriously taken into consideration and carefully monitored.

The lack of personal support related to violence in our subjects generally reflected the absence of a reliable support system of peers and relatives. It is of particular practical importance since it has been shown that both family adaptive resources and social support network serve as strong buffers which alleviate life difficulties and, consequently, facilitate social adjustment and adaptation in persons suffering from chronic PTSD [58–62]. In that respect, there was a striking discrepancy between what was necessary and what was actually provided to our subjects and their deeply troubled families. Numerous studies, have also shown that stress increases the likelihood of aggressive behavior and our findings obviously support this relationship [28–39, 63, 64]. Much more difficult than helping veterans with PTSD to learn how to identify situations that would be stressful, was to help them arrange living and working environment which would include as few of these situations as possible. Namely, after they had been dismissed from the army, they found the situation to be particularly stressful at home due to numerous problems produced by an extremely turbulent transition period in a former socialist country (poverty, social conflicts, decline of social institutions and health care system) as well as a criticism of war by common people. In general, the results of our study provide a strong evidence base that the HCR-20 as an actuarial measure is a reliable and valid predictor of violent behavior in veterans suffering from PTSD. However, a consideration of our results regarding predictive validity of the HCR-20, in terms of structured clinical judgment approach, led us to a less optimistic evaluation of the diagnostic utility of the instrument. Among specific risk factors involved in the HCR-20 assessment scheme, previous violence, the lack of insight, unresponsiveness to treatment, the lack of personal support and stressful environment proved to be strongly associated with violent behavior detected in the follow-up period. A strong association established between violence and the lack of insight, unresponsiveness to treatment, the lack of personal support and stressful environment was of particular practical significance for our clinical practice because it pointed at critical issues of violence management strategies to help individuals undergoing treatment for PTSD.

At least two substantial limitations of our study should be noted. Firstly, the findings presented in this paper may not be generalizable to a general or forensic population, given that the sample consisted of a male treatment-seeking veterans. Secondly, it would be also useful to establish a relationship between current symptoms of PTSD, treatment efficiency and violence at each of the assessments in the follow-up interval. These important issues were beyond the scope and design of this study and deserve to be addressed by further research.

Conclusion

The results of this research confirm that the HCR-20 may also be applied in prediction violent behavior in the population of patients suffering from PTSD with reliability and validity comparable with the results of previous studies where this instrument was administered to other populations of psychiatric patients.

REFERENCES

1. *Stone MH*. Prediction of violent recidivism. Acta Psychiatr Scand Suppl 2002; (412): 44–6.
2. *Menzies RJ, Webster CD, Sepejak DS*. The dimensions of dangerousness: Evaluating the accuracy of psychometric predictions of violence among forensic patients. Law and Human Behavior 1985; 9: 49–70.
3. *Hare RD, Harpur TJ, Hakstian AR, Forth AE, Hart SD, Newman JP*. The revised psychopathy checklist: Reliability and factor structure. Clin Consult Psychol 1990; 2(2): 338–41.
4. *Rice ME, Harris GT*. Violent recidivism: assessing predictive validity. J Consult Clin Psychol 1995; 63(5): 737–48.
5. *Webster CD, Douglas KS, Eaves D, Hart SD*. HCR-20: Assessing the Risk for Violence. Version 2. Burnaby BC, Canada: Mental Health, Law, and Policy Institute, Simon Fraser University; 1997.
6. *Monahan J, Steadman HJ, Robbins PC, Appelbaum P, Banks S, Grisso T*, et al. An actuarial model of violence risk assessment for persons with mental disorders. Psychiatr Serv 2005; 56(7): 810–5.
7. *Dolan M, Doyle M*. Violence risk prediction. Clinical and actuarial measures and the role of the Psychopathy Checklist. Br J Psychiatry 2000; 177: 303–11.
8. *Grove WM, Meehl PE*. Comparative efficiency of informal (subjective, impressionistic) and formal (mechanical, algorithmic) prediction procedures: The clinical-statistical controversy. Psychology, Public Policy, and Law 1996; 2(2): 293–323.
9. *Hart SD*. The role of psychopathy in assessing risk for violence: Conceptual and methodological issues. Legal and Criminological Psychology 1998; 3: 121–37.
10. *Boer DP, Hart, SD, Kropp PR, Webster CD*. Manual for the sexual violence risk—20: Professional guidelines for assessing risk of sexual violence.Vancouver, Canada BC: British Columbia Institute Against Family Violence; 1997.
11. *Kropp PR, Hart SD*. The Spousal Assault Risk Assessment (SARA) Guide: reliability and validity in adult male offenders. Law Hum Behav 2000; 24(1): 101–18.

12. *Borum R.* Improving the clinical practice of violence risk assessment. Technology, guidelines, and training. Am Psychol 1996; 51(9): 945–56.
13. *Otto RK.* Assessing and managing violence risk in outpatient settings. J Clin Psychol 2000; 56(10): 1239–62.
14. *Douglas KS, Kropp PR.* A prevention-based paradigm for violence risk assessment: Clinical and research applications. Criminal Justice and Behavior 2002; 29: 617–58.
15. *Douglas KS.* HCR-20 violence risk assessment scheme: Overview and annotated bibliography [On-line]. Available from http://www.sfu.ca/psychology/groups/faculty/hartviolink.htm; 2002.
16. *Dernevik M.* Preliminary findings on reliability and validity of the Historical-Clinical-Risk Assessment in a forensic psychiatric setting. Psychology, Crime, and Law 1998; 4: 127–37.
17. *Belfrage H.* Implement the HCR-20 scheme for risk assessment in a forensic psychiatric hospital: Integrating research and clinical practice. Journal of Forensic Psychiatry 1998; 9: 328–38.
18. *Douglas KS, Ogloff JR, Hart SD.* Evaluation of a model of violence risk assessment among forensic psychiatric patients. Psychiatr Serv 2003; 54(10): 1372–9.
19. *Gray NS, Taylor J, Snowden RJ.* Predicting violent reconvictions using the HCR-20. Br J Psychiatry 2008; 192(5): 384–7.
20. *Douglas KS, Ogloff JR, Nicholls TL, Grant I.* Assessing risk for violence among psychiatric patients: the HCR-20 violence risk assessment scheme and the Psychopathy Checklist: Screening Version. J Consult Clin Psychol 1999; 67(6): 917–30.
21. *McDermott BE, Edens JF, Quanbeck CD, Busse D, Scott CL.* Examining the role of static and dynamic risk factors in the prediction of inpatient violence: variable- and person-focused analyses. Law Hum Behav 2008; 32(4): 325–38.
22. *Belfrage H, Franson G, Strand S.* Prediction of violence using the HCR-20: A prospective study in two maximum-security correctional institutions. Journal of Forensic Psychiatry 2000; 11(1): 167–75.
23. *Dahle KP.* Strengths and limitations of actuarial prediction of criminal reoffence in a German prison sample: a comparative study of LSI-R, HCR-20 and PCL-R. Int J Law Psychiatry 2006; 29(5): 431–42.
24. *Dietiker J, Dittmann V, Graf M.* Risk assessment of sex offenders in a German-speaking sample : Applicability of PCL-SV, HCR-20+3, and SVR-20. Nervenarzt 2007; 78(1): 53–61. (German)
25. *Lindsay WR, Hogue TE, Taylor JL, Steptoe L, Mooney P, O'Brien G,* et al. Risk assessment in offenders with intellectual disability: a comparison across three levels of security. Int J Offender Ther Comp Criminol 2008; 52(1): 90–111.
26. *Grann M, Belfrage H, Tengstrom A.* Actuarial assessment of risk for violence: Predictive validity of VRAG and the historical part of the HCR-20. Criminal Justice and Behavior 2000; 27(1): 97–114.
27. *Bjørkly S, Moger TA.* A secondstep in development of a checklist for screening risk for violence in acute psychiatric patients: evaluation of interrater reliability of the Preliminary Scheme 33. Psychol Rep 2007; 101(3 Pt 2): 1145–61.
28. *Van der Kolk BA.* The complexity of adaptation to trauma: Self-regulation, stimulus discrimination, and characterological development. In: Van der Kolk BA, McFarlane AC, Weisaeth L, editors. Traumatic Stress. New York: Guilford Press; 1966. p. 182–213.
29. *Jakupcak M, Tull MT.* Effects of trauma exposure on anger, aggression, and violence in a nonclinical sample of men. Violence Vict 2005; 20(5):589–98.
30. *Sparr LF, Reaves ME, Atkinson RM.* Military combat, posttraumatic stress disorder, and criminal behavior in Vietnam veterans.Bull Am Acad Psychiatry Law 1987; 15(2): 141–62.
31. *Jordan BK, Marmar CR, Fairbank JA, Schlenger WE, Kulka RA, Hough RL,* et al. Problems in families of male Vietnam veterans with posttraumatic stress disorder. J Consult Clin Psychol 1992; 60(6): 916–26.
32. *Kubany ES, Gino A, Denny NR, Torigoe RY.* Relationship of cynical hostility and PTSD among Vietnam veterans. J Trauma Stress 1994; 7(1): 21–31.
33. *Byrne CA, Riggs DS.* The cycle of trauma; relationship aggression in male Vietnam veterans with symptoms of posttraumatic stress disorder. Violence Vict 1996; 11(3): 213–25.
34. *Beckham JC, Moore SD, Reynolds V.* Interpersonal hostility and violence in Vietnam combat veterans with chronic posttraumatic stress disorder: A review of theoretical models and empirical evidence. Aggression and Violent Behavior 2000; 5(5): 451–66.
35. *Novaco RW, Chemtob CM.* Anger and combat-related posttraumatic stress disorder. J Trauma Stress 2002; 15(2): 123–32.
36. *Galovski T, Lyons JA.* Psychological sequelae of combat violence: A review of the impact of PTSD on the veteran's family and possible interventions. Aggression and Violent Behavior 2004; 9(5): 477–501.
37. *Lasko NB, Gurvitis TV, Kuhne AA, Orr SP, Pittman RK.* Aggression and its correlates in Vietnam veterans with and without chronic posttraumatic stress disorder. Comprehensive Psychiatry 1994; 35: 373–81.
38. *Begic D, Jokic-Begic N.* Aggressive behavior in combat veterans with post-traumatic stress disorder. Military Medicine 2001; 166: 671–76.
39. *Taft CT, Pless AP, Stalans LJ, Koenen KC, King LA, King DW.* Risk factors for partner violence among a national sample of combat veterans. J Consult Clin Psychol 2005; 73(1): 151–9.
40. *First MB, Gibbon M, Sppitzer RL, Williams JBW, Benjamin LS, eds.* Structured Clinical Interview for DSM-IV Axis I Disorders. Washington DC: American Psychiatric Press; 1977.
41. *First MB, Sppitzer RL, Gibbon M, Williams JBW.* Structured Clinical Interview for DSM-IV Axis II Disorders. Washington DC: American Psychiatric Press; 1977.
42. *Hart SD, Cox D, Hare RD.* Manual for the Screening Version of the Hare Psychopathy Checklist-Revised. Toronto: Multi-Health Systems; 1995.
43. *Bartko JJ, Carpenter WT Jr.* On the methods and theory of reliability. J Nerv Ment Dis 1976; 163(5): 307–17.
44. *Cicchetti DV, Sparrow SA.* Developing criteria for establishing interrater reliability of specific items: applications to assessment of adaptive behavior. Am J Ment Defic 1981; 86(2): 127–37.
45. *Mossman D, Somoza E.* ROC curves, test accuracy, and the description of diagnostic tests. J Neuropsychiatry Clin Neurosci 1991; 3(3): 330–3.
46. *Hosmer DW, Lemeshow S.* Applied logistic regression. New York: John Wiley & Sons; 2000.
47. *Douglas KS, Webster CD, Jart SD, Eaves D, Ogloff JRP.* HCR-20 Violence Risk Management Companion Guide. Burnaby BC: Simon Fraser University, Mental Health, Law, and Policy Institute; 2001.
48. *Kraemer HC, Kazdin AE, Offord DR, Kessler RC, Jensen PS, Kupter DJ.* Coming to terms with the term of risk. Arch of Gen Psychiatry 1977; 54(4): 337–43.
49. *Fontana A, Rosenheck R.* Treatment-seeking veterans of Iraq and Afghanistan: comparison with veterans of previous wars. Journal of Nervous and Mental Diseases 2008; 196: 513–21.
50. *Webster CD, Douglas KS, Belfrage H, Link BG.* Capturing change: An approach to managing violence and improving mental health. In: *Hodgins S,* editor. Violence among the mentally ill: Effective treatment and management strategies. Dodrecht: Kluwer; 2000. p. 119–44.

51. *Lambert MJ*. Psychotherapy outcome research: Implications for integrative and eclectic therapists. In: *Norcross JC, Goldfried MR,* ed. Handbook of Psychotherapy Integration. New York: Basic Books; 1992. p. 94–129.
52. *Polovina N, Divac Lj*. Posttraumatic stress disorder and psychotherapeutic approach. Vojnosanitetski pregled 1992; 49: 115–25. (Serbian)
53. *Kostić P*. War experience and behavior of veterans. Psihologija 1994; 1-2: 99–109. (Serbian)
54. *Shalev A, Bonne O, Eth S*. Tretament of posttraumatic stress disorder. Psychosomatic Medicine 1996; 58: 165–82.
55. *Samardžić R, Mandić-Gajić G, Alačov T, Bosić B*. The role of day-hospital in psychosocial rehabilitation of patients with war psychotraumas. Vojnosanit Pregl 1998; 55: 385–90. (Serbian)
56. *Rogers R, Webster CD*. Assessing treatability in mentally disordered offenders. Law and Human Behavior 1989; 13: 19–29.
57. *Heilburn KS, Bennett WS, Evans JH, Offult RA, Reiff HJ, White AJ*. Assessing treatability in mentally disordered offenders: Strategies for improving reliability. Forensic Reports 1992; 5: 85–96.
58. *Solomon Z, Mikulincer M, Freid B, Wosner Y*. Family characteristics and posttraumatic stress disorder: A follow-up of Israeli combat stress reaction causalities. Family Process 1987; 26: 383–94.
59. *Orner RJ*. Post-traumatic stress disorders and European war veterans. British Journal of Clinical Psychology 1992; 31: 387–40.
60. *Horowitz MJ*. Stress-response syndromes: A review of post-traumatic stress and adjustment disorders. In: *Jensen SB* (ed). Trauma and Healing Under War Conditions. Zagreb: WHO; 1994. p. 49–60.
61. *Jovanović AA, Aleksandrić VB, Dunjić D, Todorović VS*. Family hardiness and social support as predictors of posttraumatic stress disorder. Psychiatry, Psychology and Law 2004; 11: 263–8.
62. *Špirić Ž*. Postwar adaptation of war veterans: health and social status and risk factors for posttraumatic stress disorder. In: *Špirić Ž,* editor. War psyhotrauma of Serbian veterans. Beograd: UBR90; 2008. p. 323–67. (Serbian)
63. *Felson RB*. Kick 'em when they're down: explanations of the relationship between stress and interpersonal aggression and violence. Sociologica Quarterly 1992; 33: 1–16.
64. *McFarlane AC, Weber DL, Clark CR*. Abnormal stimulus processing in PTSD. Biol Psychiatry 1993; 34: 311–22.

The paper received on June 18, 2008.

ORIGINAL ARTICLE UDC: 616.711-001.52-089:615.849.11

Pulse low-intensity electromagnetic field as prophylaxis of heterotopic ossification in patients with traumatic spinal cord injury

Pulsno elektromagnetno polje niskog intenziteta u prevenciji heterotopske osifikacije kod bolesnika sa traumatskim povredama kičmene moždine

Aleksandar Đurović*, Dejan Miljković*, Zorica Brdareski*, Aleksandra Plavšić†, Miodrag Jevtić‡

Military Medical Academy, *Clinic for Physical Medicine and Rehabilitation, ‡Head Office, **Belgrade, Serbia; †Tor Vergata University, Rome, Italy**

Abstract

Background/Aim. Heterotopic ossification (HO) is an important complication of head and spinal cord injuries (SCI). Pulse low-intensity electromagnetic field (PLIMF) therapy increases blood flow to an area of pain or inflammation, bringing more oxygen to that area and helps to remove toxic substances. The aim of this study was to determine the effect of PLIMF as prophylaxis of HO in patients with SCI. **Methods.** This prospective random control clinical study included 29 patients with traumatic SCI. The patients were randomly divided into experimental (n = 14) and control group (n = 15). The patients in the experimental group, besides exercise and range of motion therapy, were treated by PLIMF of the following characteristics: induction of 10 mT, frequency of 25 Hz and duration of 30 min. Pulse low-intensity electromagnetic field therapy started in the 7th week after the injury and lasted 4 weeks. The presence or absence of HO around the patients hips we checked by a plane radiography and Brookers classification. Functional capabilities and motor impairment were checked by Functional Independent Measure (FIM), Barthel index and American Spinal Injury Association (ASIA) impairment class. Statistic analysis included Kolmogorov-Smirnov test, Shapiro-Wilk test, Mann Whitney Exact test, Exact Wilcoxon signed rank test and Fischer Exact test. Statistical significance was set up to $p < 0.05$. **Results.** At the end of the treatment no patient from the experimental group had HO. In the control group, five patients (33.3%) had HO. At the end of the treatment the majority of the patients from the experimental group (57.14%) moved from ASIA-A to ASIA-B class. **Conclusion**. Pulse low-intensity electromagnetic field therapy could help as prophylaxis of HO in patients with traumatic SCI.

Key words:
spinal cord, injuries; ossification, heterotopic; electromagnetic fields; physical medicine.

Apstrakt

Uvod/Cilj. Heterotopska osifikacija (HO) glavna je komplikacija povrede glave i kičmene moždine (*spinal cord injury* – SCI). Terapija primenom pulsnog elektromagnetnog polja niskog intenziteta (*pulse low-intensity electromagnetic field* – PLIMF) ubrzava protok krvi u zoni bola ili upale, dovodeći više kiseonika u tu zonu i pomažući u uklanjanju toksičnih materija. Cilj ove studije bio je da se odrede efekti primene PLIMF u prevenciji HO kod bolesnika sa SCI. **Metode.** U ovu prospektivnu randomiziranu kliničku studiju bilo je uključeno 29 bolesnika sa trauamatskim SCI. Bolesnici su randomizirani u eksperimentalnu (n = 14) i kontrolnu (n = 15) grupu. Bolesnici iz eksperimentalne grupe, osim vežbi i terapije kretanjem, bili su podvrgnuti terapiji PLIMF indukcije 10 mT, frekvencije 25 Hz u trajanju od 30 min. Primena PLIMF počela je u sedmoj nedelji od povrede i trajala je četiri nedelje. Prisustvo ili odsustvo HO oko kukova bolesnika proveravano je radiografskim snimkom i Brookersovom klasifikacijom. Funkcionalne mogućnosti i oštećenje motorike proveravni su primenom *Functional Independent Measure* (FIM), *Barthel* indeks i klasom oštećenja prema *American Spinal Injury Association* (ASIA). Statistička analiza vršena je testovima *Kolmogorov-Smirnov, Shapiro-Wilk, Mann-Whitney Exact, Exact Wilcoxon Signed Rank* i *Fischer Exact*. Statistička značajnost bila je do vrednosti $p < 0,05$. **Rezultati.** Na kraju lečenja nijedan bolesnik iz eksperimentalne grupe nije imao HO. U kontrolnoj grupi pet bolesnika (33,3%) imalo je HO. Na kraju lečenja većina bolesnika eksperimentalne grupe (57,14%) prešla je iz klase ASIA-A u ASIA-B. **Zaključak.** Primena PLIMF pomaže u profilaksi HO kod bolesnika sa traumatskim SCI.

Ključne reči:
kičmena moždina, povrede; osifikacija, patološka; elektromagnetna polja; medicina, fizikalna.

Correspondence to: Aleksandar Đurović, Mylitary Medical Academy, Clinic for Physical Medicine and Rehabilitation, Crnotravska 17, 11 000 Beograd. Tel.: +381 11 266 19 11.

Introduction

Heterotopic ossification (HO) is an important complication of head and spinal cord injuries (SCI). Heterotopic ossification produces metaplastic formation of new bone in connective tissues and muscles surrounding joints [1, 2]. In patients with SCI, HO is usually found in muscles below the level of injury. In adult patients with SCI, the incidence of HO is approximately from 11 to 75% [1–5]. The onset of HO, regardless of its origin, ranges from 4–12 weeks. A peak occurrence is at 2 months after the head trauma, SCI or specific insult [6]. The rehabilitation process of patients with SCI is disturbed by the presence of HO. Approximately one third of SCI patients develop restricted hip motion or ankylosis, more frequently in patients with cervical than thoracic and lumbar injuries [3]. Because of that, they need more time for a successful rehabilitation, which is also more expensive. Fiedler et al. [8] found that $ 2 million were spent because of medical complications in postacute stage of the 115 persons with SCI. Medicaments, range of motion (ROM) and exercise therapy and radiation therapy are used for prophylaxis of HO formation [2, 4, 5, 9, 10]. The treatment of HO consists of ROM and exercise, medicaments, radiation therapy and surgery [2, 4, 5, 9, 11].

Magnets and electromagnetic fields have been used for a long time in clinical medicine. Electromagnetic fields can be static or pulse [12]. It has been estimated that $ 500 million is spent on magnetic devices annually in the United States and Canada [13]. Several brands of static magnets are currently available on the market: such as magnetic necklaces or magnetic insoles [13, 14]. A dosage of static magnets implies the strength of magnetic fields and length of the magnetic procedure. Electromagnetic fields therapy mostly means pulse low-intensity electromagnetic field (PLIMF) therapy [12, 15]. A dosage of PLIMF implies induction around the inductor, frequency of the field, length of the procedure and number of the procedures. Magnets appear to increase blood flow to an area of pain or inflammation, bringing more oxygen to the area and removing toxic substances. Magnets seem to affect positive and negative charges of sodium and potassium ions within the membranes around blood vessels and nerves and to relax small smooth muscle valves in the capillaries [16]. The results of the experimental investigations demonstrate possibilities of PLIMF in the treatment of damaged parts of the spinal cord [17].

There are different opinions in the review literature about HO in patients with SCI. Beside the fact that in the classic rehabilitation textbooks HO is discussed as an important complication of SCI, this complication was not reported in some professional reports [4, 11, 18–20]. In the large data review from the American National SCI Center, in patients who had injuries between 1973 and 1998, McKinley et al. [21] did not find HO as long-term medical complication. Many authors consider a radiation therapy as indivisible part of HO prophylaxis [4, 5, 9–11]. McKinley et al. [21], however, explicitly claim that only biphosphonates may prevent tissue ossification. The role of physical therapy in the treatment of patients after SCI is still controversial. Functional electrical stimulation (FES) is used for motor skill improvement in a late stage of rehabilitation [18]. Triceps surae electrical stimulation reduces spasticity in the patients after SCI [22]. Exercise is the first line in prophylaxis or treatment of HO. Unfortunately exercise has little or no direct effect on blood volume or hemoglobin content [23]. Investigators believe that ROM activity provided by physical therapy and occupational therapy can minimize the risk of joint ankylosis without promoting HO [4, 6, 11]. On the other hand, there are authors who have experimentally established that forcible manipulation induced heterotopic bone formation [5]. Serial casting and dynamic splinting are used to maintain joint motion in the presence of HO [24]. There is no evidence about efficiency of these treatments. Miller et al. [25] speak about good treatment effect of iontophoresis with dexamethasone in patients with myositis ossificans. In the available literature we have not found anything about the use and efficiency of magnetic fields in the prophylaxis of HO. Etiology of HO is not yet known. Decreased blood flow and changes in pH may be important [1]. Taking into consideration a well proved influence of magnetic fields on blood flow, circulation and inflammation, we presume that magnetic fields could be useful in prophylaxis of HO [12, 15–17, 26, 27]. The aim of this study was to determine the effect of PLIMF as prophylaxis of HO in patients with traumatic SCI.

Methods

We performed a prospective random control clinical study. The patients were recruited from the Neurosurgery Clinic and Clinic for Physical Medicine and Rehabilitation, Military Medical Academy, Belgrade. To be eligible, they had to be between 18 and 45 years of age, have completeness or incompleteness traumatic SCI, have no HO in 2 months after SCI, have no other prominent complications in acute stage of rehabilitation, were not taking medications which influence HO, have no any contraindications for the treatment by the PLIMF [5, 12]. Patients were excluded if they had pressure ulcer or severe spasticity because of these conditions are positively related to the formation of HO [4].

The study protocol consisted of determining demographic characteristics of patients, some biochemistry parameters (erythrocyte sedimentation rate – ESR, serum calcium – Ca, serum alkaline phosphatase – ALP), functional capabilities of patients defined by the Functional Independent Measure (FIM) and the Barthel index, neurological deficit defined by the American Spinal Injury Association (ASIA), and presence or absence of HO around patients hips toward Brookers classification [2, 5, 7, 28]. The study protocol was approved by the local ethic committee. All the patients gave the written consent before participating in the study.

The patients who met inclusion criteria were randomly divided into the experimental and control group. They started with ROM and exercise therapy in both groups as soon as they achieved their vital steady state. The patients in the experimental group, besides ROM and exercise therapy, were treated by PLIMF. This treatment started on the average in seventh week after the injury. The treatment by PLIMF lasted four weeks and was performed by the use of an apparatus "Magnemed MT-91, Electromedicina Nis". This apparatus is solenoid, so a patient can comfortably lie

(Figure 1). A dosage of PLIMF implied: induction of 10 mT (miliTesla), frequency of 25 Hz and duration of 30 min. We performed this therapy five times a week. We checked the presence and grade or absence of HO at the start and the end of the treatment. The plain radiographies were red by the same radiologist. Functional capabilities of the patients were checked by the same physiotherapist at the start and the end of the treatment.

domized. One patient from the experimental group was withdrawn because of the lack of protocol compliance. A total of 29 patients participated in the study. The groups were homogeneous in terms of age and sex of the patients. The majority of the patients in the experimental group (50%) had cervical level of SCI; the majority of the patients in the control group (53.3%) had thoracic level of SCI (Table 1).

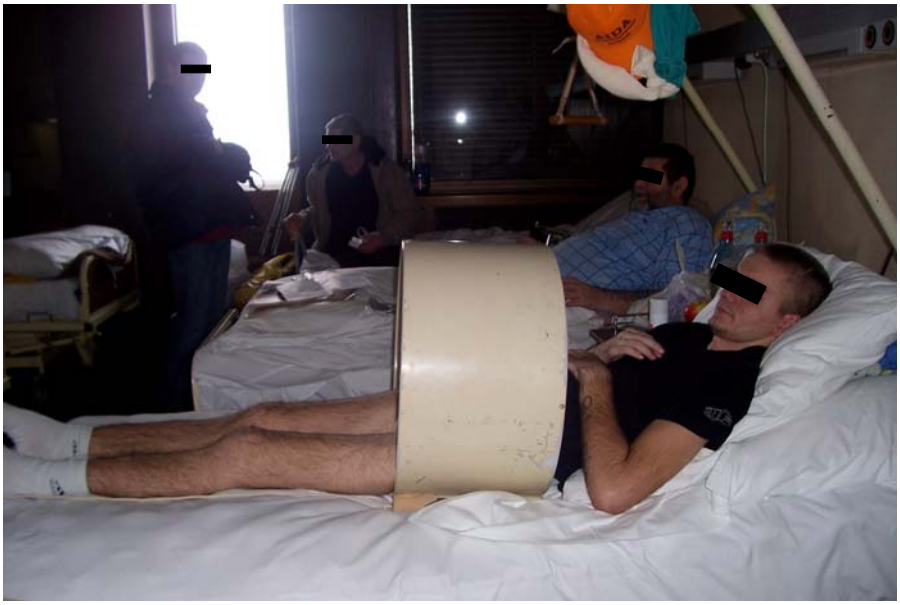


Fig. 1 – A patient during the treatment with pulse low-intensity electromagnetic field (PLIMF) ("Magnemed MT-91, Electromedicina Nis")

Table 1

Characteristics of the patients

Patients characteristics	Experimental group (n = 14) $\bar{x} \pm SD$	Control group (n = 15) $\bar{x} \pm SD$	*p*
Mean age (years), $\bar{x} \pm SD$	30.57 ± 11.97	31.47 ± 10.78	0.64*
Sex [n (%)]			
male	14 (100)	14 (93.3)	1.0 †
female	0 (0)	1 (6.67)	
Start of magnetotherapy (week), $\bar{x} \pm SD$	7.43 ± 3.25		
Duration of magnetotherapy (week), $\bar{x} \pm SD$	4.21 ± 0.58		
Level of spinal cord injury [n (%)]			
cervical	7 (50)	2 (13.3)	
thoracic	4 (28.5)	8 (53.3)	
lumbosacral	1 (7.14)	1 (6.60)	
cervical-thoracic	1 (7.14)	2 (13.3)	
thoracic-lumbosacral	1 (7.14)	2 (13.3)	

* Analysis conducted using Mann Whitney Exact Test

† Analysis conducted using Fischer Exact Test

Statistic analysis included Kolmogorov-Smirnov test, Shapiro-Wilk test, Mann Whitney Exact test, Exact Wilcoxon signed rank test and Fischer's Exact test. Statistical significance was set up to $p < 0.05$. The data was assessed by SPSS version 10.0 for Windows.

Results

A total of 33 patients were recruited by a rehabilitation specialist, neurosurgical specialist and physiotherapist. Out of them three refused to participate. Thirty patients were ran-

There was no significant difference between the groups in terms of functional capabilities: at the end of the treatment, the patients of both groups achieved a significant functional improvement (Table 2).

There were significant differences between the groups in terms of ASIA impairment class. At the end of the treatment the majority of the patients from the experimental group (57.14%) moved from the ASIA-A to the ASIA-B class; at the end of the treatment the majority of the patients from the control group (60%) remained in the ASIA-A class (Table 3).

Table 2

Functional capability defined by the Functional Independent Measure (FIM) and the Bartel Index

Clinical test	Experimental group		Control group		*p**
	start $\bar{x} \pm SD$	end $\bar{x} \pm SD$	start $\bar{x} \pm SD$	end $\bar{x} \pm SD$	
FIM	51.64 ± 11.71	78.07 ± 23.10	61.31 ± 20.84	78.54 ± 26.00	WEG = 0.001 WCG = 0.008 BGS = 0.16 BGE = 0.62
Bartel Index	17.14 ± 11.04	62.50 ± 29.66	28.46 ± 26.25	54.62 ± 28.54	WEG = 0.001 WCG = 0.008 BGS = 0.32 BGE = 0.63

* Mann Whitney Exact Test and Exact Wilcoxon Signed Rang Test; WEG – within experimental group; WCG – within control group; BGS – between groups at the start; BGE – between groups at the end

Table 3

American Spinal Injury Association (ASIA) impairment at the start and at the end of the treatment

ASIA class	Experimental group		Control group		*p**
	start n (%)	end n (%)	start n (%)	end n (%)	
A	13 (92.87)	2 (14.29)	13 (86.67)	9 (60.00)	BGS = 1.0
B		8 (57.14)		1 (6.67)	
C	1 (7.14)	2 (14.29)	2 (13.33)	2 (13.33)	
D		1 (7.14)		1 (6.67)	BGE = 0.01
E		1 (7.14)		2 (13.33)	

* Fischer Exact Test. BGS – between the groups at the start; BGE - between groups at the end

There were significant differences between the groups in terms of the presence of HO at the end of the treatment. In the experimental group, no one had HO. In the control group, five patients (33.3%) had several grades of HO (Table 4). These HO were mostly in the Brooker classes I and II (Figure 2).

Discussion

This study showed that the patients with traumatic SCI, who were treated by PLIMF, had no HO at the end of the treatment. On the other hand, 33.33% of the patients who were not treated by the PLIMF had HO around their hips. Inflammation was significantly diminished by PLIMF treatment. The majority of patients who were treated by PLIMF moved into the better ASIA class. These results could be explained by the biological effect of magnetic field. Pathophysiology of HO is not clear. Important contributing factors include tissue hypoxia, hypercalcemia, and changes in sympathetic nerve activity, prolonged immobilization and mobilization after that, disequilibrium between parathyroid hormone and calcitonin. Metabolic and vascular changes resulting from autonomic nervous system alterations might play a major role in HO metaplasia. Eicosanoids (prostaglandins and leukotriens) are important factors in bone metabolism. Subcutaneous injection of prostaglandin E2 induces HO bone formation. An important step in the ossification process is fibroblastic metaplasia [5]. The membranous ossification usually predominates in the process of HO for-

Table 4

Heterotopic ossification at the end of the treatment

Grade	Experimental group (n = 14) n (%)	Control group (n = 15) n (%)	*p**
0	14 (100)	10 (66.67)	
1	0 (0)	2 (13.33)	
2	0 (0)	2 (13.33)	0.04
3	0 (0)	1 (6.67)	
4	0 (0)	0 (0)	

*Fischer Exact Test. Abbreviations

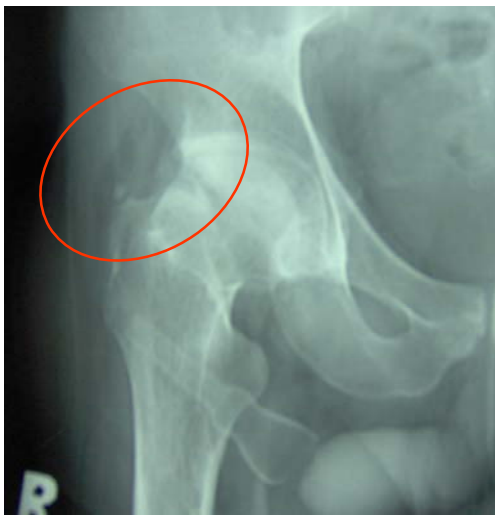


Fig. 2 – A patient with Brooker class I/II

mation [4]. Rehabilitation, in terms of ROM and exercise therapy, drug treatment and radiation therapy are considered the mainstay of HO prevention [1, 4, 5]. However, all of these therapies have the notable side effects. An experimental investigation was demonstrated that forcible manipulation during ROM and exercise therapy can induce HO formation [4]. Nonsteroidal anti-inflammatory drugs (NSAIDs) have well-known side effects that most commonly affect the gastric, hepatic and renal systems. A treatment with bisphosphonate, etidronate disodium (EHDP), generally is a safe method of prevention and treatment of HO. But, there is a potential risk of bone fracture when it is used for prolonged periods. A "rebound ossification" secondary to prolonged osteoclast inhibition has also been postulated. Radiation therapy is rarely associated with malignancy. However, increased rates of trochanteric non-union with high dose fractionated radiotherapy in populations following total hip arthroplasty were found [2]. Magnetic fields, like other physical procedures, have common and specific contraindications, but their side effects are minimal [12, 15.] Mild insomnia or some kind of psychological disturbances, were described mostly at the elderly [12].

The fact that we have not recorded any side effect during the magnetic field therapy, testifies that PLIMF is safe and useful physical procedure. Before creation of the study we had a few dilemmas regarding the biological effect of PLIMF. Namely, in Western medicine magnets are not considered as medical remedy [16]. In some well designed clinical studies the value of magnetic fields were not confirmed [13, 14]. In the absence of randomized, placebo control trials, the medical community is understandably skeptical regarding to acceptance of magnets as a valid option. We believed that PLIMF can help in prevention of HO formation, but, on the other hand, we were aware about the influence of PLIMF on the bone adhesion [12]. Histologically, HO cannot be differentiated from calus formation of a healing fracture. Nevertheless, the results of this study confirmed our assumptions that PLIMF can help in prevention of HO formation in patients with traumatic SCI. Therefore, we chose high-dosage PLIMF**.** We suppose that the main reason for the prevention HO in this study was the effect of magnetic field on microcirculation and cell membranes. Contributing factors in HO formation, a tissue hypoxia and sympathetic nerve activity, in the first place, were diminished or eliminated by PLIMF. Pulse low-intensity electromagnetic field promoted blood flow and red cell increase in the treated area. It is possible that the influence on the central nervous system and local effect on intra- and extracellular water were achieved**.** There is a theoretical possibility that magnetic fields could realign chromosomes [5]. This possibility could be important due to a link of some ligaments ossification with a genetic locus to the HLA region on the short arm of chromosome Gp [5]. A very important step in the ossification process is fibroblastic metaplasia. It is possible that PLIMF inhibited this process changing an arrangement of ions in the cell membranes [12]. Phospholipids in cell membranes have both diamagnetic and paramagnetic properties. We explain significant reduction of inflammation in the experimental group by the fact that magnetic field can increase the partial pressure of tissue oxygen and improve oxygen delivery to tissues. It is also known that magnetic field can raise the common adaptation capabilities of organism [12, 15, 17, 26, 27]. In such a way, we can explain significantly higher number of patients in the experimental group who moved from A to B ASIA class at the end of the treatment.

We could not compare our results directly with those of other studies. Many authors researched HO in different conditions. Massive ectopic calcification of muscles is possible after the injury of femoral artery [29]. Incidence of HO in some neurological diseases, such as Guillain-Barre Syndrome (41.6%), was higher than the incidence of HO after SCI toward the statements of some authors [5, 30]. However, our results confirm the statements of some authors that incidence of HO in patients with SCI are from 11 to 75% [2, 4]. Additionally, some authors compared different ways of prophylaxis of HO in several orthopedic conditions [31, 32]. The prophylaxis of HO could be incomplete in patients with internal fixation of an acetabular fracture. Contrary to our results, Schafer et al. [9] have found that of 32 patients treated with indomethacin 14 had HO; of 36 patients treated with radiation therapy 13 had HO. In our group of patients treated with PLIMF no one had HO. We concluded that passing of a significant number of the patients in the experimental group from A to B ASIA class at the end of the treatment is important and can be related with PLIMF. This is in accordance with the results of Scivoleto et al. [33] who found that ASIA impairment designations had significant prognostic value. In subject with paraplegia proximal femoral bone mineral density (BMD) is lower than at able-bodied people. It is known that magnetic field can improve an energy cell balance and accelerate the basal metabolic rate (BMR) [12]. It can be important for our study because of Yilmaz et al. [34] have found that BMR is closely associated with BMD. Magnets, as well as acupuncture, are a kind of complementary therapies used in rehabilitation [16]. Magnetic field, beside others, can act across the acupuncture points [12, 16]. This is relevant for our results as acupuncture diminishing a shoulder pain in the patient with SCI [35]. Biochemical parameters in our study were similar to parameters of other authors. The fact that ALP was not significantly different between the groups at the start and the end of the treatment is in accordance with the opinion that elevated ALP has no value in predicting HO [3]. These results confirmed our assumptions that PLIMF can help in prophylaxis of HO after traumatic SCI. Regarding a record that treatment of HO by the combination of NSAIDS, radiation therapy and surgery have well-known side effect and serious limitations, the question is if PLIMF treatment of HO could be successful.

Limitations of this study come out of a relatively small sample size that may reduce interpretation of the same observations. We did not carry out the most accurate diagnostics. Ultrasonography, computed thomography (CT), or bone scintigraphy have an important role in the diagnosis of early unmineralised HO. Although plain radiography is highly specific in the diagnosis of HO, this method lacks sensitivity

in early diagnosis. Similarly, an increased ECR is an important mark of inflammation. But C-reactive protein (CRP) may also be elevated in acute HO [4]. We did not check serum creatine phosphokinase (CPK) as well, beside the fact that elevated CPK have value in predicting HO [3]. At the end, as mineralization and true bone formation are usually completed in 6–18 months after SCI, there is a need for further follow-up with intention to answer the question of the eventual remote effects of PLIMF on the HO in patients with traumatic SCI [2].

Conclusion

Pulse low-intensity electromagnetic field therapy can help as prophylaxis of HO in the patients with traumatic SCI.

R E F E R E N C E S

1. *Wittenberg RH, Peschke U, Bötel U.* Heterotopic ossification after spinal cord injury. Epidemiology and risk factors. J Bone Joint Surg Br 1992; 74(2): 215–8.
2. *Blount PJ, Bockenek WL.* Heteroptopic ossification. In: *Frontera WR, Silver JK,* editors. Essentials of physical medicine and rehabilitation 1st ed. Hanley and Belfus, 2002; 569–74
3. *Singh RS, Craig MC, Katholi CR, Jackson AB, Mountz JM.* The predictive value of creatine phosphokinase and alkaline phosphatase in identification of heterotopic ossification in patients after spinal cord injury. Arch Phys Med Rehabil 2003; 84(11): 1584–8.
4. *Banovac K, Banovac T.* Heterotopic ossification. In: *Kirshblum S, Campagnolo DI, DeLisa JA*, editors. Spinal cord medicine. Lippincot Williams and Wilkins, 2002: 253–60.
5. *Vanden Bossche L, Vanderstraeten G.* Heterotopic ossification: a review. J Rehabil Med 2005; 37(3): 129–36.
6. *Guo Y, Collaco CR, Bruera E.* Heterotopic ossification in critical illness and cancer: a report of 2 cases. Arch Phys Med Rehabil 2002; 83(6): 855–9.
7. *Ho CH, Wuermser LA, Priebe MM, Chiodo AE, Scelza WM, Kirshblum SC.* Spinal cord injury medicine. 1. Epidemiology and classification. Arch Phys Med Rehabil 2007; 88(3 Suppl 1): 49–54.
8. *Fiedler IG, Laud PW, Maiman DJ, Apple DF.* Economics of managed care in spinal cord injury. Arch Phys Med Rehabil 1999; 80(11): 1441–9.
9. *Schafer SJ, Schafer LO, Anglen JO, Childers M.* Heterotopic ossification in rehabilitation patients who have had internal fixation of an acetabular fracture. J Rehabil Res Dev 2000; 37(4): 389–93.
10. *Garland DE, Semenov E.* Heterotopic ossification. In: *Woo BH, Nesathurai S*, editors. The rehabilitation of people with traumatic brain injury vol. 1. Malden, mass: Blackwel Sci 2000; 95–9.
11. *Kirshblum S.* Rehabilitation of spinal cord injury. In: *DeLisa JA, Gans BM, Walsh NE*, editors. Physical medicine and rehabilitation. Principles and practice. 4th ed. vol. 1. Philadelphia: Lippincot Williams and Willkins 2005; 1715–51.
12. *Mihajlovic V*, ed. Physical therapy. 3rd ed. Obodsko slovo. Rijeka Crnojevica; 2002. (Serbian)
13. *Reeser JC, Smith DT, Fischer V, Berg R, Liu K, Untiedt C,* et al. Static magnetic fields neither prevent nor diminish symptoms and signs of delayed onset muscle soreness. Arch Phys Med Rehabil 2005; 86(3): 565–70.
14. *Weintraub MI, Wolfe GI, Barohn RA, Cole SP, Parry GJ, Hayat G,* et al. Magnetic Research Group. Static magnetic field therapy for symptomatic diabetic neuropathy: a randomized, double-blind, placebo-controlled trial. Arch Phys Med Rehabil 2003; 84(5): 736–46.
15. *Djurovic A.* The effect of pulsating low-frekvent magnetic field in early rehabilitation of patients after thotal hip arthroplasty. [thesis]. Belgrade: Military Medical Academy; 1999. (Serbian)
16. *Davis CM.* Complementary therapies in rehabilitation. In: *Gonzales EG, Myers SJ, Edelstein JE, Lieberman JS, Downey JA*, edutirs. Physiological basis of rehabilitation medicine 3rd ed. Boston: Butterworth – Heinemann 2001: 777–95.
17. *Nikitina VV.* Dynamics of neurophysiological indices in experimental animals with chronic circulatory vertebrobasillar disorders and chronic lumbosacral myeloid ischemia in response to magnetic fields and electric stimulation. Vopr Kurortol Fizioter Lech Fiz Kult 2005; (4): 8–10. (Russian)
18. *Palmer SP, Kriegsman KH, Palmer JB*, editors. Spinal cord injury: a guide for living. Baltimore: The Jon Hopkins University Press; 2000.
19. *Chen D, Apple DF Jr, Hudson LM, Bode R.* Medical complications during acute rehabilitation following spinal cord injury-current experience of the Model Systems. Arch Phys Med Rehabil 1999; 80(11): 1397–401.
20. *Becker BE, DeLisa JA.* Model Spinal Cord Injury System trends, and implications for the future. Arch Phys Med Rehabil 1999; 80(11): 1514–21.
21. *McKinley WO, Gittler MS, Kirshblum SC, Stiens SA, Groan SL.* Spinal cord injury medicine. 2. Medical complications after spinal cord injury: identification and managements. Arch Phys Med Rehabil 2002, 83(3 Suppl 1): 58–64.
22. *van der Salm A, Veltink PH, Ijzerman MJ, Groothuis-Oudshoorn KC, Nene AV,Hermens HJ.* Comparison of electric stimulation methods for reduction of triceps surae spasticity in spinal cord injury. Arch Phys Med Rehabil 2006; 87(2): 222–8.
23. *Lacourse MG, Lawrence KE, Cohen MJ, Young RR.* Spinal cord injury. 3rd ed. In: *Frontera WR, Dawson DM, Slovik DM*, editors. Exercise in rehabilitation medicine. Champaign: Human Kinetics 1999: 267–92.
24. *Fuller KS.* Traumatic brain injury. In: *Cevallaro Goodman C, Boissonnanet WG, Fuller KS,* editors. Pathology: Implications for the physical therapists. 2nd ed. Philadelphia: Sounders 2002; 1072–87.
25. *Miller AE, Davis BA, Beckleey OA.* Bilateral and recurrent myositis ossificans in an athlete: a case report and review of treatment options. Arch Phys Med Rehabil 2006; 87(2): 286–90.
26. *Dolgikh VV, Bimbaev AB, Bairova TA, Duĭbanova NV.* Impulse low-intensity electromagnetic field in the treatment of adolescents with essential arterial hypertension. Vopr Kurortol Fizioter Lech Fiz Kult 2005; (6): 13–5. (Russian)
27. *Moliavchikova OV, Cherevashchenko LA, Grinzaĭd IuM, Aĭvazov VN, Zhuravlev ME.* Effects of combined action of radon baths and transcranial magnetotherapy on cerebral circulation in patients in an intermediate period of a mild craniocerebral trauma. Vopr Kurortol Fizioter Lech Fiz Kult 2007; (3): 19–22. (Russian)
28. *Hall KM, Cohen ME, Wright J, Call M, Werner P.* Characteristics of the Functional Independence Measure in traumatic spinal cord injury. Arch Phys Med Rehabil 1999; 80(11): 1471–6.
29. *Poon KB, Chien SH, Tsai KB, Lin GT.* Massive ectopic calcification of muscles in the lower leg following femoral artery injury-a case report. Acta Orthop 2005; 76(5): 728–9.
30. *Zeilig G, Weingarden HP, Levy R, Peer I, Ohry A, Blumen N.* Heterotopic ossification in Guillain-Barré syndrome: incidence

and effects on functional outcome with long-term follow-up. Arch Phys Med Rehabil 2006; 87(1): 92–5.

31. *Günal I, Hazer B, Seber S, Göktürk E, Turgut A, Köse N*. Prevention of heterotopic ossification after total hip replacement: a prospective comparison of indomethacin and salmon calcitonin in 60 patients. Acta Orthop Scand 2001; 72(5): 467–9.
32. *Sell S, Phillips O, Handel M*. No difference between two doses of diclofenac in prophylaxis of heterotopic ossifications after total hip arthroplasty. Acta Orthop Scand 2004; 75(1): 45–9.
33. *Scivoletto G, Morganti B, Molinari M*. Neurologic recovery of spinal cord injury patients in Italy. Arch Phys Med Rehabil 2004; 85(3): 485–9.
34. *Yilmaz B, Yasar E, Goktepe AS, Onder ME, Alaca R, Yazicioglu K,* et al. The relationship between basal metabolic rate and femur bone mineral density in men with traumatic spinal cord injury. Arch Phys Med Rehabil 2007; 88(6): 758–61.
35. *Dyson-Hudson TA, Kadar P, LaFountaine M, Emmons R, Kirshblum SC, Tulsky D*, et al. Acupuncture for chronic shoulder pain in persons with spinal cord injury: a small-scale clinical trial. Arch Phys Med Rehabil 2007; 88(10): 1276–83.
36. *Freebourn TM, Barber DB, Able AC*. The treatment of immature heterotopic ossification in spinal cord injury with combination surgery, radiation therapy and NSAID. Spinal Cord 1999; 37(1): 50–3.

The paper received on July 28, 2008.

ORIGINALNI ČLANAK UDC: 616.8-009.86:575.1

Dopa-reaktivna distonija

Dopa-responsive dystonia

Gordana Đurić*, Marina Svetel†, Eleonora Džoljić†, Vladimir Kostić†

***Zavod za zdravstvenu zaštitu radnika „Železnice Srbije", Beograd;**
Klinički centar Srbije, †Institut za neurologiju, **Beograd**

Apstrakt

Uvod/Cilj. Distonija predstavlja produženu nevoljnu kontrakciju koja dovodi do uvrtanja, repetitivnih pokreta ili zauzimanja abnormalnog položaja. Etiološki može se klasifikovati kao primarna i sekundarna distonija. Dopa-reaktivna distonija pripada grupi primarnih distonija. Cilj rada bio je otkrivanje prisustva mutacije u genu GCH-I u našoj populaciji kod bolesnika sa dopa-reaktivnim distoničkim diskinezijama i analiza kliničkih specifičnosti obolelih. **Metode**. Iz grupe bolesnika sa distonijama različite distribucije izdvojena su četiri bolesnika kod kojih je klinička slika ukazivala na dijagnozu dopa-reaktivne distonije (DRD). Dva bolesnika imala su pozitivnu porodičnu anamnezu, a dva slučaja bila su sporadični. Genetička analiza izvršena je pomoću standardnog protokola koji je uključivao PCR amplifikaciju i sekvenciranje DNK po metodi Sengera sa korišćenjem autoradiografije. **Rezultati.** Kod bolesnika iz porodice DRD-1 otkrivena je nova, heterozigotna *point* mutacija 520G→A u 4-m egzonu gena GCH-I. Prvi simptomi bolesti počeli su u sedmoj godini života uvrtanjem levog stopala, progresivno su napredovali i doveli do razvoja ukočenosti u nogama, otežanog hoda koji se u večernjim satima pogoršavao, a uvođenje u terapiju levodope (500 mg) uslovilo je „dramatičan" efekat. Druga mutacija kod bolesnice iz porodice DRD-2 bila je homozigotna delecija u 1-m intronu gena GCH-I (IVS1-85delA). Nevoljno uvrtanje stopala, osećaj slabosti donjih ekstremiteta zbog čega je bolesnica padala bez gubitka svesti bile su kliničke manifestacije bolesti. Primena levodope u dozi od 300 mg dovela je do regresije simptoma bolesti. Heterozigotna delecija adenina u poziciji 209 u prvom ekzonu (209del A) identifikovana je kod bolesnika DRD-3 sa negativnom porodičnom anamnezom, kod koga se u 10. godini života prvo javilo uvrtanje stopala prema unutra, potom podrhtavanje leve i desne noge u miru; u daljem toku bolesti posle nekoliko godina javio se i tremor ruku, koji se pogoršavao u stresnim situacijama. Otac našag bolesnika bio je asimptomatski nosilac mutacije. Četvrta mutacija u genu GCH-I nađena je u I egzonu gena GCH-I, 208delA. Bolest je počela uvrtanjem levog stopala, sporo se razvijala, pri čemu je pogoršanje tegoba nastupalo u večernjim satima, a oko 30. godine kretanje je postalo teže sa pojačanim zamaranjem i bolovima u mišićima, a u 40. godini bolesnica je primetila da se i govor izmenio. Primena levodope u dozi od 300mg/dnevno učinila je da se bolesnica dobro oseća i samostalno kreće. **Zaključak.** U radu su prikazana četiri bolesnika sa genetskom potvrdom dijagnoze dopa-reatkivne distonije, pošto se radi o entitetu koji je veoma važan u diferencijalnoj dijagnostici ranih distonija (< 26 godina) i ranog parkinsonizma (< 40 godina). Postavljanje dijagnoze ove bolesti od velikog je značaja jer se bolest može izvanredno kontrolisati primenom relativno malih doza levodope u dugom vremenskom periodu.

Ključne reči:
distonički poremećaji; dijagnoza; lečenje lekovima; levodopa; lečenje, ishod; dijagnoza, diferencijalna; mutacija.

Abstract

Backgrround/Aim. Dystonia is considered to be a prolonged involuntary contractions of the muscles leading to twisting, repetitive movements or irregular postures. Etiologically, it could be classified as primary and secondary dystonia. Dopa-responsive dystonia (DRD) belongs to a group of primary dystonia. The aim of this study was to detect the presence of gene GCH-I mutation in our population in patients with dopa-responsive dystonic dyskinesia and to analyse clinical specificity of the affected. **Methods.** Out of the group of patients with dystonia of different distribution four patients were separated whose clinical picture indicated the diagnosis of DRD. Two patients had a positive family anamnesis while the other two were sporadic. Genetic analysis was performed by the use of a standard protocol, which included PCR amplification and DNK sequencing according to the method of Senger and autoradiografy. **Results**. In the patients from the family DRD-1 new hetaerazygote point mutation 520G→A in 4-m exson gene GCH-I was revealed. First symptoms of the disease showed in the age of seven by the torsion of the left foot, progressively advanced and got into the evolution of numbness in the legs, aggravated gait, tending to worsen in the evening, and the therapy with levodopa (500 mg) produced a dramatic efect. The second mutation in the female patient from the family DRD-2 was homozygote deletion in1-m intron gene GCH-I (IVS1-85delA). Unwilling torsion of the foot, feeling of weakness in the lower extremities (that caused falling without loss of the consciousness) were clinical demonstrations of the disease. The application of levodopa (300 mg) caused regression of the symptoms of the disease. Hetaerazygote deletion of adenine in the position 209 in the first exon (209del A) was identificated in the patient DRD-3 with negative family anamnesis, in who in the age of ten the torsion of the foot inside occured for the first time following by trembling of both the left and right legs at rest; after a few years, tremor of hands also appeared, which became worse in stressful situations. The father of the patient was an asymptomatic bearer of mutation. The fourth mutation in gene GCH-I was found in I exon gene GCH- I, 208delA. The disease was started by torsion of the left foot, progressing easily, and worsening in the evenings, but at the age of 30, moving became harder, fatigue and pain in muscles, increased and at the age of 40 the patient recognised the change of speech. The application of levodopa (300 mg/daily) made the patient feel better and walk independently. **Conclusion.** The study presented four patients with genetic confirmation of the diagnosis of dopa-responsive dystonia. This entity is very significant in differential diagnostics of both early dystonia (< 26 years) and early parkinsonism (< 40 years) since it can be successfully managed by applyng relatively low doses of levodopa over a long period of time.

Key words:
dystonic disorders; diagnosis; drug therapy; levodopa; treatment outcome; diagnosis differential; mutation.

Correspondence to: Gordana Đurić, Zavod za zdravstvenu zaštitu radnika "Železnica Srbije", Savska 23, 11 000 Beograd, Srbija.
Tel.: +381 64 166 54 83. E-mail: dugod@ptt.yu

Uvod

Distonija je produžena nevoljna kontrakcija koja dovodi do uvrtanja, repetitivnih pokreta ili zauzimanja abnormalnog položaja [1]. U etiološkom smislu ona može biti klasifikovana kao primarna distonija, koja ima distoniju kao jedinu kliničku manifestaciju bolesti, i kao sekundarna ili simptomatska. U grupi primarnih izdvajaju se distonija plus sindromi u kojima je distonija samo jedna od postojećih diskinezija (tj. nevoljnih pokreta). Upravo u ovu kategoriju spada dopa-reaktivna disotnija (DRD).

Rani opisi ove bolesti potiču sa kraja pedesetih godina prošlog veka, kada su slične tegobe kod dva srodnika tada prikazane bolesnice pobudile sumnju na nasledljivost njene bolesti [2]. Kada je 1994. godine mutacija u genu za guanozin trifosfat hidrolazu-I (GCH-I) identifikovana kao glavni uzročnik DRD, sa zakašnjenjem od 49 godina mutacija je potvrđena *post mortem* i kod ove bolesnice [3, 4].

Segawa i sar. [1], i pre otkrića odgovorne mutacije, ukazali su na različitost i karakteristične osobine ove distonije, a pre svega reaktivnost na levodopu, po čemu je bolest i dobila ime. Verovatno je da ova bolest čini oko 5–10% distonija detinjstva i adolescentnog perioda, mada studije o prevalenciji govore o jednom obolelom na dva miliona stanovnika [6]. U svakom slučaju, klinički je značajno pravilo da kod svih bolesnika sa ranim razvojem distonije (< 26 godina) treba *ex juvantibus* na početku lečenja napraviti probu sa primenom levodope.

Beogradu, izdvojena su četiri bolesnika kod kojih je klinička slika ukazivala na DRD. Kriterijumi za postavljanje dijagnoze i uključivanje bolesnika u studiju bili su: početak u ranom detinjstvu, između 18 meseci i osam godina života; posturalna distonija češće na donjim ekstremitetima; dnevne fluktuacije tegoba; „dramatičan“ odgovor na levodopu; pretpostavljeno dominantno nasleđe sa nepotpunom penetracijom; odsustvo poznatog moždanog oštećenja (normalni rezultati dopunskih dijagnostičkih procedura: kompjuterizovane tomografije (KT), nuklearne magnetne rezonance (NMR) i elektroencefalografskog ispitivanja (EEG); normalno kognitivno funkcionisanje.

Članovi porodica bolesnika, takođe, ambulantno su ispitivani, kada su im posle detaljnih pregleda, a posle davanja informisanog pristanka, uzimani uzorci krvi.

Molekularnogenetička istraživanja obavljena su u DNK laboratoriji Neurogenetičkog odeljenja Državne ustanove Naučno-istraživačkog instituta neurologije Ruske akademije medicinskih nauka, u Odeljenju humane molekularne genetike Instituta molekularne genetike Ruske akademije nauka i u Genetskoj laboratoriji u Luebecku. U istraživanju je korišćen kompleks bazičnih molekularnogenetičkih metoda ispitivanja, kao što je ranije opisano [8].

Rezultati

Kod dva bolesnika (tabela 1) postojala je porodična anamneza za sličnu bolest u porodici, dok je kod ostala dva u pitanju bila sporadična bolest (slika 1).

Tabela 1

Kliničko-demografske karakteristike bolesnika sa dopa-reaktivnom distonijom (DRD)

Bolesnici (proband)	Porodična anamneza	Uzrast (god.)	Početak bolesti (god.)	Prvi simptom	Tremor ruku	Pojačani mišićni refleks	Forma bolesti	Dnevne fluktuacije	Tip mutacije
DRD-1	+	44	7	distonija stopala	+	–	distonija + parkinsonizam	+	4 ekzon, tačkasta mutacija 520G→A
DRD-2	+	75	~2 decenije	distonija stopala	+	–	generalizovana distonija	–	I intron homozigotna delecija IVS1.85 delA
DRD-3	–	18	10	distonija stopala	+	–	distonija nogu	–	I ekzon 208delA
DRD-4	–	54	~2 decenije	distonija stopala	–	+	distonija nogu	+	I ekzon 208delA

Obično se DRD ispoljava klasičnim generalizovanim fenotipom sa početkom bolesti u prvoj deceniji života, razvojem distoničnih pokreta u nogama, poremećajem hoda, ali u nekim slučajevima bolest ima atipičnu kliničku sliku sa razvojem neobičnog hoda, spastične paraplegije, parkinsonizma ili fokalne distonije [4, 7].

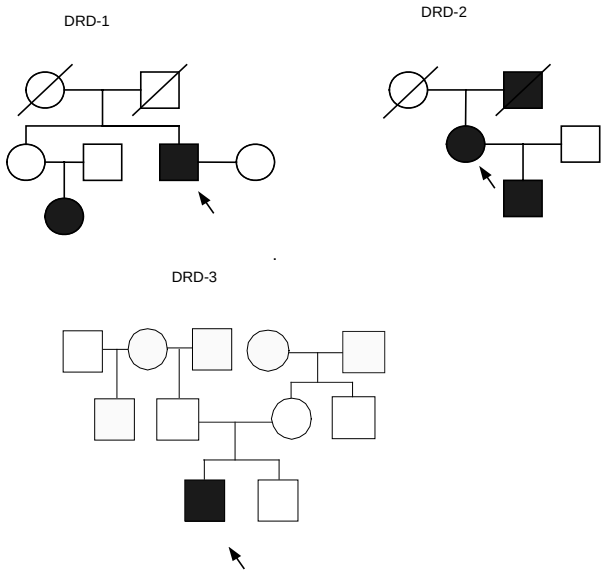
Cilj našeg rada bio je otkrivanje prisustva mutacije u genu GCH-I u našoj populaciji kod bolesnika sa dopa-reaktivnim distoničkim diskinezijama i analiza kliničkih specifičnosti obolelih.

Metode

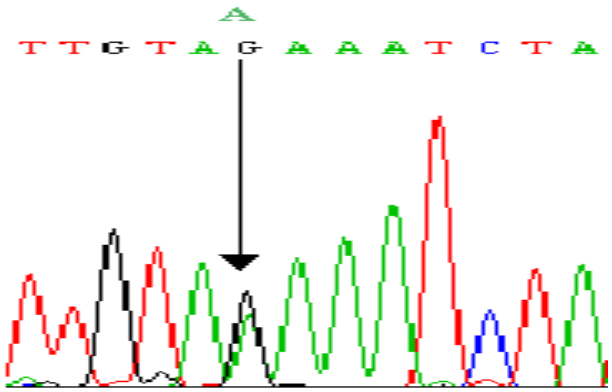
Iz grupe bolesnika sa distonijama različite distribucije koji su lečeni u Odeljenju za poremećaje pokreta i degenerativne bolesti CNS Instituta za neurologiju Kliničkog centra Srbije u

Porodica DRD1. Kod probanda prvi simptomi počeli su u sedmoj godini života uvrtanjem levog stopala, zamorom, osećajem ukočenosti u nogama, naročito posle dužeg hoda, te podrhtavanjem ruku. Bolest je imala fluktuirajući karakter sa lakšim simptomima u jutarnjim satima uz brzo napredovanje, što je uslovilo da se bolesnik u 15. godini života mogao kretati samo uz tuđu pomoć. Primena antiholinergika (biperidin, 6–10 mg dnevno) dovela je do značajnog poboljšanja, a povoljan efekat terapije održavao se nekoliko godina. Usledilo je značajno pogoršanje tremora ruku koji se javljao u paroksizmima, a uvrtanje, nevoljni pokreti u stopalima i ukočenost u nogama otežavali su hod koji je postao nespretan i usporen. Uvođenje levodope u terapiju (500 mg dnevno) uslovilo je „dramatičan“ efekat, koji se održava i sada, posle više godina, bez komplikacija. Genetičkom analizom uzoraka DNK kod bolesnika otkri-

vena je nova, heterozigotna tačkasta mutacija 520G→A u četvrtom egzonu gena GCH-I (slika 2).



Sl. 1 – Geneološka analiza ispitivanih porodica



Sl. 2 – Mutacija 520G→A u 4-m ekzonu gena GCH-I (u heterozigotnom stanju)

Kod drugog bolesnika iz ove porodice bolest je počela, takođe, u prvoj deceniji života generalizovanom distonijom i poboljšanjem simptoma bolesti u jutarnjim satima ili u toku dana posle spavanja, a lečenje malim dozama levodope (400 mg dnevno) dovelo je do potpune regresije bolesti.

Porodica DRD2. Prvi simptom bolesti kod bolesnika bio je nevoljno uvrtanje stopala koje je počelo u ranom detinjstvu. Posle porođaja uvrtanje stopala se pogoršalo, hod je postao otežan, a u 50. godini života javilo se i podrhtavanje ruku, nespretnost i otežan hod, kao i česti padovi bez gubitka svesti, ali sa povređivanjem. Primenom levodope (300 mg dnevno) distonični pokreti značajno su smanjeni, hod poboljšan, a padova nije bilo.

Kod još jednog člana porodice postojao je blagi poremećaj hoda sa sporom progresijom od detinjstva.

Homozigotna delecija u prvom intronu gena GCH-I (IVS1-85delA) otkrivena je kod probanda.

Porodica DRD3. Treća otkrivena mutacija u našem istraživanju bila je heterozigotna delecija adenina u poziciji 209 u prvom egzonu (209del A) gena GCH-1; identifikovana je kod bolesnika sa naizgled negativnom porodičnom anamnezom. Bolesnik je imao uobičajen psihomotorni razvoj, a u 10. godini života prvo se javilo uvrtanje stopala pri hodu prema unutra, koje je vremenom postalo učestalo, potom podrhtavanje leve, a potom i desne noge u miru. U daljem toku bolesti, posle nekoliko godina, javio se i tremor ruku, prvo leve, a onda i desne, koji se pogoršavao u stresnim situacijama. Dobar odgovor na levodopu uočen je odmah po uvođenju leka. Otac našag bolesnika bio je asimptomatski nosilac mutacije.

Porodica DRD4. Četvrta mutacija u genu GCH-I nađena je u I egzonu gena GCH-I, 208delA (delecija adenina u poziciji 208), kod naizgled sporadične bolesnice (slika 3). Prve tegobe počele su, u srednjoškolskom uzrastu, uvrtanjem levog stopala pri hodu, a pogoršavale su se u popodnevnim i večernjim satima. Bolest je imala sporo progresivan tok. Oko 30. godine kretanje je postalo teže sa pojačanim zamaranjem i bolovima u mišićima, a u 40. godini bolesnica je primetila da se i govor izmenio. Poslednjih 10 godina kretanje je postalo moguće samo uz pomagalo, a tri godine pre prve hospitalizacije u Institutu za neurologiju nije mogla da samostalno obavlja svakodnevne aktivnosti i zavisila je od tuđe pomoći. Postavljena je dijagnoza DRD i uvedena je levodopa u dozi od 300 mg/dnevno, od kada se bolesnica dobro oseća i samostalno kreće.

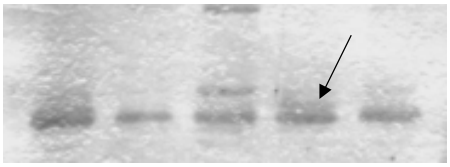
Diskusija

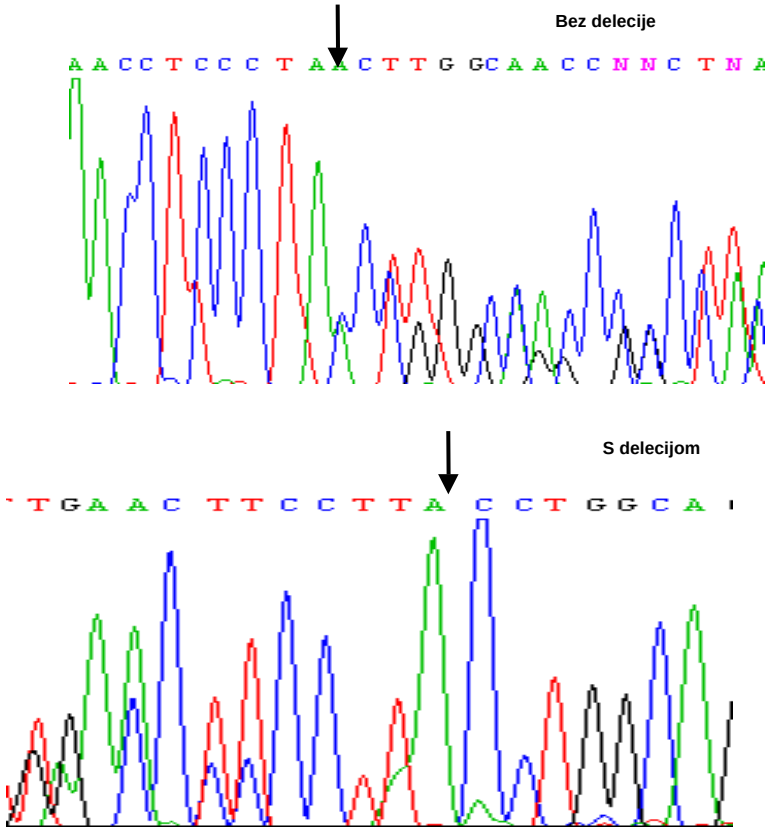
Analizom DNK kod naših bolesnika sa kliničkom slikom DRD oktrivene su četiri mutacije u genu GCH-I. Dva bolesnika imala su pozitivnu porodičnu anamnezu za ovo oboljenje, a kod dva bolesnika bolest je imala sporadičan karakter (slika 1).

U porodici DRD-1 i DRD-2 kliničkogenetička analiza ukazala je na jasan autosomnodominantni tip nasleđa, pri čemu u porodici DRD-1, oboljenje nije prisutno kod majke bolesnice, čiji je rođeni brat imao istu kliničku sliku, što bi govorilo o nepotpunoj penetrantnosti mutiranog gena (slika 1). Nepotpuna penetrantnost mutantnog gena GCH-I opisana je kod više porodica sa DRD različite etničke pripadnosti [9]. Opisana mutacija u genu GCH-1 češća je kod žena [10].

Gotovo svi bolesnici sa mutacijom u genu GCH-I imali su početak bolesti u prvoj deceniji života (3/4), a prema podacima iz literature ona se može razviti još intrauterino [11].

Kod svih naših bolesnika prve distoničke smetnje nastale su u nogama, kako se to uobičajeno i uočava, mada se izuzetno retko prvi simptomi mogu ispoljiti u rukama [12]. Samo jedan bolesnik iz naše grupe imao je znake parkinsonizma. Kod nekih članova porodica obolelih od DRD parkinsonizam može biti i jedina manifestacija bolesti, kada uobičajeno postoji rigiditet (nekada kao monosimptom), bradi- i hipokineza, posturalni tremor, posturalna nestabilnost i tremor u miru [13, 14]. Zbog toga, nije lako napraviti diferencijalnu dijagnozu prema juvenilnom parkinsonizmu [15]. Piramidni znaci, međutim, kod DRD za razliku od juvenilnog parkinsonizma, bar kada su u pitanju pojačani mišićni refleksi, odlikuju se povlačenjem pod dejstvom levodope, što je, možda, razlog





Ekzon1

CGCTCCCGGCTCGGAGTGTGATCTAAGCAGGTTGCGTACCTTCCTCAGGT
GACTCCGGCCACAGCCCATTGTCCGCGGCCACCGGCGGAGTTTAGCCGCA
GACCTCGAAGCGCCCCGGGGTCCTTCCCGAACGGCAGCGGCTGCGGCGGG
TCC
Korirajuća oblast ATGGAGAAGGGCCCTGTGCGGGCACCGGCGGAGAAGCCGCGGGG-
CGC-47
CAGGTGCAGCAATGGGTTCCCCGAGCGGGATCCGCCGCGGCCCGGGCCCAGCAGGC-
CGGCGGAGAAGCCCCCGCGGCCCGAGGCCAAGAGCGCGCAGCCC-
GCGGACGGCTGGAAGGGCGAGCGGCCCCGCAGCGAGGAGGATAACGAGCT-197

208delA
GAACCTCCCTAACCTGGCAGCCGCCTACTCGTCCATCCTGAGCTCGCTGG
GCGAGAACCCCCAGCGGCAAGGGCTGCTCAAGACGCCCTGGAGGGCGGCC-297

Sl. 3 – DRD-4– DRD – mutacija ekzon 1 208delA

da ovom simtpomu nije posvećena velika pažnja u slučajevima DRD [15, 16]. U kojoj meri nije lako napraviti razliku između ove dve bolesti, pokazuje i činjenica da je u jednom broju klinički tipičnih ispoljavanja sa DRD potvrđeno prisustvo parkin mutacije, karakteristične za autosomnorecesivni parkinsonizam ranog početka [17].

Gen za DRD identifikovan je na hromozomu 14 i kodiran je za guanozin-trifosfat-ciklohidrolazu I (GCH-I) [3], koja je veoma značajna u metabolizmu dopamina. Ovaj enzim je prvi i ograničavajući u sintezi tetrahidrobiopterina, koji je sa svoje strane esencijalni kofaktor aminokiselinskih hidroksilaza, kakve su tirozin-hidroksilaza i triptofan-hidroksilaza.

Nedovoljna količina tetrahidrobiopterina ima udela u smanjenoj aktivnosti tirozin-hidroksilaze u proizvodnji levodope, a potom i dopamina [18]. Kao potvrda patogenetskog značaja mutacije u ovom genu govori značajno sniženje nivoa aktivnosti enzima GCH-I (< 20% od početnog nivoa) kod bolesnika sa DRD [3].

Dva naša bolesnika imala su diuralne fluktuacije motornih simptoma. I pored toga što je u ranijoj definiciji bolesti, jedna od njenih odrednica bila dnevna fluktuacija simptoma (bolje u jutarnjim, gore u večernjim satima) ne treba zaboraviti da se ona javlja kod oko 75% obolelih uz široke varijacije [6, 12]. Osim toga, dnevne fluktuacije nisu ekskluzivni simptom obolelih od DRD [5]. Naime, bolesnici sa juvenilnim parkinsonizmom, takođe, u većini slučajeva imaju varijacije izraženosti simptoma, što se viđa i u manjem broju obolelih od idiopatske torzione distonije.

Kod većine naših bolesnika lečenje je započeto sa velikom latencijom koja se kretala u rasponu od nekoliko do maksimalno 40 godina. Zanimljivo je da klinički tok bolesti kod nelečenih slučajeva može postati izuzetno ozbiljan, praćen pojavom nesamostalnosti, pa čak i vezanosti za postelju, kao što je bio slučaj kod dva naša bolesnika [14]. Smatra se da bolest kod preko 75% obolelih, ako se ne leči, postaje generalizovana u svom toku, i to u relativno kratkom intervalu, mada je ovaj period nekada i duži (10 godina) [12]. Izgleda da postoji sklonost ka ozbiljnijoj kliničkoj slici i bržoj generalizaciji kod žena, ali i kod onih osoba kod kojih je bolest ranije počela [12].

Pojava bolesti u ranom detinjstvu sa distoničkim nevoljnim pokretima razlog je za često postavljanje pogrešne dijagnoze dečje cerebralne oduzetosti. Zbog toga, na ovu bolest treba misliti i ne zaboraviti da svaki neobjašnjeni poremećaj hoda u ranom detinjstvu mora da pobudi sumnju i na DRD [11]. Neretko, zbog nekada pojačanih mišićnih refleksa, prisustva strijatnog palca, za bolesnika se može misliti da ima dečju cerebralnu paralizu, a opisani su bolesnici sa višegodisnjim odlaganjem u započinjanju lečenja, upravo zbog postavljanja pogrešne dijagnoze [4].

Neurološkim pregledom mogu biti zapaženi pojačani mišićni refleksi kod najviše 20% obolelih (najčešće bez znaka Babinskog), što je zapaženo kod jedne naše bolesnice. Tvrdi se da refleksi mogu biti normalizovani primenom levodope što je i bio slučaj kod naše bolesnice [15, 19]. Normalno centralno vreme sprovođenja motornog korteksa pri elektromagnetnoj stimulaciji sugeriše nepiramidnu prirodu ovog znaka [20].

Kod nekih porodica klinička slika je različita kod njenih članova. Kod probanda u DRD3 porodici niko od članova porodice nije imao slične smetnje, ali genetička analiza pokazala je da je otac bolesnika asimptomatski nosilac mutacije, što govori u prilog nepotpune penetrantnosti mutiranog gena. Ako bi jedino prisustvo distonije bilo prihvaćeno kao znak postojanja bolesti kod srodnika, onda je penetrantnost DRD 31%, a ako uzmemo u obzir i članove porodice sa slikom moguće i verovatne distonije, ona raste na 42–62%. Ukoliko se kao izraz nasleđene bolesti shvati parkinsonizam, onda vrednost penetratnosti pada na 25%. Kada se, međutim, uzmu u obzir svi oblici moguće DRD (definitivna, verovatna i moguća distonija, parkinsonizam), onda penetratnost postaje gotovo kompletna [13].

Primena preparata levodope praktično dovodi do potpune remisije bolesti. Kod bolesnika u porodici DRD1 početno je primenjena veća doza levodope od 500 mg dnevno, koja je potom smanjena na dozu od 100 mg dnevno, dok se kod drugih naših bolesnika raspon dnevne doze levodope kretao od 100–300 mg. Kao što i ime bolesti govori, osnovna terapijska strategija podrazumeva primenu levodope i preporučena je doza od 10 mg na kg telesne mase na dan [15]. Lek se mora primenjivati dovoljno dugo, a uobičajeno je da odrasla osoba mora uzimati prve četiri nedelje 400 mg levodope, a sledeće četiri nedelje po 600 mg [4]. Ipak, latencija između pojave prvih simptoma i započinjanja terapije u nekim studijama izuzetno je duga (10–30 godina), a opisan je i bolesnik kod koga je terapija otpočela 58 godina posle zapažanja prvih simptoma [12]. Na sreću, čak i kada se dijagnoza postavi ovako kasno i sa razvijenom slikom bolesti, efekat lečenja neće biti loš i neće zaostajati po uspešnosti za bolesnicima kod kojih je bolest dijagnostikovana na vreme [11]. Pozitivan efekat lečenja može se zapaziti nekoliko dana do nekoliko meseci od započinjanja terapije i, u principu je trajan [12].

Ni kod jednog od naših bolesnika nisu primećeni neželjeni efekti primene leka. To je u skladu sa zapažanjem da se kod ovih bolesnika ni posle duže primene levodope ne razvijaju neželjena dejstva leka (diskinezije, fluktuacije terapijskog odgovora, psihoze), čak ni posle višedecenijske primene, što je različito od bolesnika sa Parkinsonovom bolešću, kod kojih je ova komplikacija gotovo pravilo [6, 12, 21]. Odsustvo neželjenih dejstava lečenja može biti objašnjeno postojanjem očuvanog mehanizma skladištenja dopamina u presinaptičkim dopaminergičkim završecima kod obolelih sa DRD [6]. Ipak i od ovog, nazovi pravila, postoje izuzeci. Kod izvesnog broja obolelih zapaženi su blagi horeički pokreti, ali su oni nestajali brzo posle smanjenja ili posle samo lakog povišenja dnevne doze levodope [12].

Bolesnik iz porodice DRD-1, pre nego što je bio hospitalizovan u našoj ustanovi i pre nego što je postavljena dijagnoza DRD, u 15. godini života lečen je primenom antiholinergika, posledičnim delimičnim smanjenjem tegoba, što se održavalo više od 10 godina. To je u skladu sa sugestijom da se genetsko testiranje na DRD obavi kod slučajeva idiopatske torzione distonije koji su reagovali na antiholinergičku terapiju [4].

Zaključak

Dopa-reaktivna distonija jeste klinički entitet koji je veoma važan u diferencijalnoj dijagnozi ranih distonija (< 26 godina) i ranog parkinsonizma (< 40 godina). Ukoliko se prepozna, može izvanredno da se kontroliše primenom relativno malih doza levodope u dugom vremenskom periodu.

Zahvalnica

Rad na ovom istraživanju finansiralo je Ministarstvo nauke Republike Srbije (projekat osnovnih istraživanja 145057).

L I T E R A T U R A

1. *Segawa M, Ohmi K, Itoh S, Hayanowa H*. Childhood basal ganglia disease with remark-able response to L-dopa, 'hereditary basal ganglia disease with marked diurnal fluctuation. Chirio (Tokyo) 1971; 24: 667–72.
2. *Beck D*. Dystonia Musculorum Deformans with Another Case in the Same Family. Proc R Soc med 1947; 40(10): 551–2.
3. *Ichinose H, Ohye T, Takahashi E, Seki N, Hori T, Segawa M,* et al. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. Nat Genet 1994; 8(3): 236–42.
4. *Bandmann O, Nygaard TG, Surtees R, Marsden CD, Wood NW, Harding AE*. Dopa-responsive dystonia in British patients: new mutations of the GTP-cyclohydrolase I gene and evidence for genetic heterogeneity. Hum Mol Genet 1996; 5(3): 403–6.
5. *Nygaard TG, Marsden CD, Duvoisin RC*. Dopa-responsive dystonia. Adv Neurol 1988; 50: 377–84.
6. *Nygaard TG, Snow BJ, Fahn S, Celue DB*. Dopa-responsive dystonia: clinical characteristis and definition. In: *Segawa M*, editors. Hereditary Progressive Dystonia with Marked Diurnal Fluctuation. Publishing Lanes, MM: Parthenon group; 1993. p. 3–35.
7. *Steinberger D, Weber Y, Korinthenberg R, Deuschl G, Benecke R, Martinius J*, et al. High penetrance and pronounced variation in expressivity of GCH1 mutations in five families with dopa-responsive dystonia. Ann Neurol 1998; 43(5): 634–9.
8. *Illarioshkin SN, Markova ED, Slominsky PA, Miklina NI, Popova SN, Limborska SA*, et al. The GTP cyclohydrolase I gene in Russian families with dopa-responsive dystonia. Arch Neurol 1998; 55(6): 789–92.
9. *Eldridge R*. The torsion dystonias: literature review and genetic and clinical studies. Neurology 1970; 20(11): 1–78.
10. *Segawa M, Hosaka A, Miyagawa F, Nomura Y, Imai H*. Hereditary progressive dystonia with marked diurnal fluctuation. Adv Neurol 1976; 14: 215–33.
11. *Charles PD, Davis TL, Robertson D, Fenichel GM*. Dystonia and unique muscle features. A 23-year follow-up and correction of diagnosis in two brothers. Arch Neurol 1995; 52(8): 825–6.
12. *Nygaard TG, Marsden CD, Fahn S*. Dopa-responsive dystonia: long-term treatment response and prognosis. Neurology 1991; 41 (Pt 1): 174–81.
13. *Nygaard TG, Trugman JM, de Yebenes JG Fahn S*. Dopa-responsive dystonia: the spectrum of clinical manifestations in a large North American family. Neurology 1990; 66: 66–9.
14. *Rajput AH, Gibb WR, Zhong XH, shannak KS, Kish S, Chang LG*, et al. Dopa-responsive dystonia: pathological and biochemical obserbation in a case. Ann Neurolo 1994; 35(4): 396–402.
15. *Wang PJ, Ko YM, Young C, Hwu WL, Shen YZ*. Hereditary progressive dystonia with marked diurnal fluctuation (Segawa syndrome) in Taiwan: Brain Dev; Brain 1994; 16(2): 126–31.
16. *Fink JK, Barton N, Cohen W, Lovenberg W, Burns RS, Hallett M*. Dystonia with marked diurnal variation associated with biopterin deficiency. Neurology 1988; 38(5): 707–11.
17. *Tassin J, Dürr A, Bonnet AM, Gil R, Vidailhet M, Lücking CB*, et al. Levodopa-responsive dystonia. GTP cyclohydrolase I or parkin mutations? Brain 2000; 123(Pt 6): 1112–21.
18. *Ozelius LJ, Breakefield XO*. Co-factor insufficiency in dystonia-parkinsonian syndrome. Nat Genet 1994; 8(3): 207–9.
19. *Nygaard TG*. Dopa-responsive dystonia: 20 years into the levodopa era. In: *Quinn NP, Jenner PG*, eds. Disorders of movement: Clinical, pharmacological an physiological aspects. London: Academic Press, 1989; 323–37.
20. *Müller K, Hömberg V, Lenard HG*. Motor control in childhood onset dopa-responsive dystonia (Segawa syndrome). Neuropediatrics 1989; 20(4): 185–91.
21. *Poewe WH, Lees AJ, Stern GM*. Low-dose L-dopa therapy in Parkinson's disease: a 6-year follow-up study. Neurology 1986; 36(11): 1528–30.

Rad primljen 1. VIII 2008.

ORIGINALNI ČLANAK UDC: 616.28-008.14-08

Da li je akutna senzorineuralna nagluvost hitno stanje?

Does acute sensorineural deafness befall to urgent conditions?

Ljiljana Čvorović*, Dragoslava Đerić†, Ljubomir Pavićević‡, Rudolf Probst§, Stefan Hegemann§

Kliničko bolnički centar "Zemun", *Odeljenje za otorinolaringologiju i maksilofacijalnu hirurgiju, **Beograd, Srbija; Klinički centar Srbije,** †Institut za otorinolaringologiju i maksilofacijalnu hirurgiju, **Beograd, Srbija; Vojnomedicinska akademija,** ‡Klinika za otorinolaringologiju, **Beograd, Srbija; University Hospital Zurich,** §Department of Otorhinolaryngology, **Zurich, Switzerland**

Apstrakt

Uvod/Cilj. Akutna idiopatska senzorineuralna nagluvost (AISNN) jedna je od najkontroverznijih tema u otologiji. Cilj istraživanja bio je da se utvrdi da li vreme započinjanja terapije ima ikakav efekat na bolji oporavak sluha kod AISNN. **Metode.** Studija je dizajnirana kao retrospektivno istraživanje elektronske baze podataka bolesnika Klinike za uho, nos i grlo, Univerzitetske bolnice u Cirihu, u jedanaestogodišnjem periodu od 1995. do 2006. Identifikovan je 541 bolesnik sa dijagnozom AISNN. U analiziranom periodu, bolesnici su lečeni sedam dana inhalacijom karbogena (95% O_2 i 5% CO_2) i oralnim prednizolonom. Inicijalni gubitak sluha definisan je kao prosečni prag sluha u dB (PPS inicijalni) u 4 frekvence (0,5; 1; 2 i 4 kHz) zahvaćenog uha. Na isti način određena je vrednost finalnog praga sluha nakon terapije (PPS finalni). Poboljšanje sluha definisano je na tri načina: apsolutno poboljšanje sluha (dB) = PPS inicijalni – PPS finalni; relativno poboljšanje sluha (%) = apsolutno poboljšanje / (PPS inicijalni – PPS drugog uva) × 100; značajnim oporavkom smatrao se finalni PPS ≤ 30 dB ili ukoliko je bio jednak sa PPS drugog uha. **Rezultati.** Prosečni apsolutni oporavak sluha bio je 15,1 dB, a prosečni relativni oporavak 47%. Tristotinejedan bolesnik (57%) imao je značajan oporavak, dok 228 (43%) nije. Među bolesnicima koji su primili terapiju u prva 24 h od početka nagluvosti, značajan oporavak sluha imalo je 56% i nije postojala značajna razlika između ove grupe bolesnika i grupe koja je primila terapiju posle 24 h, ali unutar sedam dana ($\chi^2 = 0{,}007$, DF = 1, $p > 0{,}01$). **Zaključak.** Na osnovu rezultata retrospektivne studije može se zaključiti da akutni gubitak sluha nije urgentno stanje i da terapiju nije potrebno započeti u prva 24 h, nego u prvih sedam dana.

Ključne reči:
sluh, senzornonervni gubitak; dijagnoza; lečenje; lečenje, ishod.

Abstract

Background/Aim. Idiopathic sudden sensorineural hearing loss (ISSHL) is one of the most controversial issues in otology. The aim of this study was to determine whether a delay in treatment has any influence on hearing recovery in ISSHL. **Method.** This study was designed as a retrospective evaluation of an electronic patient data base of the University Hospital Zürich from January 1995 to August 2006. Five hundred and forty one patients with a sudden hearing loss were identified. The standard treatment was carbogen inhalation (95% O_2 and 5% CO_2 eight times per day in the duration of 30 minutes) and prednisone orally (100 mg in one morning dose) for 7 days. Factor that was analyzed included the interval between the onset of symptoms and the beginning of the treatment. The initial hearing loss was described using the pure tone average (PTA in dB) hearing level at 4 frequencies (0.5, 1, 2 and 4 kHz). Hearing gain was expressed either as absolute hearing gain (dB values from initial PTA minus dB values from final PTA) or as relative hearing gain (absolute hearing gain divided by initial PTA minus baseline PTA) × 100. Significant recovery of hearing was defined as the final PTA ≤ 30 dB (or same as PTA of the opposite ear). **Results.** An absolute hearing gain between the initial audiogram and the final audiogram was 15.1 dB. The mean relative hearing gain was 47%. Three hundred one (57%) patients had a significant recovery of hearing, and 228 (43%) had not. If the patients received treatment in the first 24 hours after onset of symptoms, then the rate of significant recovery was 56%, and no significant difference existed between this group and the patients who received the therapy after 24 hours, but within seven days ($\chi^2 = 0.007$, DF = 1, $p > 0.01$). **Conclusion.** These results suggest that it is not critical to begin the treatment of ISSHL immediately as an emergency, but within seven days.

Key words:
hearing loss, sensorineural; diagnosis; therapy; treatment outcome.

Correspondence to: Ljiljana Čvorović, Kliničko bolnički centar, Odeljenje za otorinolaringologiju i maksilofacijalnu hirurgiju, Ul Vukova br. 9, 11 080 Beograd, Srbija. +381 11 138 99 24. E-mail: ljiljanamil@sezampro.rs

Uvod

Akutna idiopatska senzorineuralna nagluvost (AISNN) je gubitak sluha još uvek nejasne etiologije, veći od 30 dB u tri uzastopne frekvencije nastao u periodu od tri dana [1]. Zbog nejasnoća u etiologiji i patogenezi akutne nagluvosti, terapija je empirijska.

Većina autora preporučuje aktivno lečenje, iako je spontani oporavak sluha prisutan kod 65% bolesnika. Zaključak nekoliko studija bio je da ako bolesnik primi terapiju ranije, bolji je i odgovor na nju [2–4]. Stoga je cilj istraživanja bio da se utvrdi da li vreme započinjanja terapije ima bilo kakav efekat na bolji oporavak sluha kod AISNN.

Metode

Studija je dizajnirana kao retrospektivno istraživanje elektronske baze podataka bolesnika Klinike za uho, nos i grlo, Univerzitetske bolnice u Cirihu, u 11-godišnjem periodu od 1995 do 2006. Identifikovano je 970 bolesnika sa primarnom dijagnozom akutne senzorineuralne nagluvosti. Bolesnici uključeni u studiju imali su nagluvost veću od 30 dB u tri uzastopne frekvencije, nastalu u tri dana. Iz studije bili su isključeni bolesnici kod kojih je detaljnom dijagnostikom utvrđen uzrok akutne senzorineuralne nagluvosti: kongenitalne anomalije – Mondini displazija i uvećan vestibularni akvedukt; infekcije – virusne, bakterijske; inflamacije - sarkoidoza, Cogan sindrom, Wegenerova granulomatoza; traume – prelom temporalne kosti, akutna akustična trauma; tumori – vestibularni švanom, metastaze u temporalnoj kosti, karcinomatozni meningitis; druga oboljenja unutrašnjeg uha sa sindromom akutne nagluvosti – *Morbus Meniére*; primena ototoksičnih lekova; multipla skleroza.

Bolesnici su morali imati kompletne podatke bar dva audiograma, prvi pre terapije, i drugi najmanje četiri nedelje nakon završetka lečenja. Ukoliko je bilo više audiograma, poslednji se uzimao kao finalni.

Akutna nagluvost dijagnostikovana je kao simptom kod 40 bolesnika sa Menièreovom bolesti; sedam sa barotraumom; sedam sa akutnom akustičnom traumom; četiri sa vestibularnim švanomom; tri sa Coganovim sindromom; jedan sa Fabrijevom bolesti; HIV infekciju imalo je dvoje bolesnika; boreliozu tri bolesnika; mumps dva; fibroznu displaziju jedan; Mondini displaziju jedan; fistulu labirinta dva; i multiplu sklerozu jedan bolesnik. Svi ovi bolesnici isključeni su iz dalje obrade.

Upotrebom unapred navedenih kriterijuma identifikovan je 541 bolesnik sa akutnom idiopatskom senzorineuralnom nagluvosti sa potpunim podacima. Kod 12 bolesnika (2,2%) oštećenje je bilo bilateralno, te su i oni isključeni iz dalje analize zbog drugačije prirode bolesti. U daljem istraživanju koristili smo podatke 529 bolesnika.

Svi bolesnici bili su hospitalizovani i primali su istu terapiju. U analiziranom periodu, bolesnici su lečeni sedam dana inhalacijom karbogena (95% O_2 i 5% CO_2, osam puta dnevno u trajanju od 30 minuta) i oralnim prednisolonom (100 mg u jednoj jutarnjoj dozi).

Inicijalni gubitak sluha definisan je kao prosečni prag sluha u dB (PPS inicijalni) u 4 frekvencije (0,5; 1, 2 i 4 kHz) zahvaćenog uha. Na isti način određena je vrednost finalnog praga sluha nakon terapije (PPS finalni).

Za pretpostavljeni nivo sluha na zahvaćenom uhu pre naglog gubitka sluha, smatrao se prosečni prag sluha u 4 frekvencije kod zdravog uha (PPS drugog uha).

Poboljšanje sluha definisalo se na tri načina: apsolutno poboljšanje sluha (dB) = PPS inicijalni – PPS finalni; relativno poboljšanje sluha (%) = apsolutno poboljšanje / (PPS inicijalni – PPS drugog uha) × 100 i kao značajni oporavk (finalni PPS ≤ 30 dB ili ukoliko je bio jednak sa PPS drugog uha).

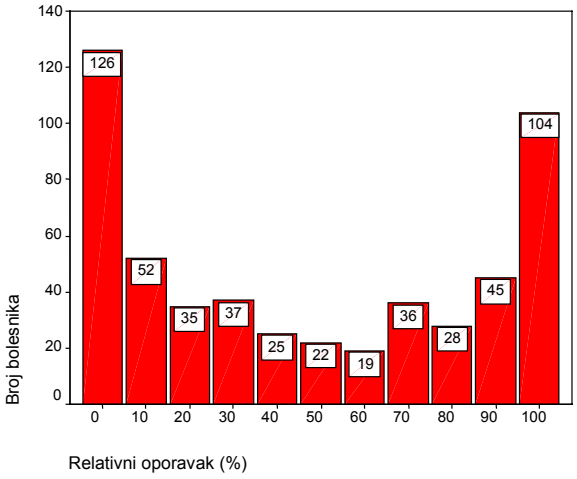
Rezultati

Istraživanjem je obuhvaćen 541 bolesnik sa akutnom idiopatskom senzorineuralnom nagluvosti (329 muškaraca i 212 žena), starosti od 13 do 88 godina. Desnostrano oštećenje sluha imalo je 249 bolesnika, a levostrano 280.

Kod dvanaestoro bolesnika (2,2%) oštećenje je bilo bilateralno i oni su isključeni iz dalje analize.

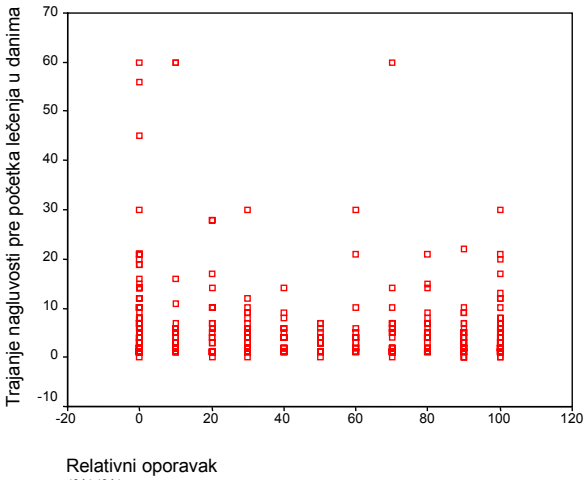
Prosečno vreme praćenja bolesnika bilo je 42 dana (od 28 do 125 dana).

Prosečni apsolutni oporavak sluha bio je 15,1 dB, a prosečni relativni oporavak 47%. Tristotine jedan bolesnik (57%) imao je značajan oporavak, dok 228 (43%) nije. Na slici 1 prikazan je broj bolesnika sa relativnim oporavkom sluha kategorisanim u 10% -grupe.



Sl. 1 – Broj bolesnika sa relativnim oporavkom sluha kategorisanim u 10% – grupe

Oporavak sluha u odnosu na trajanje simptoma nagluvosti pre početka lečenja prikazan je na slici 2. U prvih sedam dana trajanja nagluvosti 451 bolesnik primio je terapiju (85%), i značajno poboljšanje sluha imalo je 60%. Ovaj procenat pada na 40% ukoliko je terapija započela nakon sedam dana od pojave simptoma. Korelacija između trajanja nagluvosti i apsolutnog i relativnog oporavka je značajna (*Spearmanov* koeficijent korelacije = 0,178; p = 0,000 za apsolutni oporavak i 0,149; p = 0,001 za relativni oporavak).



Sl. 2 – Oporavak sluha i trajanje nagluvosti pre početka lečenja

Od bolesnika koji su primili terapiju tokom prva 24 h od pojave nagluvosti, značajan oporavak sluha imalo je 56%, i nije postojala značajna razlika između ove grupe bolesnika i grupe koja je primila terapiju posle 24 h ($\chi^2 = 0{,}007$; DF = 1, $p > 0{,}01$).

Diskusija

Analizom odnosa vremena od započinjanja terapije i oporavka sluha kod 529 bolesnika sa unilateralnom AISNN, zaključeno je da akutna nagluvost nije urgentno stanje i da terapiju nije neophodno započeti tokom prva 24 h. Efekat terapije na oporavak sluha bolji je ukoliko se terapija primi u prvih sedam dana.

U nekoliko studija se zaključuje da što ranije bolesnik primi terapiju, bolji je i odgovor na nju [2, 3]. Byl [3] navodi kompletni oporavak kod 56%, kada se bolesnici leče u prvih sedam dana, i samo 27% ukoliko se leče posle više od 30 dana od početka AISNN. Shaia i Sheehy [2] navode da je bolja prognoza kada bolesnici prime terapiju tokom mesec dana od nastanka nagluvosti. S obzirom na spontani tok oporavka sluha koji se dogodi kod oko 2/3 bolesnika bez tretmana, najčešće u prve dve nedelje, ne postoji nijedna studija kojom je jasno istražen povoljan uticaj ranog lečenja [5]. U našoj studiji 60% bolesnika koji su primili terapiju u prvih sedam dana od nastanka simptoma imalo je značajan oporavak. Ovaj procenat pada na 40% ukoliko su terapiju primili nakon više od sedam dana od nastanka nagluvosti. Nasuprot tome, nema značajne razlike u oporavku sluha ukoliko je terapija započeta u prva 24 h ili ukoliko je započeta u prvoj nedelji. Ovaj rezultat sugeriše da nije obavezno započeti terapiju akutne nagluvosti u prva 24 h kao da je hitno stanje. Eksperimentalne studije Tabuchi i sar. [6] prikazuju da 60-minutna anoksija uzrokovana pritiskom na labirintnu arteriju, izaziva ireverzibilne lezije kohlee zamorčića. Zaključak bi mogao biti da ukoliko je idiopatska akutna nagluvost nastala zbog vaskularnog prekida, tada bi terapiju trebalo započeti tokom prvog sata od nastanka, što je nerealan cilj koji nije podržan kliničkim iskustvom. Drugi autori publikovali su slične rezultate [7, 8].

Osnovni nedostatak naše studije je retrospektivni pristup. Bolesnici nisu bili deo protokola, već su lečeni na bazi kliničke procene u datom trenutku. Standardni terapijski protokol u Univerzitetskoj bolnici Cirih, u analiziranom periodu, bio je inhalacija karbogena (95% O_2 i 5% CO_2, osam puta dnevno u trajanju od 30 min) i oralni prednizolon (100 mg u jednoj jutarnjoj dozi), sve u trajanju od sedam dana. S obzirom na retrospektivni pristup i nedostatak kontrolne grupe, nismo vrednovali uticaj terapije na ishod lečenja. Ipak, stepen oporavka u analiziranoj grupi bolesnika čini se nizak u poređenju sa drugim publikovanim rezultatima, bilo spontanog oporavka, bilo oporavka nakon lečenja. Rezultati naše studije ukazuju da je prosečni relativni oporavak sluha kod bolesika oko 47%. Prosečno apsolutno poboljšanje sluha između inicijalnog i kontrolnog audiograma bilo je 15,1 dB. Weinaug [9] publikuje spontani oporavak sluha bez terapije za akutnu nagluvost od 25,6 dB i relativni oporavak sluha od 47%. Stepen spontanog oporavka sluha, definisan kao poboljšanje sluha za najmanje 30 dB, bio je 73% u studiji Mattoxa i Simmonsa [5]. Wilson i sar. [1] navode da 29 od 52 nelečena bolesnika dosegnu normalnu čujnost kod aficiranog uha (oko 56%). Prema ovim podacima iz literature, standardni protokol lečenja upotrebljen u analiziranom periodu nema značajan efekat na oporavak sluha. Ipak, ne može se zaključiti tako, zbog retrospektivne analize. Takođe, značajan uticaj su mogli imati i drugi faktori, kao što je selekcija grupe bolesnika koji su ispunjavali kriterijume za lečenje u hospitalnim uslovima.

Zbog nejasnoća u etiologiji i patogenezi akutne nagluvosti, terapija je empirijska. Trenutno, nijedna studija ne daje jasno značajan efekat primenjene terapije koja bi nesumnjivo prešla stepen spontanog oporavka. Čini se da je osnova oboljenja multifaktorijalna etiopatogeneza, što rezultira u primeni mnogih terapijskih protokola, uključujući primenu vazodilatatora, antikoagulanata, kortikosteroida, vitamina, plazma ekspandera, histamina, antvirusne terapije, kontrasnih sredstva, hiperbarične oksigenacije, ili oksigenacije karbogenom. Trenutno, većina studija podržava steroidnu terapiju u lečenju akutne nagluvosti. Analizom svih objavljenih kliničkih randomiziranih studija o efektu steroida na lečenje akutne nagluvosti, autori dolaze do zaključka da je malo pravih studija na tu temu, da je većina sa malim brojem bolesnika, te da se validan zaključak o vrednosti steroida i ne može dati [10].

Zaključak

Odloženi početak terapije kod akutne senzorineuralne nagluvosti nema uticaja na konačni oporavak sluha. Akutni gubitak sluha nije urgentno stanje i terapiju nije neophodno započeti u prva 24 h, već u prvih sedam dana.

L I T E R A T U R A

1. *Wilson WR*. Sudden sensorineural hearing loss. In: *Cummings CW*, ed. Otolaryngology Head and Neck Surgery, St. Luis: C.V. Mosby. p. 3219–24.
2. *Shaia FT, Sheehy JL*. Sudden sensori-neural hearing impairment: a report of 1,220 cases. Laryngoscope 1976; 86(3): 389–98.
3. *Byl FM Jr*. Sudden hearing loss: eight years' experience and suggested prognostic table. Laryngoscope 1984; 94(5 Pt 1): 647–61.
4. *Cvorović L, Deric D, Probst R, Hegemann S*. Prognostic model for predicting hearing recovery in idiopathic sudden sensorineural hearing loss. Otol Neurotol 2008; 29(4): 464–9.
5. *Mattox DE, Simmons FB*. Natural history of sudden sensorineural hearing loss. Ann Otol Rhinol Laryngol 1977; 86(4 Pt 1): 463–80.
6. *Tabuchi K, Kusakari J, Ito Z, Takahashi K, Wada T, Hara A*. Effect of nitric oxide synthase inhibitor on cochlear dysfunction induced by transient local anoxia. Acta Otolaryngol 1999; 119(2): 179–84.
7. *Huy PT, Sauvaget E*. Idiopathic sudden sensorineural hearing loss is not an otologic emergency. Otol Neurotol 2005; 26(5): 896–902.
8. *Tran Ba Huy P, Sauvaget E*. Idiopathic sudden sensorineural hearing loss is not, at this time, an otologic emergency. Ann Otolaryngol Chir Cervicofac 2007; 124(2): 66–71. (French)
9. *Weinaug P*. How high is the rate of spontaneous healing of sudden deafness? Comments on the contribution "Spontaneous healing of sudden deafness". HNO 2001; 49(6): 431–2; discussion 433. (German)
10. *Conlin AE, Parnes LS*. Treatment of sudden sensorineural hearing loss: II. A Meta-analysis. Arch Otolaryngol Head Neck Surg 2007; 133(6): 582–6.

Rad je primljen 19. VIII 2008.

ORIGINALNI ČLANAK UDC: 616.248:616.24-073.173

Simptomi, fizikalni nalaz i bronhijalna hipersenzitivnost kod bolesnika sa bronhijalnom astmom i normalnim spirometrijskim nalazom

Symptoms, physical findings and bronchial hypersensitivity in patients with bronchial asthma and normal spirometry

Slobodan Aćimović, Goran Plavec, Ilija Tomić, Vukoica Karličić, Svetlana Aćimović, Jelena Vuković, Olivera Lončarević

Vojnomedicinska akademija, Klinika za plućne bolesti, **Beograd**

Apstrakt

Uvod/Cilj. Dijagnoza bronhijalne astme, hroničnog inflamatornog oboljenja disajnih puteva, postavlja se na osnovu anamneze, patološkog auskultatornog nalaza nad plućima, poremećaja plućne funkcije, kožnih testova i osnovnih pokazatelja imunološkog stanja u bronhijalnom stablu. Cilj rada bio je da se kod obolelih od bronhijalne astme sa normalnim spirometrijskim nalazom proceni međusobna povezanost objektivnih parametara bolesti, kao i njihova veza sa simptomima oboljenja. **Metode.** U studiju su bili uključeni bolesnici nepušači (60 mladih muškaraca), sa višegodišnjim simptomima bronhijalne astme kao što su gušenje, sviranje u grudima, otežano disanje, suv ili produktivan kašalj, zamaranje i noćno gušenje. Nije bilo simptoma ni znakova respiratorne infekcije tokom prethodna dva meseca i radiografija pluća i spirometrijski nalaz bili su normalni. Na osnovu rezultata nespecifičnog bronhoprovokacijskog testa formirane su dve grupe bolesnika: grupa I (30 bolesnika) sa pozitivnim histaminskim testom, prosečna vrednost koncentracije udahnutog histamina sa padom FEV1 za 20% u odnosu na početnu vrednost (PC20) bila 2,99 ± 0,51 mg/ml i grupa II (30 bolesnika) sa negativnim histaminskim testom (PC20(a) = 14,58 ± 6,34 mg/ml). **Rezultati.** Analizom rezultata spirometrije utvrđeno je da je postojala statistički značajna razlika vrednosti FEV1 među grupama: grupa I – FEV1 = 93,2%; grupa II – FEV1 = 101,8%; ($p < 0,05$, *Wilcoxon's* test), iako su sve vrednosti FEV1 bile u području referentnih. U zastupljenosti najčešćih simptoma nije bilo značajne razlike među grupama ($p > 0,05$, hi-kvadrat test). Patološki auskultatorni nalaz nad plućima postojao je kod 73,4% bolesnika u grupi I, a u grupi II kod 27,5% bolesnika ($p < 0,05$, hi-kvadrat test). Potvrđena je pozitivna korelacija između stepena hipersenzitivnosti i fizičkog nalaza na plucima ($p < 0,05$, *Spearman*-ov koeficijent korelacije) dok nije bilo korelacije sa vrednostima FEV1. **Zaključak:** Postoji povezanost patološkog auskultatornog nalaza nad plućima, nižih vrednosti FEV1 (u granicama referentnih vrednosti) i stepena nespecifične bronhijalne hipersenzitivnosti kao objektivnih pokazatelja aktivnosti bronhijalne astme. Nema korelacije tih parametara sa ispoljenim simptomima kao subjektivnim pokazateljima aktivnosti bronhijalne astme.

Ključne reči:
astma; dijagnoza; respiratorni znaci i simptomi; respiratorna funkcija, testovi; spirometrija; ekspiratorni volumen, forsirani; hipersenzibilnost, respiratorna.

Abstract

Background/Aim. The diagnosis of bronchial asthma, a chronic inflammatory disease of the respiratory tract, is made on the basis of anamnesis, pathologic auscultatory findings of the lungs, lung function disturbances, skin tests, as well as the basic indices of immunologic condition in bronchial trunk. The aim of the study was to find out correlation of objective indices of the disease and than relation with the symptoms in the patients with bronchial asthma. **Methods.** The study included 60 young male non smokers with long lasting symptoms of bronchial asthma including shortness of breath, wheezing, hard breathing, nonproductive or productive cough, weakness and night hard breathing. There were no symptoms of respiratory infection over the past two months and lung radiography and spirometry were normal. Based on the results of nonspecific bronchoprovocative test two groups of the patients were formed, group I (n = 30) with positive histamine test (average value of the inhaled histamine concentration with FEV1 drop by 20% in regard with the initial value (PC20) = 2.99 ± 0.51 mg/ml of histamine) and group II (n = 30) with negative histamine test (PC20(a) = 14.58 ± 6.34 mg/ml of histamine). **Results.** The obtained spirometry results revealed a statistically significant difference in values of FEV1 between groups: I group – FEV1 = 93.2%; II group – FEV1 = 101.8%; ($p < 0.05$, Wilcoxon test), although all the FEV1 values were normal. Regarding the presence of the most common symptoms there was not statistically significant difference between the groups ($p > 0.$ 05, chi-square test). Pathologic auscultatory lung findings were found in 73.4% of the patients in the group I and 27.5% of the patients in the group II. There was statistically significant difference ($p < 0.05$, chi-squared test). A positive correlation between the degree of hypersensitivity and lung physical findings was confirmed ($p < 0.05$ Spearman's rho), but there was no correlation with FEV1 values. **Conclusion.** There is a correlation with lung pathologic physical findings, lower values of FEV1 (in a range of normal values) and the degree of nonspecific bronchial sensitivity as objective indices of activity of bronchial asthma. There is no correlation of these parameters with patient's symptoms as subjective indices of bronchial asthma.

Key words:
asthma; diagnosis; signs and simptoms, respiratory; respiratory function tests; spirometry; forced expiratory volume; respiratory hypersensitivity.

Correspondence to: Slobodan Aćimović, Vojnomedicinska akademija, Klinika za plućne bolesti, Crnotravska 17, 11 040 Beograd, Srbija. Tel.: +381 11 3609 249.

Uvod

Bronhijalna astma je hronična inflamatorna bolest disajnih puteva koja se klinički odlikuje napadima otežanog disanja, posebno u fazi ekspirijuma, praćenim zviždanjem u grudima, kašljem i iskašljavanjem žilavog sekreta. Do tegoba dovodi promenljiva bronhoopstrukcija u čijoj osnovi je hiperreaktivnost disajnih puteva [1–4].

Dokazano je da u razvoju bronhijalne astme najveći značaj imaju hronična inflamacija bronhijalne sluznice u kojoj učestvuju brojne ćelije i medijatori i bronhijalna hiperreaktivnost [1, 3–14].

Dijagnoza bronhijalne astme postavlja se na osnovu anamneze, patološkog fizikalnog nalaza nad plućima, poremećaja plućne funkcije uzrokovanog ograničenjem protoka vazduha, kožnih testova sa inhalacionim alergenima, i osnovnih pokazatelja imunološkog stanja u bronhijalnom stablu (broj eozinofilnih leukocita u perifernoj krvi, nivo imunoglobulina E u serumu i broj eozinofilnih leukocita u sputumu) [4, 15–17].

Mogući patofiziološki poremećaji u bronhijalnoj astmi su: regionalni poremećaji distribucije ventilacije, izražena hiperinflacija pluća, poremećen odnos ventilacije i perfuzije, a u odmakloj fazi alveolarna hipoventilacija sa poremećajem difuzije gasova, što može dovesti do plućne insuficijencije [1, 2, 18–20].

Bronhijalna astma odlikuje se promenljivom težinom kliničke slike u čijoj osnovi postoji varijabilna opstrukcija protoku vazduha u disajnim putevima. Varijabilnost je posledica prirode bolesti čiju osnovu takođe čini varijabilna hiperreaktivnost disajnih puteva uzrokovana hroničnom inflamacijom.

Testovi plućne funkcije u fazi ispoljene bolesti najčešće pokazuju poremećaje i služe u dijagnostici, proceni težine astme, proceni težine napada astme, proceni efekta terapije, kao i za praćenje bolesnika. Za verifikaciju ograničenja protoka vazduha u disajnim putevima najviše se koristi merenje plućne ventilacije spirometrijskim testom i određivanje vrednosti vršnog ekspirijumskog protoka – *Peak Expiratory Flow* (PEF) [3, 4, 21, 22].

Spirometrija je osnovni test kojim procenjujemo ventilaciju pluća kod bolesnika sa bronhijalnom astmom. Spirometrijom se mere: forsirani vitalni kapacitet (FVC), forsirani ekspirijumski volumen u prvoj sekundi (FEV1) i odnos forsiranog ekspirijumskog volumena u prvoj sekundi i forsiranog vitalnog kapaciteta (FEV1/FVC × 100 – *Tiffneau* indeks). Dobijeni rezultati upoređuju se sa referentnim vrednostima.

U fazi aktivnosti bronhijalne astme spirometrijski se obično registruje opstrukcijski poremećaj ventilacije (smanjenje FEV1 i *Tiffneau* indeksa). Međutim, spirometrijski test je često i normalan kod bolesnika sa bronhijalnom astmom [2–4, 21, 23, 24].

Ukoliko testovi plućne funkcije ne pokazuju poremećaje koji bi potvrdili dijagnozu, a klinička slika ukazuje na astmu, vrši se bronhoprovokacijsko testiranje. Cilj testiranja je da se utvrdi da li postoji i kog je stepena hipersenzitivnost/hiperreaktivnost bronha [25, 26].

Dijagnoza bronhijalne astme, hroničnog inflamatornog oboljenja disajnih puteva, postavlja se na osnovu anamneze, patološkog auskultatornog nalaza nad plućima, poremećaja plućne funkcije, kožnih testova i osnovnih pokazatelja imunološkog stanja u bronhijalnom stablu. Cilj rada bio je da se kod obolelih od bronhijalne astme sa normalnim spirometrijskim nalazom proceni međusobna povezanost objektivnih parametara bolesti, kao i njihova veza sa simptomima oboljenja.

Metode

Studijom je bilo obuhvaćeno 60 bolesnika muškog pola, u dobi od 17 do 29 godina, nepušača, sa višegodišnjim simptomima kao što su gušenje, sviranje u grudima, otežano disanje, suv ili produktivan kašalj, zamaranje i noćno gušenje.

Svim bolesnicima, nakon uzimanja anamneze, fizičkog pregleda, kutanih proba sa inhalacionim alergenima i spirometrijskog testa, urađeno je bronhoprovokacijsko testiranje histaminom. Spirometrijski test rađen je na ekspirografu firme „Godart“ i „Jaegger“.

Po određivanju bazalnih vrednosti parametara plućne ventilacije bronhoprovokacijsko testiranje vršeno je kumulativnom tehnikom, a prag senzitivnosti označavan je sa PC20 što predstavlja koncentraciju udahnutog rastvora histamina nakon koje se beleži pad vrednosti FEV1 za 20%. Vrednost PC20 dobija se algoritamskom transformacijom iz rezultata merenja. Test je negativan kada je PC20 ≥ 8 mg/ml histamina [27–29].

Na osnovu rezultata nespecifičnog bronhoprovokacijskog testa formirane su dve grupe bolesnika: I grupa (30 bolesnika) sa pozitivnim histaminskim testom kojim je utvrđeno postojanje umerene hipersenzitivnosti bronhijalnog stabla, u kojoj je prosečna vrednost PC20 = 2,99 +/-0,51 mg/ml histamina i grupa II (30 bolesnika) sa negativnim histaminskim testom (PC20(a) = 14,58 ± 6,34 mg/ml histamina).

Tokom prethodna dva meseca bolesnici nisu imali simptome ni znake respiratorne infekcije, a radiografija pluća i spirometrijski nalaz bili su normalni (FEV1 i FVC > 80% vrednosti predviđenih normom).

Rezultati

Nije postojala statistički značajna razlika u starosti bolesnika i dužini bolesti između grupe sa umerenim stepenom hipersenzitivnosti bronha i grupe sa negativnim nespecifičnim bronhoprovokacijskim testom sa histaminom (tabela 1).

U zastupljenosti najčešćih simptoma nije bilo značajne razlike među grupama ($p > 0,05$) (tabela 2).

Fizikalni nalaz nad plućima kod bolesnika obe grupe prikazan je u tabeli 3.

Analizom rezultata spirometrije utvrđeno je da su vrednosti FEV1 u grupi sa izraženom hipereaktivnošću bronha niže u apsolutnom iznosu, odnosno u procentu norme i da je ta razlika statistički značajna: FEV1 (grupa I) = 93,2%; FEV1 (grupa II) = 101,8%; ($p < 0,05$, *Wilcoxon* test), premda su sve vrednosti FEV1 u području referentnih (tabela 4).

Tabela 1

Demografske osobine bolesnika sa bronhijalnom astmom i pozitivnim (grupa I) i negativnim (grupa II) histaminskim testom

Parametri	grupa I (n = 30)	grupa II (n = 30)
Godine života [n(%)]		
17–20	13 (43,5)	26 (65)
21–25	13 (43,5)	8 (20)
26–29	4 (13)	6 (15)
Prosečna starost (god), x ± SD	21,9 ± 2,6	20,8 ± 1,6
Trajanje bolesti (god), x ± SD	11,2 ± 2,3	8,2 ± 2,2

Tabela 2

Simptomi astme kod bolesnika sa pozitivnim (grupa I) i negativnim (grupa II) histaminskim testom

Tegobe	grupa I	grupa II
	broj (%)	broj (%)
Gušenje	24 (80)	21 (52,5)
Suv kašalj	6 (20)	15 (37,5)
Sviranje u grudima	6 (20)	9 (22,5)
Produktivan kašalj	6 (20)	2 (5)
Otežano disanje	3 (10)	4 (10)
Zamaranje	3 (10)	2 (5)
Stezanje u grudima	3 (10)	6 (15)
Curenje nosa	3 (10)	6 (15)
Kijavica	3 (10)	13 (32,5)
Noćno gušenje	2 (6,6)	9 (22,5)
Crvenilo očiju	2 (6,6)	2 (5)
Svrab po koži	2 (6,6)	1 (2,5)

Tabela 3

Fizikalni nalaz nad plućima obolelih od astme sa pozitivnim (grupa I) i negativnim (grupa II) histaminskim testom

Fizikalni nalaz	Bolesnici	
	grupa I (n = 30)	grupa II (n = 30)*
	broj (%)	broj (%)
Uredan	8 (26,6)	22 (72,5)
Visokotonski zvižduci	9 (30)	1 (2,5)
Produžen ekspirijum	9 (30)	1 (2,5)
Oslabljeno disanje	5 (10,6)	
Polifoni zvižduci	3 (10)	1 (2,5)
Niskotonski zvižduci	3 (10)	1 (2,5)
Pooštreno disanje	4 (13)	7 (23)

*$p < 0,05$ *vs* grupa I (hi-kvadrat test)

Tabela 4

Plućna ventilacija obolelih od bronhijalne astme sa pozitivnim (grupa I) i negativnim (grupa II) histaminskim testom

Parametar	grupa I (n = 30)		grupa II (n = 30)	
	x ± SD	% norme	x ± SD	% norme
FVC† (L)	5,24 ± 0,77	95,6	5,36 ± 0,71	96,8
FEV1‡(L)	4,35 ± 0,94	93,2	4,67 ± 0,71	101,8*
Tiffneau indeks (%)	83,65 ± 5,79	96,1	86,7 ± 5,73	104,5

*$p < 0,05$ *vs* grupa I (*Wilcoxon* test); †forsirani vitalni kapaciatet; ‡forsirani ekspirijumski volumen u prvoj sekundi

Patološki auskultatorni nalaz nad plućima postojao je kod 73,4% bolesnika u grupi I i kod 27,5% bolesnika u grupi II ($p < 0,05$).

Potvrđena je pozitivna korelacija između stepena hipersenzitivnosti i fizičkog nalaza nad plućima ($p < 0,05$, *Spearman*-ov koeficijent korelacije), ali nije postojala korelacija sa nižim vrednostima FEV1.

Diskusija

Hiperreaktivnost bronha osnovna je odlika bronhijalne astme i predstavlja pojačan odgovor bronha na različite endogene i egzogene stimuluse koji se manifestuje sužavanjem lumena ili bronhokonstrikcijom. Hiperreaktivnost je uz inflamaciju i varijabilnost i jedan od osnovnih pojmova u defi-

niciji bronhijalne astme. Uzrok hiperreaktivnosti bronha nije u potpunosti razjašnjen [4, 14, 26–30].

Varijabilnost je razlog što se često kod bolesnika sa ispoljenim simptomima spirometrijskim testom ne registruju poremećaji plućne ventilacije.

Ako anamneza odgovara bronhijalnoj astmi, a testovi spirometrije su normalni, u cilju potvrde ili eventualnog isključivanja dijagnoze bronhijalne astme treba izvršiti ispitivanje bronhijalne hiperreaktivnosti [3, 4, 31, 32].

Kod svih ispitivanih bolesnika izvršeno je nespecifično bronhoprovokacijsko testiranje histaminom, koje je standardizovano [33, 34]. Stepen dobijene nespecifične hipersenzitivnosti bio je kriterijum za randomizaciju. Analizom starosti i dužine trajanja tegoba utvrđeno je da se radilo o homogenim grupama bolesnika kojima je isključeno postojanje nekog drugog akutnog ili hroničnog oboljenja ili stanja koje je moglo dovesti do hiperreaktivnosti bronha [35–37].

Analizom učestalosti najzastupljenijih simptoma koje su bolesnici navodili, kao što su gušenje, kašalj ili sindrom zahvaćenosti gornjih disajnih puteva, zapaženo je da je veća zastupljenost gušenja bila u grupi sa dokazanom hiperreaktivnošću, ali ni za jedan od simptoma nije nađena statistički značajna razlika po grupama. Noćno gušenje, kao važan pokazatelj težine astme, bilo je manje zastupljeno u grupi sa pozitivnim histaminskim testom, što je paradoksalno [1, 4].

U prvoj grupi bolesnika patološki nalaz nad plućima bio je zastupljen kod 73,4%, a u drugoj grupi kod 27,5% bolesnika i tu postoji statistički značajna razlika. Može se zaključiti da postoji povezanost između inicijalno utvrđenog stepena nespecifične hipersenzitivnosti bronha i zastupljenosti patološkog auskultatornog nalaza nad plućima u smislu pozitivne korelacije. Pozitivna korelacija u fizikalnom nalazu i odsustvo korelacije sa prikazom simptoma mogu se objasniti time što je fizikalni nalaz objektivniji parametar od subjektivnog osećaja bolesnika koji rezultira isticanjem pojedinih simptoma bolesti [38, 39].

Niže vrednosti FEV1 registrovane su u grupi sa dokazanom umerenom hipersenzitivnošću bronha i razlika prosečnih vrednosti je statistički značajna. Statističkom analizom nije potvrđeno postojanje korelacije nižih vrednosti FEV1 sa stepenom hipersenzitivnosti i kliničkim nalazom. Ipak, rezultati nam daju za pravo da u drugoj prilici činjenice posmatramo obrnutim redosledom, tj. da pretpostavimo da bolesnik sa karakterističnim simptomima oboljenja, patološkim fizikalnim nalazom nad plućima i nešto nižim vrednostima parametara plućne ventilacije ima i značajnu hiperreaktivnost bronha. To može biti značajno za dijagnostiku, terapijski pristup i praćenje bolesnika sa bronhijalnom astmom.

Zaključak

Postoji pozitivna međusobna korelacija patološkog auskultatornog nalaza nad plućima, stepena nespecifične bronhijalne hipersenzitivnosti i nižih vrednosti FEV1 (u granicama referentnih) kao objektivnih parametara bolesti ali nema korelacije tih parametara sa simptomima kod obolelih od bronhijalne astme.

L I T E R A T U R A

1. National Heart, Lung, and Blood Institute, National Institutes of Health. International consensus report on diagnosis and treatment of asthma. Eur Respir J 1992; 5(5): 601–41.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. NHLB/WHO Workshop Report. NIH Publication 1995. No 02–3659. Available from: www.smj.org.sa/PDFFiles/Jun03/01Efficacy.pdf
3. Workshop Report: Global strategy for Asthma Management and Prevention. Scientific information and recommendations for asthma programs. NIH publication 2002. No 02-3659. Available from: www.ginasthma.com/GuidelineList.asp?l1=2&l2=1&archived
4. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention. NHLB/WHO Workshop Report. (Revised 2006.). Available from: www.intute.ac.uk/healthandlifesciences/cgi-bin/browse.pl?gateway=omni&id=252552
5. *Lacoste JY, Chanez P, Paganin F, Godard P, Michel FB, Bousquet J.* Bronchial inflammation in asthma. Evaluation by bronchial biopsies. Rev Mal Respir 1991; 8(6): 533–41. (French)
6. *Jeffery PK.* Bronchial biopsies and airway inflammation. Eur Respir J 1996; 9(8): 1583–7.
7. *Corrigan SJ, Kay AB.* T-cell/eosinophil interactions in the induction of asthma. Eur Respir J 1996; 22(Supp l 9): 72–8.
8. *James E, Fish J*R. Airway hyperresponsiveness in Asthma. Is it unique. CHEST 1995; 107: 154–6.
9. *Kraft M, Đukanović R, Torvik J, Cunningham L, Henson J, Wilson S,* et al. Evaluation of Airway Inflamation by Endobronchial and Transbronchial Biopsy in Nocturnal And Nonnocturnal Asthma. CHEST 1995; 107(Suppl 3): 162s.
10. *Drazen JM.* Leukotrienes as mediators of airway obstruction. Am J Respir Crit Care Med 1998; 158(5 Pt 3): S193–200.
11. *Gauvreau GM, Watson RM, O'Byrne PM.* Kinetics of allergen-induced airway eosinophilic cytokine production and airway inflammation. Am J Respir Crit Care Med 1999; 160(2): 640–7.
12. *Gonzalez MC, Diaz P, Galleguillos FR, Ancic P, Cromwell O, Kay AB.* Allergen-induced recruitment of bronchoalveolar helper (OKT4) and suppressor (OKT8) T-cells in asthma. Relative increases in OKT8 cells in single early responders compared with those in late-phase responders. Am Rev Respir Dis 1987; 136(3): 600–4.
13. *Wilson JW, Djukanović R, Howarth PH, Holgate ST.* Lymphocyte activation in bronchoalveolar lavage and peripheral blood in atopic asthma. Am Rev Respir Dis 1992; 145(4 Pt 1): 958–60.
14. *Chapman ID, Foster A, Morley J.* The relationship between inflammation and hyperreactivity of the airways in asthma. Clin Exp Allergy 1993; 23(3): 168–71.
15. *Stevanović M.* Chronical obstruction of lung disease and bronchial asthma. In: *Stevanović M*, editor. Chronical obstruction of lung disease and bronchial asthma. Beograd: Jugoslavijapublik; 1994. p. 8–13. (Serbian)
16. *Bright P, Burge PS.* Occupational lung disease 8. The diagnosis of occupational asthma from serial measurements of lung function at and away from work. Thorax 1996; 51(8): 858–63.
17. *Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P*, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet 2002; 360(9347): 1715–21.

18. *Stevanović M.* Zone ventilation disorders in chronical obstructive respiratory syndrome. In: *Stevanović M,* editor. Proceedings of the Symposium on Clinical Physiology of Breathing; 1972; Kruševac: Srpsko lekarsko drustvo; 1972. p. 50–60. (Serbian)
19. *Štangl B.* Pathophysiology of breathing in bronchial asthma. Modern approach to bronchial asthma prophylaxis. Krka in medicine and pharmacy 1986; (suppl 1): 17– 26. (Serbian)
20. *Rebić P.* Significance of the issue of asthma. In: *Bošnjaković-Petrović V*, editor. Significance questions about asthma. Beograd: Medicina moderna 1998. (Serbian)
21. *Official statement of the European Respiratory Society.* Standardized lung function testing. Eur Respir J Suppl 1993; 16: 1–100.
22. *Reddel HK, Salome CM, Peat JK, Woolcock AJ.* Which index of peak expiratory flow is most useful in the management of stable asthma? Am J Respir Crit Care Med 1995; 151(5): 1320–5.
23. *American Thoracic Society.* Standardization of Spirometry, 1994 Update. Am J Respir Crit Care Med 1995; 152(3): 1107–36.
24. *Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R,* et al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26(5): 948–68.
25. *Ryan G, Latimer KM, Dolovich J, Hargreave FE.* Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway calibre. Thorax 1982; 37(6): 423–9.
26. *O'Byrne PM, Inman MD.* Airway Hyperresponsiveness. CHEST 2003; Suppl 123: 414s–6s.
27. *Cropp GJA, Bernstein IL, Boushey HA.* Guidelines for bronchial inhalation challeng with pharmacologic and antigenic agents. Am Thorac Soc News, Spring 1980: 11–9.
28. *Cockcroft DW, Killian DN, Mellon JJ, Hargreave FE.* Bronchial reactivity to inhaled histamine: a method and clinical survey. Clin Allergy 1977; 7(3): 235–43.
29. *Lötvall J, Inman M, O'Byrne P.* Measurement of airway hyperresponsiveness: new considerations. Thorax 1998; 53(5): 419–24.
30. *Tanurdzić S, Balaban J, Durić V, Dimcić Z.* Etiopathogenic mechanisms of increased airway responsiveness. Plucne Bolesti 1990; 42(1–2): 5–9. (Croatian)
31. *Koh YY, Kang EK, Kang H, Yoo Y, Park Y, Kim CK.* Bronchial hyperresponsiveness in adolescents with long-term asthma remission: importance of a Family history of bronchial hyperresponsiveness. Chest 2003; 124(3): 819–25.
32. *Zhong NS, Chen RC, Yang MO, Wu ZY, Zheng JP, Li YF.* Is asymptomatic bronchial hyperresponsiveness an indication of potential asthma? A two-year follow-up of young students with bronchial hyperresponsiveness. Chest 1992; 102(4): 1104–9.
33. *Cockcroft DW, Berscheid BA.* Standardization of inhalation provocation tests. Dose vs concentration of histamine. Chest 1982; 82(5): 572–5.
34. *Ninković M, Radojicić M.* Standardization of bronchial provocation tests using histamine. Vojnosanit Pregl 1988; 45(5): 350–2. (Serbian)
35. *Boushey HA, Avila PC.* Viral respiratory infections and asthma. Resp Care, 1997; 2: 10–1.
36. *Pauwels R, Peleman R, Van der Straeten M.* Airway inflammation and non allergic bronchial responsiveness. Eur J Respir Dis Suppl 1986; 144: 137–62.
37. *Belousova EG, Haby MM, Xuan W, Peat JK.* Factors that affect normal lung function in white Australian adults. Chest 1997; 112(6): 1539–46.
38. *Killian KJ, Summers E, Watson RM, O'Byrne PM, Jones NL, Campbell EJ.* Factors contributing to dyspnoea during bronchoconstriction and exercise in asthmatic subjects. Eur Respir J 1993; 6(7): 1004–10.
39. *Killian KJ, Watson R, Otis J, St Amand TA, O'Byrne PM.* Symptom perception during acute bronchoconstriction. Am J Respir Crit Care Med 2000; 162(2 Pt 1): 490–6.

Rad primljen 21. VIII 2008.

ORIGINAL ARTICLE UDC: 618.177:618.14–002]:618.111:615.357

Effects of physical exercise on inflammatory parameters and risk for repeated acute coronary syndrome in patients with ischemic heart disease

Efekat fizičkog vežbanja na parametre inflamacije i rizik od relapsa akutnog koronarnog sindroma kod bolesnika sa ishemijskim oboljenjem srca

Goran Ranković*, Branislava Miličić†, Todorka Savić‡, Boris Đinđić||, Zorica Mančev||, Gordana Pešić§

University in Niš, School of Medicine, ***Institute of Physiology, ||Institute of Pathophysiology, §Institute of Pharmacology, **Niš, Serbia; †Clinical Centre, Maribor, Slovenija; ‡Institute for Prevention, Treatment and Rehabilitation of Rheumatic and Cardiovascular Diseases, Niška Banja, Serbia

Abstract

Background/Aim. Inflammation is an important factor in the pathogenesis of atherosclerosis, and several markers of inflammation have been associated with an increased risk of cardiovascular events. Physical activity may lower the risk for coronary heart disease (CHD) by mitigating inflammation. The aim of this study was to investigate the effects of aerobic physical exercise on systemic inflammatory response in patients with stable coronary disease participating in a cardiovascular rehabilitation exercise program. **Methods.** Male (n = 29) and female (n = 23) patients with stable coronary heart disease were enrolled in this study. All the patients were divided into two groups: the group with regular aerobic physical training during cardiovascular rehabilitation program phase II for 3 weeks in our rehabilitation center and 3 weeks after that in their home setting, and sedentary lifestyle group. There were no significant differences in gender distribution among the analysed groups. Student's *t*-test showed no significant differences in average age, waist circumference (OS) and waist/hip ratio (WHR). **Results.** The degree of obesity was measured by BMI and there was a significant improvement in BMI in the patients who undertook 6-week physical training compared to the controls ($p < 0.05$). Physical training during 6-week appeared not to have any effects on leukocite count and ICAM-1 levels compared to controls. Exercise induced reduction in plasma CRP levels by 23.72% ($p < 0.001$) and reduction in plasma VCAM-1 levels by 10.23%, ($p < 0.05$). **Conclusion.** Moderate aerobic exercise resulted in a significant reduction of inflammatory state by decreasing CRP and VCAM-1 levels with significant obesity reduction but without visceral obesity reduction. The obtained results indicate that regular physical activity is clinically desirable in primary and secondary prevention of coronary heart disases.

Key words:
coronary disease; inflammation mediators; exercise therapy; treatment outcome; risk factors.

Apstrakt

Uvod/Cilj. Inflamacija predstavlja važan patogenetski faktor u pojavi i progresiji ateroskleroze. Fizička aktivnost smanjuje rizik od pojave koronarne bolesti srca. Smatra se da je jedan od osnovnih mehanizama pozitivnog delovanja redukcija sistemskog inflamacijskog odgovora. Cilj rada bio je da se ispita efekat aerobnog fizičkog treninga umerenog intenziteta na inflamacijske pokazatelje kod bolesnika sa preležanim infarktom miokarda. **Metode.** U istraživanje je bio uključeno 52 bolesnika (29 muškaraca i 23 žene) sa stabilnom koronarnom bolešću koji su bili podeljeni na grupu sa redovnim fizičkim treningom u trajanju od šest nedelja i sedentarnu grupu. Bolesnici u ispitivanim grupama bili su slične starosti i bez značajnijih razlika u vrednostima obima struka i odnosa struk/kuk. Svi bolesnici uključeni u istraživanje imali su pozitivnu istoriju za postojanje preležanog infarkta miokarda, koronarne revaskularizacije ili angiografske potvrde 50% stenoze jednog ili više koronarnih sudova. **Rezultati.** Stepen gojaznosti meren kroz BMI ukazuje na nešto manju gojaznost bolesnika koji su bili podvrgnuti fizičkom treningu. Nije nađena značajnija razlika u vrsti terapijskog rešavanja akutnog koronarnog sindroma. Broj leukocita i koncentracija ICAM-1 molekula nisu se razlikovali između ispitivanih grupa. Efekat fizičkog treninga ogleda se u značajnom smanjenju vrednosti hsCRP za 23,72% ($p < 0,01$) i redukciji koncentracije VCAM-1 molekula za 10,23% ($p < 0,05$). **Zaključak.** Aerobni fizički trening sa submaksimalnim opterećenjem dovodi do značajnog pada inflamacijskih markera CRP i VCAM, čak i bez značajnije redukcije telesne težine ili smanjenja visceralne gojaznosti. Svi ovi efekti fizičkog treninga imaju korisne efekte u redukciji kardiovaskularnog rizika od pojave nakanadnih koronarnih događaja i ukazuju da fizička aktivnost ima značajno mesto u primarnoj i sekundarnoj prevenciji koronarne bolesti.

Ključne reči:
koronarna bolest; zapaljenje, medijatori; lečenje vežbanjem; lečenje, ishod; faktori rizika

Correspondence to: Goran Ranković, University in Niš, School of Medicine, Institute of Physiology, Novoprojektovana bb, 18 000 Niš, Serbia. Tel.: +381 062 127 28 72. E-mail: boris_dj@medfak.ni.ac.yu

Introduction

Inflammation is an important factor in the pathogenesis of atherosclerosis and several markers of inflammation have been associated with an increased risk of cardiovascular events [1, 2]. The acute phase reactant, C-reactive protein (CRP) is a sensitive marker of inflammation [3]. Researches have showed that elevated concentration of CRP is a independent prognostic factor for increased cardiovascular mortality and morbidity, as well as the occurrence of certain clinical manifestations of acute coronary syndrome in both genders [4].

Physical activity may lower the risk of coronary heart disease. It is thought that one of the basic mechanisms of its favorable impact is the reduction of systemic inflammatory response [5]. Regular physical training can lower the values of CRP [6]. Smith et al.[7] have reported that there was a CRP reduction trend after 6 months of physical training in persons at high risk of ischemic heart disease. This type of training produces similar tendency of reduction of inflammatory markers in healthy individuals as well [6]. Moreover, physical exercise is most important in the group of individuals at highest risk of coronary disease, since it has been demonstrated that physically active elderly men and women have lower CRP values compared to their less physically active peers [8]. Similar results have been obtained comparing active sportsmen to controls with similar body mass index and sedentary lifestyle [9].

In addition to these inflammatory indices, significant effects of physical training have been described regarding the reduction of Intracellular Adhesion Molecule-1 (ICAM-1) molecule values and leukocyte count in diabetic individuals [10]. Alterations of Vascular Cell Adhesion Molecule-1 (VCAM-1) molecule values after physical exercise in patients with peripheral vascular disease have not been demonstrated; however, it should be mentioned that in animal models long-term training has significantly reduced the expression of P-selectin, VCAM-1, Monocyte Chemoattractant Protein-1 (MCP-1) and Inducible Nitric Oxide Synthese (iNOS) in both healthy and hypercholesterolemic animals [11, 12].

In spite of the well known effects of aerobic physical training, the published data on its effect on the spectrum of inflammatory markers in individuals with coronary disease are scarce. The aim of this study was, therefore, to investigate the effect of aerobic physical training of moderate intensity on inflammatory indices in patients with stable coronary disease.

Methods

This study enrolled 52 patients with coronary disease treated at the Institute for Prevention, Treatment and Rehabilitation of Rheumatic and Cardiovascular Diseases in Niška Banja. All the patients were divided into two groups.

In the group I there were 22 patients with stable coronary disease and regular aerobic physical exercise within the program of cardiovascular rehabilitation during 3 weeks, continuing their training for further 3 weeks at home.

In the group II there were 30 patients with stable coronary disease who in the last 6 months did not have physical training recommended after their program of cardiovascular rehabilitation, except for usual household activities.

All the enrolled subjects had positive history of myocardial infarction, coronary revascularization or angiographic confirmation of 50% stenosis of one or more coronary vessels. Unsuitable for our study were those with arrhythmia, hypertension with systolic tension above 180 mmHg or diastolic below 100 mmHg, unstable angina pectoris, poorly controlled cardiac insufficiency, poor hemodynamic response or ischemic changes on ECG during phase 1 of ergotest (Bruce protocol), or some of the metabolic disorders (diabetes mellitus, hyperthyrosis).

During the study, the enrolled patients took regularly their usual medication, and the same refers to diets recommended during the program of cardiovascular rehabilitation. All the subjects used beta-blockers, ACE inhibitors and statins included in their therapy.

Physical training

The patients undertook regular aerobic physical training for 6 weeks, which consisted of continual aerobic exercise for 45 minutes on a treadmill, room bicycle or walking. The intensity of physical exercise was limited to the submaximal physical capacity at the level of 70-80% of maximal heart frequency at the stress test taken before cardiovascular rehabilitation.

Physical exercise was applied 3 times a week for 6 weeks.

Biochemical tests were done at the start and after 6 weeks' training and compared to the control group values. Blood samples in the group with physical training were taken 24 hours after the last physical training.

Blood pressure was measured by auscultation (sphygmomanometer, Becton Dickinson, USA) three times accordingly to American Heart Association procedure and the average values were adopted.

The methods to assess inflammatory risk factors involved leukocyte count determination with autoanalyzer for blood count Haematolog H1-Technicon. Highly sensitive C reactive protein (hsCRP) determination was done with commercial Dade Behring test on Dimension Expand analyzer. The values were expressed in mg/l. ELISA method and commercial Beckman Coulter Company test (Dual Monoclonal Antibody Sandwich Enzyme Immunoassay)on Bio Sistems-elisa reader were employed to determine adhesive molecules ICAM-1 and VCAM-1. The results were expressed in ng/ml.

Anthropometric measurements

Body mass index (BMI) was determined on the occasion of blood sampling; waist curcumference (WC) and waist/hip (W/H) ratio were the dimensions of interest. Obesity assessment was done complying with the recommendations of the American Association for Diabetes.

The data was processed using the standard descriptive statistic methods (mean value, standard deviation, percentage). The results were analyzed using the Student's *t*-test for

paired and unpaired samples, χ^2 test and Fisher test of exact probability, depending on the group size, type of variables and type of distribution.

Statistical processing was done in Excel 7.0 and SPSS 11.0 in Windows 98 settings, with results presented in tables and graphs.

Results

Our study enrolled 29 men and 23 women. Their basic characteristics are presented in Table 1.

Table 1

Patients characteristics

	Exercise training group	Control group	*p*
Men/women (n)	12/10	17/13	NS
Age (yrs), $\bar{x} \pm SD$	62.7 ± 7.1	58.4 ± 7.6	NS
MI [n (%)]	15 (68)	21 (70)	NS
CAB [n (%)]	3 (14)	4 (13)	NS
PTCA [n (%)]	4 (18)	5 (17)	NS

The results are shown as averages ± standard deviation; MI-myocardial infarct; CABG-coronary artery by pass grafting; PTCA-percutaneous transluminal coronary angioplasty; CAB – coronary artery bypass

Analysis demonstrated balanced gender distribution and similar average age in the studied groups of coronary patients. The chi-squared test indicated that there were no significant differences in therapeutic approaches to acute coronary syndrome.

Estimation of obesity and the characteristics of some cardiovascular markers before and after finishing of cardiovascular rehabilitation programe are summarized in Table 2.

Student's *t*-test demonstrated that investigated patients were without significant differences in WC, W/H ratio and dTA at start and at the end of observed period. Obesity, measured by way of BMI, was similar at the begining of observed period, but after 6 weeks it was significantly lower in subjects who undertook physical training ($p < 0.05$) (Table 2).

Table 2

Influence of exercise training on obesity and arterial blood pressure

	Exercise training group		Control group	
	before	after	before	after
BMI (kg/m^2)	29.3 ± 3.2	26.9 ± 3.6*†	29.1 ± 2.7	28.5 ± 2.76
WC (cm)	102.8 ± 4.7	101 ± 5.42	101.9 ± 5.2	103.16 ± 6.04
W/H ratio	0.98 ± 0.06	0.97 ± 0.07	0.97 ± 0.06	0.99 ± 0.06
sTA (mmHg)	144.7 ± 5,8	136.1 ± 4.3†	139.1 ± 4.9	135 ± 6.4
dTA (mmHg)	90.1 ± 6.7	86.8 ± 5.2	87.7 ± 6.5	85.2 ± 8.3

The results are shown as averages ± standard deviation; BMI-body mass index; WC-waist circumference; W/H – waist/hip; sTA-sistolic blood pressure; dTA diastolic blood pressure; *$p < 0.05$ vs. control; †$p < 0.05$ vs. starting values

The characteristics of inflammatory response before and after physical exercise were examined by way of leukocyte counts, concentration of hsCRP and serum concentration of adhezion molecules (VCAM-1 i ICAM-1). The results are summarized in Table 3.

Leukocyte counts and concentrations of ICAM-1 molecule did not differ between the studied groups. The effects of physical exercise were reflected in a significant reduction of hsCRP and concentration of VCAM-1 molecule ($p < 0.05$), which became significantly lower in this group compared to control ($p < 0.01$ and $p<0.05$ prospective) (Table 3).

All examined inflamatory markers were reduced after 6 weeks' training, but only concentration of hsCRP VCAM-1 showed significant reduction ($p<0.05$).

Discussion

The investigation initiated to examine the effect of aerobic physical training on the degree of inflammation and indices of endothelial function in patients with ischemic heart disease on the program of cardiovascular rehabilitation confirmed the hypothesis that physical activity has favorable impact on the reduction of inflammatory indices and improvement of endothelial dysfunction. The studies comparing a wide spectrum of antiinflammatory indices and indices of endothelial function in patients in the physical training programs compared to physically inactive coronary disease patients are very rare in the relevant literature.

In this study there were no differences in gender distribution, age, type of obesity and therapeutic approaches to coronary disease between the groups of patients on physical training and sedentary controls (Table 1).

The effect of 6 weeks' physical exercise is evident in a significant reduction of obesity measured as BMI, but wihout any important impact on visceral obesity (Tabel 2). This is important effect because obesity and visceral obesity correlated with many inflammatory markers[13] and are frequently asocciated with lipid disorders, hypertension, insulin resistention and coronary artery disease.[14]

In the patients with clinically evident atherosclerosis and confirmed coronary heart disease, CRP values before and after the observed period are significantly higher than

those in healthy population (the average value in men in general population is 0.93 mg/l [15]). This study demonstrated that physical training and improvement of aerobic capacity in coronary disease patients was followed by the proportional reduction of plasmatic concentration of hsCRP and VCAM-1 molecule, while ICAM-1 and leukocyte count remained unchanged (Table 3).

scribed [10], this effect was not observed in the group of non-diabetic patients in our study (Table 3). Some authors have not observed changes in VCAM-1 molecules after physical training in patients with peripheral vascular disease [11]; in animal models long-term training has significantly reduced the expression of P-selectin, VCAM-1, MCP-1 and iNOS both in healthy and in hypocholesterolemic animals [12].

Table 3

Influence of exercise training of inflammatory markers

	Exercise training group			Control group		
Inflammatory markers	before	after	Δ (%)	before	after	Δ (%)
Leukocite count ($\times 10^9$/l)	6.9 ± 1.7	6.23 ± 1.87	-9.7	6.5 ± 1.9	6.32 ± 1.33	-2.8
hsCRP (mg/l)	5.2 ± 3.1	3.89 ± 2.85**†	-25.2	4.9 ± 2.9	5.1 ± 3.2	+4.1
VCAM-1 (ng/ml)	11.1 ± 2.2	9.3 ± 1.21*†	-16.2	10.8 ± 3.5	10.36 ± 3.67	-4.1
ICAM-1 (ng/ml)	7.8 ± 1.56	7.48 ± 1.35	-4.1	7.2 ± 4.3	7.5 ± 6.03	+4.2

The results are shown as averages ± standard deviation; hsCRP – Highly sensitive C reactive protein; VCAM–1 – Vascular Cell Adhesion Molecule-1; ICAM–1 – Intracellular Adhesion Molecule-1; *$p < 0.05$, **$p < 0.01$ vs. control; †$p < 0.05$ vs. starting values in the same group

Physical activity exerts its cardioprotective effects most commonly via a large number of mechanisms, including obesity reduction, blood pressure reduction, reduction of the risk and incidence of diabetes mellitus type 2, correction of dyslipidemia and improvement of insulin sensitivity and glycoregulation, improvement of fibrinolysis and endothelial function [5]. Association of physical exercise with lowered level of inflammation and hsCRP can be an additional protective mechanism.

It is well known that high CRP levels are associated with an increased risk for subsequent cardiovascular events, and the results which reflect its reduction after long-term aerobic physical training stress the importance of this treatment modality in coronary disease patients with associated risk factors such as diabetes mellitus [4].

The exact pathway by which increased physical activity induces CRP reduction has not been elucidated yet, but numerous cross-sectional studies and interventional studies have demonstrated the trend [6, 16]. Potential mechanisms responsible for this effect of physical training could involve the reduced values of interleukins after repeated trainings, responsible for CRP reduction [17]. One of the main interleukins responsible in this regard is IL-6, a proinflammatory cytokine secreted by fat tissue which stimulates hepatic CRP synthesis. However, numerous studies demonstrate that after obesity correction, the association of training with low CRP persists, suggesting that some other unknown mechanisms are involved in CRP reduction either via IL-6, or they directly induce reduced CRP production in the liver [6, 8, 9].

Although some significant effects of physical training on the reduction of ICAM-1 molecules in diabetics have been described [10], this effect was not observed in the group of non-diabetic patients in our study (Table 3). Some authors have not observed changes in VCAM-1 molecules after physical training in patients with peripheral vascular disease [11]; in animal models long-term training has significantly reduced the expression of P-selectin, VCAM-1, MCP-1 and iNOS both in healthy and in hypocholesterolemic animals [12].

In our study VCAM-1 molecule was markedly reduced after a moderate 6-weeks aerobic physical training. The significance of this finding lies in the fact that although ICAM-1 and VCAM-1 share some structural and functional similarities, in patients with well developed atherosclerotic disease ICAM-1 concentration in the plasma is principally a generalized inflammation marker, while VCAM-1 molecule concentration is an indicator of atheromatous plaque activity or a sign of endothelial dysfunction [18]. In that regard, the effect of training on VCAM-1 levels is of enormous importance in view of the reduction of risk for subsequent coronary events caused by destabilization or rupture of the plaque fibrous cap, especially if we are aware of its effect on the degree of oxidative stress [19]. It should be noted that our results support the findings that reduced inflammation and oxidative stress represent the best way to reduce the risk of acute coronary syndrome [20].

Conclusion

Aerobic physical training with submaximal workload during 6 weeks induces significant reduction of inflammatory markers CRP and VCAM, with significant reduction of general obesity and without changes in visceral obesity.

All these effects of physical training are beneficial regarding the reduction of cardiovascular risk for subsequent coronary events.

The results of this study suggest that physical exercise could have an important place in primary and secondary prevention of coronary disease.

REFERENCES

1. *Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M*, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice. A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003; 107(3): 499–511.
2. *Ridker PM, Bassuk SS, Toth PP*. C-reactive protein and risk of cardiovascular disease: evidence and clinical application. Curr Atheroscler Rep 2003; 5(5): 341–9.
3. *Gabay C, Kushner I*. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999; 340(6): 448–54.
4. *Ridker PM, Buring JE, Cook NR, Rifai N*. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular

events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003; 107(3): 391–7.
5. *Bassuk SS, Manson JE*. Physical activity and the prevention of cardiovascular disease. Curr Atheroscler Rep 2003; 5: 299–307.
6. *Mattusch F, Dufaux B, Heine O, Mertens I, Rost R*. Reduction of the plasma concentration of C-reactive protein following nine months of endurance training. Int J Sports Med 2000; 21(1): 21–4.
7. *Smith JK, Dykes R, Douglas JE, Krishnaswamy G, Berk S*. Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. JAMA 1999; 281(18): 1722–7.
8. *Abramson JL, Vaccarino V*. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. Arch Intern Med 2002; 162(11): 1286–92.
9. *Tomaszewski M, Charchar FJ, Przybycin M, Crawford L, Wallace AM, Gosek K*, et al. Strikingly low circulating CRP concentrations in ultramarathon runners independent of markers of adiposity: how low can you go? Arterioscler Thromb Vasc Biol 2003; 23(9): 1640–4.
10. *Zoppini G, Targher G, Zamboni C, Venturi C, Cacciatori V, Moghetti P*, et al. Effects of moderate-intensity exercise training on plasma biomarkers of inflammation and endothelial dysfunction in older patients with type 2 diabetes. Nutr Metab Cardiovasc Dis 2006; 16(8): 543–9.
11. *Arosio E, Minuz P, Prior M, Zuliani V, Gaino S, De Marchi S*, et al. Vascular adhesion molecule-1 and markers of platelet function before and after a treatment with iloprost or a supervised physical exercise program in patients with peripheral arterial disease. Life Sci 2001; 69(4): 421–33.
12. *Yang AL, Chen HI*. Chronic exercise reduces adhesion molecules/iNOS expression and partially reverses vascular responsiveness in hypercholesterolemic rabbit aortae. Atherosclerosis 2003; 169(1): 11–7.
13. *Panagiotakos DB, Pitsavos C, Yannakoulia M, Chrysohoou C, Stefanadis C*. The implication of obesity and central fat on markers of chronic inflammation: The ATTICA study. Atherosclerosis 2005; 183: 308–15.
14. *Ashen MD*. Management of Cardiometabolic Syndrome in the Primary and Secondary Prevention of Cardiovascular Disease. JNP 2008; 4(9): 673–80.
15. *Rifai N, Ridker PM*. Population distributions of C-reactive protein in apparently healthy men and women in the United States: implication for clinical interpretation. Clin Chem 2003; 49(4): 666–9.
16. *Esposito K, Pontillo A, Di Palo C, Giugliano G, Masella M, Marfella R*, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. JAMA 2003; 289(14): 1799–804.
17. *Siegel AJ, Stec JJ, Lipinska I, Van Cott EM, Lewandrowski KB, Ridker PM*, et al. Effect of marathon running on inflammatory and hemostatic markers. Am J Cardiol 2001; 88(8): 918–20.
18. *Silvestro A, Brevetti G, Schiano V, Scopacasa F, Chiariello M*. Adhesion molecules and cardiovascular risk in peripheral arterial disease.Soluble vascular cell adhesion molecule-1 improves risk stratification. Thromb Haemost 2005; 93(3): 559–63.
19. *Jovović B, Lečić N, Ilić G, Jelić M, Damnjanović G, Janković R*, et al. Dislipidemia and oxidative stress in diabetics – cumulative risk for development of coronary artery disease. Acta Medica Medianae 2005; 44(4): 35–42. (Serbian)
20. *Ilić S, Deljanin Ilić M, Nikolić A*. Acute coronary syndrome. The first part: classification, pathophysiology and diagnostic. Acta Medica Medianae 2005; 44(1): 31–7. (Serbian)

The paper received on September 1, 2008.

ORIGINALNI ČLANAK UDC: 618.11-006.555-091.8:616-053.2

Ispitivanje osetljivosti na antibiotike *Campylobacter jejuni* i *C. coli* izolovanih iz ljudi

Determination of sensitivity to antibiotics of *Campilobacter jejuni* and *Campilobacter coli* isolated from human feces

Zoran Tambur*, Biljana Miljković-Selimović†, Dubravko Bokonjić‡

Vojnomedicinska akademija, *Institut za higijenu, ‡Centar za kontrolu trovanja, **Beograd;**
Medicinski fakultet, †Institut za javno zdravlje, **Niš**

Apstrakt

Uvod/Cilj. Jedna od najznačajnijih bakterijskih zoonoza je kampilobakterioza. Oboljenja ljudi najčešće izazivaju termofilne kampilobakterije: *Campylobacter jejuni* (*C. jejuni*), *Campylobacter coli* (*C. coli*), *Campylobacter lari* (*C. lari*), *Campylobacter upsaliensis* (*C. upsaliensis*). Kampilobakterioza je bolest blagog toka i uglavnom spontano prolazi. Kod bolesnika sa težom kliničkom slikom i prolongiranom bolešću preporučuje se antibiotski tretman. U poslednje vreme zabrinjava porast rezistencije bakterija iz roda *Campylobacter* na antibiotike koji se najčešće koriste za lečenje kampilobakterioze ljudi. Pojava rezistentnih sojeva koincidira sa početkom korišćenja antibiotika, posebno hinolona u veterinarskoj medicini. Cilj rada bio je izolacija i identifikacija sojeva termofilnih *Campylobacter* vrsta iz fecesa ljudi i ispitivanje njihove osetljivosti na antibiotike i hemioterapeutike koji se najčešće koriste za lečenje kampilobakterioze. **Metode.** Ispitivana je osetljivost na eritromicin, tetraciklin, ampicilin, hloramfenikol i ciprofloksacin 24 soja kampilobakterija izolovana iz fecesa ljudi, primenom E-testa. **Rezultati.** Ispitivano je 17 sojeva *C. jejuni* i sedam sojeva *C. coli.* Od 24 ispitivana soja *C. jejuni* i *C. coli*, šest sojeva (25%) bilo je rezistentno na ampicilin, a sedam sojeva (29,2%) na tetraciklin. Od ispitivanih sojeva *C. jejuni* i *C. coli,* 12 sojeva (50%) bilo je rezistentno na ciprofloksacin. Rezistentnija vrsta bila je *C. jejuni* (52,9%). Četiri soja (23,5%) *C. jejuni* bila su rezistentna na eritromicin, a 11,7% sojeva na hloramfenikol. Nijedan ispitivani soj *C. coli* nije bio rezistentan na hloramfenikol, niti na eritromicin. **Zaključak.** Ispitivanjem osetljivosti na eritromicin, tetraciklin, ampicilin, hloramfenikol i ciprofloksacin sojeva *C. jejuni* i *C. coli* izolovanih iz ljudi ustanovljen je relativno visok procenat rezistentnih sojeva, posebno onih od *C. jejuni.*

Ključne reči:
campylobacter; ljudi; antibiotici; lekovi, rezistencija; veterina.

Abstract

Background/Aim. One of the most important bacterial zoonosis is campylobacteriosis. Human disease is mostly caused by thermophilic *Campylobacter* spp: *Campylobacter jejuni* (*C. jejuni*), *Campylobacter coli* (*C. coli*), *Campylobacter lari* (*C. lari*) and *Campylobacter upsaliensis* (*C. upsaliensis*). Campylobacteriosis is a mild and self-healing disorder. In patients with more severe and prolonged forms, an antibiotic treatment is recommended. Recommended drugs are erythromycin, ciprofloxacin, tetracyclin, chloramphenicol and ampicillin. Lately, an increase of *Campylobacter* genus resistance to antibiotics mostly used in therapy is an annoying evidence. The rise coincided with the beginning of antibiotic use, especially quinolones, in veterinary medicine. The aim of the study was to isolate and identify thermophilic *Campylobacter* spp. from human feces and to determine their sensitivity to antibiotics and hemotherapeutics mostly used in campylobacteriosis treatment. **Methods.** Sensitivity to erythromycin, tetracyclin, ampicillin, chloramphenicol and ciprofloxacin of 24 strains of *Campylobacter* spp. isolated from humans was investigated by E-test. **Results.** Seventeen *C. jejuni* and seven *C. coli* strains were investigated. Six (25%) out of 24 *C. jejuni* and *C. coli* investigated strains were resistant to ampicillin and seven (29.2%) were resistant to tetracycline. Twelve (50%) *C. jejuni* and *C. coli* investigated strains were resistant to ciprofloxacin. *C. jejuni* was more resistant (52.9%). Four (23.5%) *C. jejuni* strains were resistant to erythromycin and 11.7% to choramphenicol. None of *C. coli* strains were resistant to both chloramphenicol and erytromycin. **Conclusons.** Testing sensitivity to erythromycin, tetracycline, ampicillin, chloramphenicol and ciprofloxacin demonstrated a rather high resistance frequency of *C. jejuni* and *C. coli* strains isolated from humans. *C. jejuni* strains were more resistant than those of *C. coli.*

Key words:
campylobacter; humans; anti-bacterial agents; drug resistance; veterinary medicine.

Correspondence to: Zoran Tambur, Vojnomedicinska akademija, Institut za higijenu, Crnotravska 17, 11 040 Beograd, Srbija.
Tel.: + 381 11 36 09 313. E-mail: zorantvet@sbb.rs

Uvod

Jedna od najznačajnijih bakterijskih zoonoza je kampilobakterioza. U rodu *Campylobacter* nalazi se 18 vrsta, a oboljenja ljudi najčešće izazivaju termofilne kampilobakterije *C. jejuni, C. coli, C. lari, C. upsaliensis.*

Životinje retko obole ili obole sa blagim simptomima bolesti, ali su značajan rezervoar uzročnika za ljude.

C. jejuni i C. coli najvažniji su uzročnici bakterijskih crevnih infekcija u savremenom svetu sa 400 000 000 obolelih svake godine. Značajan faktor za nastanak oboljenja ljudi od crevne kampilobakterioze je niska infektivna doza od samo 500 mikroorganizama [1].

Termofilne *Campylobacter* vrste mogu izazvati i ekstraintestinalne oblike bolesti [2].

Sekundarna oboljenja, kao posledica primarne infekcije izazvane termofilnim *Campylobacter* vrstama su *Guillain-Barré* sindrom (GBS) i *Reiterov* sindrom [3, 4] .

Kampilobakterioza bolest je blagog toka i uglavnom spontano prolazi. Kod bolesnika sa težom kliničkom slikom i prolongiranom bolešću preporučuje se antibiotski tretman [5]. Lekovi izbora su eritromicin, ciprofloksacin, tetraciklin, hloramfenikol i ampicilin.

U poslednje vreme zabrinjava porast rezistencije bakterija iz roda *Campylobacter* na antibiotike koji se najčešće koriste za lečenje kampilobakterioze ljudi. Pojava rezistentnih sojeva koincidira sa početkom korišćenja antibiotika, posebno hinolona u veterinarskoj medicini [5–8].

Cilj rada bio je izolacija i identifikacija sojeva termofilnih *Campylobacter* vrsta iz fecesa ljudi i ispitivanje njihove osetljivosti na antibiotike koji se najčešće koriste za lečenje kampilobakterioze – eritromicin, ciprofloksacin, tetraciklin, hloramfenikol i ampicilin.

Metode

Ispitana su ukupno 24 soja termofilnih bakterija koje su izolovane iz fecesa obolelih ljudi u Institutu za javno zdravlje, Niš. Sojevi su izlovani u periodu od druge polovine 2004. do prve polovine 2005. godine. Duplikati nisu testirani zato što su sojevi praćeni prema imenu bolesnika u skladu sa laboratorijskim protokolom. Sojevi su izolovani tako što je uzorkovani materijal zasejavan na *Skirrow* agar sa razređenjem da se dobiju pojedinačne kolonije. Ploče su ubačene u lonce za anaerobe; mikroaerofilna atmosfera je stvorena pomoću *Campy Pack*, BBL kesica. Ploče su inkubirane mikroaerofilno na temperaturi od 42º C, u trajanju od 48 sati.

Porasle kolonije nakon inkubisanja pregledane su makroskopski i od njih su pripremani mikroskopski preparati i bojeni 2% karbol-fuksinom. Radi dobijanja čistih kultura termofilnih *Campylobacter* vrsta vršena su presejavanja pojedinačnih kolonija na krvni agar.

Dobijeni izolati čuvani su za dalja ispitivanja u moždanosrčanom infuznom bujonu (BHI) sa 30% glicerola na temperaturi od -70º C [9].

Dobijeni izolati identifikovani su klasičnim i komercijalnim biohemijskim testovima. Od klasičnih biohemijskih testova korišćeni su katalaza test, oksidaza test, hidroliza hipurata, hidroliza indoksil acetata, brzi H_2S test, test osetljivosti na cefalotin i nalidiksinsku kiselinu.

Krajnja identifikacija sojeva *Campylobacter* vrste vršena je pomoću automatskog identifikacionog sistema API *Campy*, proizvođača Bio *Mérieux* (Francuska), po uputstvu proizvođača [9].

Ispitivanje osetljivosti na antibiotike termofilnih *Campylobacter* vrsta vršeno je primenom E-testa. E-test je difuzioni test za određivanje minimalnih inhibitornih koncentracija (MIC) antibiotika za bakterije koje se ispituju. Pojedinačne kolonije izraslih bakterija sa krvne ploče suspendovane su u 4 ml *Mueller Hinton* bujona radi dobijanja suspenzije koja po gustini odgovara standardu 1 po *McFarland* skali. Zasejavanje pripremljene suspenzije ispitivanih sojeva bakterija na *Mueller Hinton* agar sa 5% defibrinisane ovčije krvi vršeno je pomoću sterilnog brisa. Nakon sušenja ploča u trajanju od dva minuta, nanošene su E-test trake (AB Biodisk, *Solna*, *Sweden*) na koje je nanešen antibiotik u koncentracijama od najniže ka najvišoj. Ploče su inkubisane 48 sati na temperaturi od 37° C mikroaerofilno, a nakon toga su očitavane vrednosti MIC. Za minimalnu inhibitornu koncentraciju antimikrobnog sredstva uzimana je ona u kojoj porast kulture preseca površinu trake impregnisane sa ispitujućim antibiotikom određene koncentracije. Za granične vrednosti korišćene su preporuke koje su dobijene od proizvođača E-test traka.

Za proveru svih navedenih metoda i kvaliteta podloga korišćeni su i referentni sojevi *C. jejuni* ATCC–33560 i *C. coli* ATCC–33559.

U tekstu i tabelama korišćeni su uobičajeni parametri deskriptivne statistike (apsolutne vrednosti, srednje vrednosti i frekvencije pojedinih obeležja izražene u procentima). Za poređenje dobijenih rezultata u zavisnosti od porekla izolovanih sojeva *Campylobacter* vrsta korišćen je Fišerov test (tabele kontigencije 2×2).

Rezultati

Ispitana je osetljivost 24 soja termofilnih *Camphylobacter* sojeva poreklom od ljudi na eritromicin (E), tetraciklin (TET), ampicilin (AM), hloramfenikol (CHl) i ciprofloksacin (CIP). Iz fecesa ljudi izolovano je 17 sojeva *C. jejuni i* sedam sojeva *C. coli* [9]. Rezultati ispitivanja osetljivosti na antibiotike izolovanih sojeva *C. jejuni* i *C. coli* prikazani su tabelarno.

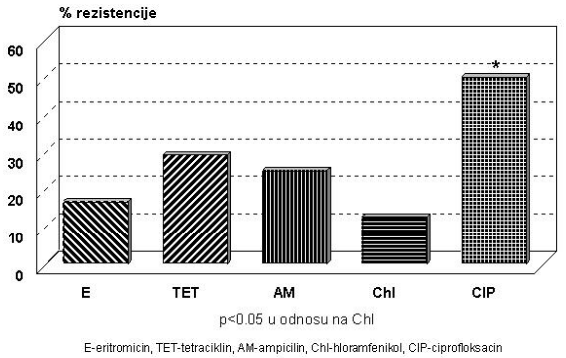
Od 17 ispitivanih sojeva *C. jejuni,* četiri soja (23,5%) bila su rezistentna na eritromicin (tabela 1). Ukupno sedam sojeva (29,2%) *C. jejuni* i *C. coli* bilo je rezistentno na tetraciklin (slika 1). Od 24 ispitivana soja *C. jejuni* i *C. coli* šest sojeva (25%) bilo je rezistentno na ampicilin (slika 1).

Ispitujući osetljivost sojeva *C. jejuni* na hloramfenikol ustanovljena je rezistencija kod 17,7% sojeva (tabela 1). Nijedan ispitivani soj *C. coli* nije bio rezistentan na hloramfenikol kao ni na ertiromicin (tabela 1). Od ispitivanih sojeva *C. jejuni* i *C. coli* 12 sojeva (50%) bilo je rezistentno na ciprofloksacin (slika 1).

Tabela 1

Minimalne inhibitorne koncentracije (MIC) antibiotika (μg/ml) za *Campylobacter jejuni* (17 izolata) i *C. coli* (7 izolata) poreklom od ljudi primenom E-testa

Antibiotik	MIC opseg		MIC 50		MIC 90		Rrezistentni sojevi (%)	
	C. jejuni	*C. coli*	*C. jejuni*	*C. coli*	*C. jejuni*	*C. coli*	*C. jejuni*	*C. coli*
Eritromicin	0,016 – >256	0,016 – 0,50	0,25	0,25	>256	0,50	23,5	0
Tetraciklin	0,016 – >256	0,032 – >256	0,16	0,25	>256	>256	29,4	28,6
Ampicilin	0,016 – >256	≤0,16 – >256	12	6	>256	16	29,4	14,3
Hloramfenikol	0,016 – >256	0,038 – 3	1,5	1,5	4	2	17,7	0
Ciprofloksacin	0,016 – >32	0,032 – >32	0,25	0,25	>32	>32	52,9	42,9



Sl. 1 – Prevalencija rezistencije izražena u procentima na osnovu vrednosti minimalnih inhibitornih koncentracija (MIC) ispitivanih antibiotika za *Campylobacter* vrste dobijenih primenom E-testa

Diskusija

U svetu primetan je stalan trend porasta rezistencije na najčešće korišćene antibiotike u kliničkoj praksi posebno na fluorohinolone. U Holandiji je enrofloksacin odobren za upotrebu u veterini 1987. godine. Godine 1998. bilo je već 8% rezistentnih sojeva *C. jejuni*/*coli* poreklom iz ljudi, 1989. godine 11% i 1997. godine 29%. Sličan trend zabeležen je i u Austriji, Danskoj, Finskoj, Francuskoj, Italiji, Španiji, Tajlandu, Velikoj Britaniji i SAD [5]. U Grčkoj, u periodu od 1987. do 1988. godine nije bilo rezistencije na hinolone. U drugom periodu, od 1998. do 2000, zabeleženo je već 30,65% termofilnih kampilobakterija rezistentnih na ciprofloksacin [10].

Visok nivo rezistencije na ciprofloksacin (71,4%) zabeležen je kod sojeva *C. jejuni*/*coli* u Indiji i to kod dece u ruralnoj sredini [11]. Takođe, visok nivo rezistencije na ciprofloksacin zabeležen je i u Španiji. Tako, 75% sojeva *C. jejuni* i 70,7% sojeva *C. coli* bilo je rezistentno na ovaj antibiotik [12].

Rezistencija na tetraciklin kod ispitivanih sojeva *C. jejuni* i *C. coli* iznosila je 29,2%. Naši rezultati su saglasni sa rezultatima ispitivanja rezistencije drugih autora [13, 14]. Rezistencija na tetracikline pripisuje se njihovoj nekontrolisanoj primeni u veterinarskoj medicini kao promotera rasta, u profilaktičke i terapijske svrhe [15]. Tetraciklini se nekontrolisano koriste i u humanoj medicini.

Rezistencija na eritromicin kod ispitivanih sojeva *C. jejuni* i *C. coli* dobijena u našem istraživanju iznosila je 29,2%. Primetan je trend porasta rezistencije i na eritromicin. Tako, u Kanadi, 1998. godine bilo je 3% rezistentnih sojeva *C. jejuni*/*coli,* a 2001. godine 12% [16]. U Nemačkoj 1991. godine bilo je 7,1% *C. coli* rezistentnih na eritromicin, a 2001. godine 29,4% [17]. Trend porasta rezistencije na eritromicin zabeležili su i autori u Severnoj Irskoj od 0,6% 1996. godine do 4,2% 2000. godine [18]. Ovaj podatak zabrinjava jer je eritromicin lek prvog izbora u lečenju kampilobakterioze.

Rezistencija na hloramfenikol kod termofilnih *Campylobacter* vrsta iznosila je 12,5%. Naši rezultati nisu saglasni sa rezultatima drugih autora koji navode da je samo 2% sojeva termofilnih *Campylobacter* vrsta ispoljilo rezistenciju na hloramfenikol. Rezistencija nije zabeležena kod sojeva *C. jejuni*/*coli* u SAD i Turskoj [19–22]. Ovu pojavu tumačimo činjenicom da se hloramfenikol u svetu restriktivno koristi i u humanoj i u veterinarskoj medicini, kao i transferom gena rezistencije u prirodi.

Deepika i sar. [11] izveštavaju o visokom procentu termofilnih *Campylobacter* vrsta, izolovanih od dece u ruralnoj sredini, rezistentnih na ampicilin (81,6%). Visok nivo rezistencije na ampicilin (čak 97%), registrovan je kod termofilnih *Campylobacter* vrsta u Australiji, ako je osetljivost ispitivana primenom disk difuzione metode. Primenom E-testa procenat rezistentnih sojeva iznosio je 67% [23]. Dodatak inhibitora beta laktamaze ampicilinu (ampicilin/sulbaktam) imao je za posledicu relativno nizak nivo rezistencije *C. jejuni*/*coli* na ovaj antibiotik kod ljudi u Bugarskoj [13].

Zaključak

Ispitivanjem osetljivosti na eritromicin, tetraciklin, ampicilin, hloramfenikol i ciprofloksacin sojeva *C. jejuni* i *C. coli* ustanovljen je relativno visok procenat rezistentnih sojeva.

Procenat rezistentnih sojeva *Campylobacter* vrsta dobijen u ovom istraživanju saglasan je sa rezultatima koje navode mnogi autori u svetu.

L I T E R A T U R A

1. *Walker IR, Caldwell MB, Lee CE, Guerry P, Trust JT, Riuz-Palacios MG.* Pathophysiology of Campylobacter enteritis. Microbiol Rev 1986; 50(1): 81–94.

2. *Frediani WV, Stephan R.* Resistance patterns of Campylobacter spp. strains isolated from poultry carcasses in a big Swiss poultry slaughterhouse. Int J Food Microbiol 2003; 89(2–3): 233–40.

3. *Avrain L, Humbert F, L´Hospitalier R, Sanders P, Vernozy RC, Kempf I.* Antimicrobial resistance in Campylobacter from broilers: association with production type and antimicrobial use. Vet Microbiol 2003; 96(3): 267–76.
4. *Butzler JP.* Campylobacter, from obscuriti to celebrity. Clin Microbiol Infect 2004; 10(10): 868–76.
5. *Aarestrup MF, Nielsen EM, Medsen M, Engberg J.* Antimicrobial susceptibility patterns of thermophilic Campylobacter spp. from humans, pigs, cattle, and broilers in Denmark. Antimicrob Agents Chemother 1997; 41(10): 2244–50.
6. *Bywater R, Deluyker H, Deroover E, de Jong A, Marrion H, McConville M,* at al. A European survey of antimicrobial susceptibility among zoonotic and commensal bacteria isolated from food-producing animals. J Antimicrob Chemother 2004; 54(4): 744–54.
7. *Cardinale E, Dromigny JA, Tall F, Ndiaye M, Konte M, Perrier Gros-Claude JD.* Antimicrobial susceptibility of Campylobacter strains isolated from chicken carcasses in Senegal. Revue Élev. Méd vét Pays trop 2002; 55(4): 259–64.
8. *Savaşan S, Çiftiçi A, Diker SK.* Emergence of Quinolone resistance among chicken isolates of Campylobacter in Turkey. Turk J Vet Anim Sci 2004; 28: 391–7.
9. *Tambur Z.* Antibiotic and hemotherapeutic sensitivity of thermophilic Campylobacter spp isolated from animals and humans. [thesis] Belgrade: School of Veterinery Medicine; 2007. (Serbian)
10. *Chatzipanagiotou S, Papavasileiou E, Lakumenta A, Makri A, Nicolau C, Chantzis K,* at al. Antimicrobial susceptibility patterns of Campylobacter jejuni strains isolated from hospitalized children in Athens. Greece. J Antimicrob Chemother 2002; 49(5): 803–5.
11. *Jain D, Sinha S, Prasad NK, Padney MC.* Campylobacter species and drug resistance in a north Indian rural community. Trans R Soc Trop Med Hyg 2005; 99(3): 207–14.
12. *Sáenz Y, Zarazaga M, Lantero M, Gastanares MJ, Baquero F, Torres C.* Antibiotic Resistance in Campylobacter strains isolated from animals, foods and humans in Spain in 1997–1998. Antimicrob Agents Chemother 2000; 44(2): 267–71.
13. *Boyanova L, Gergova G, Spassova Z, Koumanova R, Yaneva P, Mitov I,* at al. Campylobacter infection in 682 Bulgarian patients with acute enterocolitis, inlmattory bowel disease, and other chronic diseases. Diag Microb Infect Dis 2004; 49(1): 71–4.
14. *Krause R, Ullman U.* In vitro activities of new fluoroqinolones against Camylobacter jejuni and Campylobacter coli isolates from humans in 1980 to 1982 and 1997 to 2001. Antimicrob Agents Chemother 2003; 47(9): 2946–50.
15. *Desmonts MH, Dufour F, Avrain L, Kempf I.* Antimicrobial resistance in Campylobacter strains isolated from French broilers before and after antimicrobial growth promoter bans. J Antimicrob Chemother 2004; 10(1): 1–6.
16. *Gaudreau C, Gilbert H.* Antimicrobial resistance of clinical strains of Campylobacter jejuni subsp. jejuni isolated from 1985 to 1997 in Quebec, Canada. Antimicrob Agents Chemother 1998; 42(8): 2106–8.
17. *Luber P, Wagner J, Helmut H, Bartelt E.* Antimicrobial resistance in Campylobacter jejuni and Campylobacter coli isolated in 1991 and 2001–2002 from poultry and human in Berlin, Germany. Antimicrob Agents Chemother 2003; 47(12): 3825–30.
18. *Kolek B, Warr G, Bonner D, Fung-Tomc J.* Intracellular penetration and bactericidal activity of the novel des-fluoro (6) quinolone, BMS-284756. J Antimicrob Chemother 2001; 48(3): 445–6.
19. *Gupta A, Nelson MJ, Barret JT, Tauxe VR, Rossiter PS, Friedman RC,* at al. Antimicrobial resistance among Campylobacter strains, United States, 1997–2001. Emer Infect Dis 2004; 19(6): 1102–9.
20. *Hakanen AJ, Lehtopolku M, Siitonen A, Huovinen P, Kotilainen P.* Multidrug resistance in Campylobacter jejuni strains collected from Finnish patients during 1995–2000. J Antimicrob Chemother 2003; 52(6): 1035–9.
21. *Ge B , Bodeis S, Walker DR, White GD, Zhao S, McDermot FP,* at al. Comparasion of the E-test and agar dilution for in vitro antimicrobial susceptibility testing of Campylobacter. J Antimicrob Chemother 2002; 50(3): 487–94.
22. *Oncul Ozge, Zarakolu P, Oncul O, Gur D.* Antimicrobial susceptibility testing of Campylobacter jejuni: a comparasion between E-test and agar dilution method. Diagn Microbiol Infect Dis 2003; 45(1): 69–71.
23. *Alfredson DA, Akhurst RJ, Korolik V.* Antimicrobial resistance and genomic screening of clinical isolates of thermophilic Campylobacter spp. From south-east Queensland, Australia. J Appl Microbiol 2003; 94(3): 495–500.

Rad je primljen 3. IX 2008.

A K T U E L N E T E M E

UDC: 615.311::581.19

Značaj zakonskih propisa za racionalnu primenu biljnih lekova

Significance of herbal drugs legislation for their rational use

Snežana M. Cupara, Slobodan M. Janković

Medicinski fakultet, Kragujevac

Ključne reči:
fitoterapija; zakonodavstvo; kontrola kvaliteta; farmakopeje; lekovi, kliničko ispitivanje.

Key words:
phytotherapy; legislation; quality control; pharmacopoeias; drug evaluation.

Uvod

Upotreba lekovitih biljaka našla je svoje mesto i u savremenoj terapiji. Izraz „racionalna fitoterapija“, koji se sve češće susreće podrazumeva korišćenje biljnih proizvoda koji su formulisani, proizvedeni i stavljeni u promet na osnovu eksperimentalno i/ili klinički potvrđene efikasnosti i bezbednosti primene [1].

Racionalna fitoterapija, kao savremeni pristup, nije u suprotnosti sa tradicionalnim biljnim lečenjem, već često proističe iz njega. U tradicionalnom lečenju lekovitim biljem, u zavisnosti od podneblja primene, susrećemo se različiti pogledi. Holistički pristup, posebno uočljiv u tradicionalnoj kineskoj i indijskoj medicini, podrazumeva da jedna biljka ispoljava dejstvo na organizam u celini. Kako se ljudski organizam smatra celinom, shodno tome celina je i biljka kojom se koriguje eventualno narušena ravnoteža u zdravlju. Primer su monografije lekovitih biljaka Indijske farmakopeje koje pri opisivanju karakteristika jedne biljke navode više njenih različitih delovanja na različite organe u organizmu, koje navedena biljka može da ispolji u zavisnosti od načina kombinovanja sa drugim biljkama. U zemljama Zapadne Evrope, pak, češće je u upotrebi biljni preparat napravljen od jedne biljke ili njenog ekstrakta sa namerom da se postigne efekat na ciljnom organu. Ukoliko se koriste kombinacije lekovitog bilja u jednom biljnom preparatu ovaj cilj se postiže tako što se izabere više različitih biljaka koje istovremeno deluju na oboleli organ.

Bilo da je reč o racionalnoj fitoterapiji ili tradicionalnom lečenju lekovitim biljem u upotrebi su često identični termini. Tradicionalnu upotrebu lekovitog bilja npr. često nazivaju fitoterapijom, dok se, s druge strane, naučni podaci o lekovitom bilju često koriste za opravdanje ili potvrdu njegove tradicionalne upotrebe. U oblast biljnih lekova grubo se svrstavaju i homeopatski lekovi. Međutim izrazi „biljni“ i „homeopatski“ lek nisu sinonimi. Biljni lek se izrađuje od svežeg ili suvog biljnog materijala ili ekstrakta nekog dela biljke i koristi se za prevenciju ili suzbijanje jasno određenih simptoma po čemu on liči na konvencionalni lek. Homeopatski lek sadrži minimalne količine susptancije koja bi u većoj dozi kod zdravog čoveka izazvala simptome nalik onima koje taj lek može da suzbije. Za razliku od biljnog, homeopatski lek deluje na organizam kao celinu (psihički, fizički i emocionalno), a izrađuje se drugačije od biljnog leka. Iako mnogi homeopatski lekovi potiču od biljnih sirovina, oni ne spadaju u biljne lekove, jer se homeopatski lekovi prave i od drugih sirovina (mineralnih i životinjskih) posebnom tehnologijom razblaživanja početne supstancije.

Prema podacima Svetske zdravstvene organizacije (SZO) preparate na bazi lekovitog bilja koristi 80% svetskog stanovništva. Medicinska primena lekovitog bilja u Evropi ima dugu tradiciju, dok u nekim delovima sveta (npr. Kina, Indija) biljni lekovi još uvek predstavljaju centralnu kariku u lancu zdravstvenih usluga [2].

Institucije koje regulišu biljne lekove na tržištu Evrope i SAD

Biljni lekovi prisutni su na tržištu svih zemalja u Evropi, iako se veličina tržišta razlikuje u svakoj od zemalja. Zbog velikih razlika u klasifikaciji biljnih proizvoda među zemljama članicama Evropske unije (EU), zakonski propisi za ove preparate postali su prioritet za EU krajem 80-tih godina. Naime, neujednačenost kriterijuma za klasifikaciju biljnih proizvoda dovela je do toga da su oni u nekim zemljama članicama bili prisutni kao medicinski preparati sa definisanim terapijskim dejstvom, u drugim registrovani kao dijetetski preparati bez posebnih terapijskih indikacija, a u trećim kao biljni suplementi sa terapijskim dejstvom. Da bi se ovaj problem rešio 1989. godine oformljeno je udruženje pod nazivom Evropsko naučno udruženje za fitoterapiju (*European Scientific Cooperative on Phythotherapy* – ESCOP), sa

Correspondence to: Snežana M Cupara, Medicinski fakultet u Kragujevcu, Svetozara Markovića 69, 34 000 Kragujevac, Srbija.
Tel.: +381 63 386 485. E-mail: snezanacupara@yahoo.com

ciljem da se postave zajednički kriterijumi za klasifikaciju biljnih lekova, da se podstaknu naučna istraživanja u domenu lekovitog bilja i da se doprinese institucionalizovanom prihvatanju fitoterapije u Evropi [3]. *European Scientific Cooperative on Phythotherapy* osnovalo je šest nacionalnih naučnih organizacija sa namerom da se fitoterapijske organizacije objedine na evropskom nivou. Danas u sastav ESCOP-a ulazi 13 nacionalnih udruženja iz Evrope, kao i Američki botanički savet (*American Botanical Council*). Jedan od osnovnih zadataka postavljenih pred ESCOP bio je sakupljanje svih naučnih podataka o jednoj biljnoj vrsti ili drogi, uključujući i predkliničke i kliničke studije. *European Scientific Cooperative on Phythotherapy* je to realizovao objavljivanjem 80 monografija za pojedinačne biljne droge [4]. Dodatno, 1997. godine osnovana je i radna grupa pod nazivom *Working Group on Herbal Medicinal Products* (HMPWG) na inicijativu Evropskog saveta i sadašnje Evropske agencije za lekove (bivše Evropske agencije za evaluaciju lekova – EMEA). Ova grupa značajno se oslonila na monografije ESCOP-a u stvaranju formata Evropskog zaključka o karakteristikama proizvoda (*European Summary of Product Characteristics* – SPC). Ovu radnu grupu danas je nasledio Komitet za biljne lekove (*Herbal Medicinal Product Committee* – HMPC) i on nastavlja saradnju sa ESCOP-om [5].

U skladu sa direktivom Evropskog saveta koja definiše medicinski proizvod (Direktiva 2001/83/EEC), svaki biljni preparat koji ispunjava kriterijume ove direktive smatra se medicinskim proizvodom i podleže istim propisima kao i drugi medicinski proizvodi [6].

Posebna Evropska direktiva koja se odnosi na tradicionalne biljne preparate stupila je na snagu u aprilu 2004. godine sa zahtevom da je zemlje članice uvrste u svoje pravilnike za registraciju proizvoda do oktobra 2005 (*Council Directive* 2004/24/EC) [7]. Ovom direktivom zahteva se da se pri registraciji tradicionalnih biljnih preparata zadovolje specifični standardi koji se odnose na kvalitet i sigurnost njihove humane upotrebe. Preporuka ove direktive je da takvi registrovani preparati budu pogodni za upotrebu bez lekarskog recepta. Pored uobičajenih zahteva za registrovanje (GMP potvrda), novinu u odnosu na prethodnu direktivu predstavlja i zahtev za dokazanom tradicionalnom upotrebom u periodu od 30 godina za datu indikaciju, od kojih najmanje 15 mora biti na teritoriji Evropske unije, kao i poseban izveštaj o bezbednosti upotrebe biljnog preparata za datu indikaciju. Sa druge strane, od proizvođača se zahteva da obezbede sistem za praćenje podataka o neželjenim dejstvima o kojima bi se izveštaji dostavljali nacionalnim regulatornim institucijama.

Ovom direktivom ustanovljen je i sadašnji Komitet za biljne proizvode (*Herbal Medicinal Product Committee* – HMPC) sa osnovnom namerom da pripremi detaljno obrađene monografije i listu biljnih supstancije i preparata koji su u medicinskoj upotrebi dovoljno dugo vremena da se njihova upotreba smatra bezbednom u normalnim uslovima korišćenja. Monografija sadrži profesionalno mišljenje Komiteta o određenom biljnom proizvodu na osnovu naučnih podataka ili tradicionalne upotrebe u okviru Evropske unije. Za svaku biljnu supstanciju navedeni su indikacija, jačina, upotreba kao i drugi relevantni podaci koji se tiču njene bezbedne upotrebe ili preparata koji je sadrži. Lista kao i verzije monografija su na raspolaganju za javnu konsultaciju obično u trajanju od 3 meseca na *web* stranici EMEA (*European Medicinal Evaluation Agency*) [5].

Iako se na nivou EU čine napori za usaglašavanje propisa koji se odnose na biljne preparate, u SAD situacija je sasvim drugačija. Kako biljni proizvodi u SAD ne spadaju u kategoriju proizvoda koje reguliše Uprava za hranu i lekove (*Food and Drug Adminitration* – FDA), to FDA nije odgovorna za donošenje odobrenja za njihovu upotrebu. Oni su regulisani posebnim zakonskim aktom o dijetetskim dodacima ili suplementima – *Dietary Supplement Health and Education Act* [8, 9]. U praksi, pokazalo se da to nije odgovarajući model za regulativu i da se javljaju brojni problemi (prisustvo biljnih supstancija opasnih po zdravlje, nedostatak upotrebe GMP, loša signatura proizvoda, neadekvatno izveštavanje o neželjenim efektima i dr). Kako bi se umanjili nedostatci postojećeg regulatornog rešenja, FDA počela je da razvija posebne strategije za praćenje i proveru biljnih proizvoda i njihovih sastojaka [10–12].

Zakonska regulativa biljnih lekova kod nas

U našoj zemlji zakonski propisi za biljne proizvode u saglasnosti su sa preporukama evropske Direktive 2001/83/EEC i dopunom Direktive 2004/24/EEC. Zakon o lekovima i medicinskim sredstvima (Službeni glasnik Republike Srbije br. 84/2004 i 85/2005) reguliše biljne lekovite proizvode.

Fitopreparati kao aktivni sastojak sadrže usitnjene ili sprašene delove biljaka, balzame, smole, lekovita masna ulja, etarska ulja ili ekstrakte biljaka. U ovu grupu spadaju čajevi i čajne mešavine, ali i moderni farmaceutski oblici (instant prašak, šumeće tablete, tablete za žvakanje, obložene tablete, kapsule, sirup, sprej i sl). Tradicionalni biljni lek sadrži biljku, biljnu drogu (pojedinačnu ili mešavinu), preparate biljne droge (pojedinačne ili mešavinu) za koje se na osnovu iskustva i dugotrajne primene zna da se bezbedno mogu koristiti u svrhu terapije i prevencije. Tradicionalni biljni lekovi podležu odredbama evropske Direktive 2001/83/EEC i dopune Direktive 2004/24/EEC, koje dozvoljavaju sadržaj vitamina i minerala, pri čemu oni tada samo doprinose delovanju glavne biljne komponente i nisu posebno naznačeni u uputstvu. Tradicionalnim biljnim lekom ne smatraju se lekovi koji sadrže hemijski definisane, izolovane sastojke biljaka (npr. mentol, kardiotonične glikozide, i dr). Ukoliko lekovite biljke ili njihovi delovi ulaze u sastav prehrambenih proizvoda ili dijetetskih preparata, onda je reč o biljnim suplementima. Stručno mišljenje o klasifikaciji proizvoda izdaje Agencije za lekove i medicinska sredtsva Srbije (ALIMS) čija je nadležnost utvrđena članom 6 Zakona o lekovima i medicinskim sredstvima [13].

Postojeći problemi u praksi

Kvalitet, bezbednost upotrebe i efikasnost biljnih preparata najvažnija su pitanja koja se regulišu propisima. Uprkos dobro postavljenom regulatornom mehanizmu za biljne pre-

parate, u praksi se javljuju problemi. Najveći problem za primenu zakonskih propisa u oblasti kvaliteta odnosi se na biljne preparate koje upotrebljavaju indijska tradicionalna kineska ili ajurvedska medicina, jer se kod njih najčešće sreću nepravilnosti kao što su namerna ili slučajna upotreba zabranjenih biljnih supstancija, kontaminacija toksičnim ili sintetskim supstancijama ili signatura koja ne odgovara upotrebljenim sastojcima. Svetska zdravstvena organizacija sprovela je ispitivanje kontrole i zakona koji se trenutno primenjuju na biljne preparate u 141 zemlji sveta [14]. U odnosu na ispitivanja iz prethodnih godina uočene su pozitivne promene, jer su postojeći problemi u praksi motivisali veći broj zemalja da u poslednje četiri godine uspostave nacionalne strategije za regulisanje upotrebe biljnih preparata [15]. U obliku vodiča SZO je ponudila i tehničku podršku za razvoj metodologije za praćenje efikasnosti, kvaliteta, pripreme, bezbedne upotrebe biljnih proizvoda, njihovog reklamiranja i razmene informacija. Nekoliko dokumentovanih problema koji su se javili u proizvodnji i distribuciji biljnih preparata u svetu jasno odslikavaju potrebu za preciznim i strogo sprovedenim zakonskim propisima:

– zamena kineskog *Illicum verum Hook. f.* japanskim *Illicum anisaticum L.* Suvi plodovi ne mogu se razlikovati golim okom, pri čemu je japanski varijetet sličan kineskom, ali pokazuje gastroenterološku i neurološku toksičnost zbog prisutnog anizatina. Godine 2001. nekoliko slučajeva trovanja zabeleženi su u Holandiji, Francuskoj i Španiji, pri čemu su se kod beba koje su greškom pile infuz od japanskog anisa javile konvulzije epileptičnog tipa [16];

– kardiotoksičnost koja se javila pri upotrebi *Aconitum* vrsta u lekovima tradicionalne kineske medicine [17]. Koren vrsta *Aconitum* u tradicionalnoj kineskoj medicini potapa se u vodu ili kuva u vreloj vodi sa ciljem da alkaloidi akonitina hidrolizuju u manje toksične akoninske derivate. Međutim, ako ovi procesi nisu kontrolisani krajnji proizvod je toksičan;

– pojava srčanih aritmija prouzrokovanih zamenom bokvice za *Digitalis lanata*. Utvrđeno je da su velike količine pogrešnog biljnog materijala bile poslate u periodu od dve godine na više od 150 adresa proizvođača, veletrgovina i distributera u SAD [18].

Više puta primećeno je da pojedini biljni preparati u svetu sadrže nedozvoljene teške metale, druge toksične supstancije ili sintetske lekove zbog čega se posebno motri na ovaj problem onečišćenja biljnih preparata kineske i ajurvedske medicine [19–22]. Teški metali u biljnim proizvodima mogu da potiču iz same biljke ili greškom dospevaju u proizvod tokom njegove izrade. Međutim, nekada se teški metali dodaju namerno kao sastojci neophodni za izradu tradicionalnih formulacija u kineskoj ili ajurvedskoj medicini. Tako npr. Kineska farmakopeja sadrži oficinalne monografije za arsenov disulfid, živin hlorid (kalomel), živin sulfid, crveni živin oksid, kao i formulacije mnogih proizvoda koji sadrže jednu ili više ovakvih supstancija [23]. U jednom od istraživanja u SAD, koje je obuhvatilo 70 ajurvedskih proizvoda, 20% preparata sadržavalo je štetne koncentracije olova, žive i arsena, dok je u drugoj studiji iz 1998, takođe u SAD, dokumentovano da je 32% uvoznih azijskih proizvoda bilo onečišćeno nedeklarisanim supstancijama (efedrin, hlorfenamin, metiltestosteron, fenacetin) ili teškim metalima (živa, olovo, arsen) [24, 25]. Zabrinjavajuća bila je pojava štetnih sintetskih supstancija (fenfluramin, sibutramin, metilfenidat) u biljnim proizvodima za mršavljenje na bazi tradicionalne kineske medicine. U cilju sprečavanja sličnih situacija u Velikoj Britaniji, *Medicines and Healthcare Products Regulatory Agency* (MHRA) otvorila je posebnu *web* stranicu, *Herbal Safety News*, na kojoj se mogu naći upozorenja koja se tiču upotrebe pojedinih biljnih lekova [26]. Nadalje, za očekivati je da će razvoj analitičkih metoda za kontrolu kvaliteta biljnih preparata omogućiti njihovu bezbedniju primenu u praksi [27–29].

Zaključak

Kvalitet i bezbednost upotrebe biljnih preparata ostaju i dalje prioritet koji treba zakonski urediti na svetskom nivou. Za registraciju biljnog preparata kao leka postoje isti zahtevi kao i za registraciju drugih lekova u pogledu dokumentacije koja treba da sadrži predklinička i klinička ispitivanja. Ovakva ispitivanja vrlo su zahtevna, a kako složenost molekulske građe, čak i jednokomponentnih biljnih preparata, ometa utvrđivanje jedinstvenih kriterijuma za jasno praćenje njihovih terapijskih efekata, ispunjavanje zahteva za registrovanje biljnih preparata kao lekova u praksi još uvek je izazov i za naučnike i za proizvođače.

L I T E R A T U R A

1. *Barnes J, Anderson LA, Phillipson JD*. Herbal Medicines. 3rd ed. London Pharmaceutical Press; 2007.
2. *Evans WC*. Trease and Evans' Pharmacognosy. 15th ed. London, WB Saunders; 2001.
3. *Steinhoff B*. The contribuition of the European Scientific Cooperative on Phythotherapy and World Health Organization monographs. Drug Inform J 1999; 33: 17–22.
4. ESCOP Monographs, editors. The Scientific Foundation for Herbal Medicinal Products. 2nd edition Exeter (UK) 2003.
5. EMEA Committee for Herbal Medicinal Products (HMPC). Community Herbal Monographs. Available from: www.emea.europa.eu/htms/human/hmpc/hmpcmonographsdopt.htm, March 2007.
6. Council Directive 2001/83/EC. Official Journal of the European Communities 2001; 311: 67–128.
7. Council Directive 2004/24/EC. Official Journal of the European Communities 2004; 136: 85–90.
8. The Dietary Supplement Health and Education Act 1994, Pub L No. 103–417, Washington: 103 congress. Available from: www.dietary-supplements.info.nila.gov/aspx
9. FDA Centre for Food Safety and Applied Nutrition. Dietary supplements. Available from: http://vm.cfsan.fda.gov/~dms/supplmnt.html
10. *Marcus DM, Grollman AP*. Botanical medicines – the need for new regulations. N Engl J Med 2002; 347(25): 2073–6.
11. *Wechsler J*. Standards for supplements. Pharmaceutical Technology Europe 2003; March: 18–20. Available from:

www.medicinescomplete.com/mc/herbals/current/1000727388.html
12. Food and Drug Adminstration. FDA announces major initiatives for dietary supplements. 2004 November. Available from: www.fda.gov/bbs/topics/nwes/2004/NEW01130.html
13. *Djurović D.* Pharmaceutical legislation – important base for the product clasiffication. Arh farm 2007; 57: 178–91. (Serbian)
14. Anon. National Policy on Traditional Medicine and Regulation of Herbal Medicines: Report of a WHO global survey. Geneva: WHO, 2005. Available from: www.correofarmaceutica.com/documents/190905_plantas.pdf
15. Anon. Legal Status of Traditional Medicine and Complementary/Alternative Medicine: A Worldwide review. Geneva: WHO, 2001. Available from: www.whqlitdoc.who.int/q/2001/WHO_EDM_TRM_2001.2.pdf
16. *Biessels GJ, Vermeij FH, Leijten FS.* Epileptic seizure after a cup of tea: intoxication with Japanese star anise. Ned Tijdschr Geneeskd 2002; 146: 808–11. (Duch)
17. *Tai YT, But PP, Joung K, Lan CP.* Cardiotoxicity after accidental herb induced aconite poisoning. Lancet 1992; 340(8830): 1254–6.
18. *Slifman NR, Obermeyer WR, Aloi BU, Masser SM, Correll WA Jr, Cichowicz SM*, et al. Contamination of botanical dietary supplements by Digitalis lanata. N Engl J Med 1998; 339(12): 806–11.
19. *Ernst E.* Contamination of herbal medicines. Pharm J 2005; 275: 167–8.
20. *De Smet.* Health risks of hearbal remedies: An update. Clin Pharmacol Therapeutics 2004; 76 (1): 1–17.
21. *Ernst E.* Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. J Intern Med 2002; 252(2): 107–13.
22. *Ernst E.* Heavy metals in traditional Indian remedies. Eur J Clin Pharmacol 2002; 57(12): 891–6.
23. Pharmakopoeia of the People's Republic of China (English edition volume I/II/III). Bejing. Chemical Industry Press, 2005.
24. *Saper RB, Vales SN, Paquin J, Burns MJ, Aisehberg DM, Davis RB,* et al. Heavy metal content of Ayurvedic herbal medicine product JAMA 2004; 292: 2868–73.
25. *Ko RJ.* Adulterans in Asian plant medicines. N Engl J Med 1998; 339(12): 847.
26. Medicines and Healthcare products Regulatory Agency (MHRA). Herbal Safety News. Available from: www.mhra.gov.uk
27. *Lau A, Holmes MJ, Woo, SO koh HL.* Analysis of adulterants in a traditional herbal medicinal product using liquid chromatography – mass spectrometry - mass spectrometry, J Pharm Biomed Anal 2003; 31(2): 401–6.
28. *Liang YZ, Xie P, Chan K.* Quality control of herbal medicines, J Chromatogr Analyt Technol Biomed Life Sci 2004; 81(1–2): 53–70.
29. *Gong F.* Information theory applied to chromatographic fingerprint of herbal medicine for quality control, J Chromatogr A 2003; 1002(1–2): 25–40.

Rad primljen 28. III 2008.

K A Z U I S T I K A

UDC: 618.177-089:616.381-089:85

Rezultati savremenog operativnog lečenja tuboperitonealnog infertiliteta

Results of modern tuboperitoneal infertility treatment

Drenka Turjačanin-Pantelić*, Dragana Bojović-Jović†, Biljana Arsić†, Eliana Garalejić†

Medicinski fakultet, *Institut za medicinsku fiziologiju, **Beograd;**
†Institut za ginekologiju i akušerstvo „Narodni front", Beograd

Apstrakt

Uvod/Cilj. Savremeni pristup operativnog lečenja tuboperitonealnog infertiliteta bazira se na primeni laporaskopskih tehnika. Cilj ovog rada bio je poređenje rezultata operativnog lečenja tuboperitonealnog infertiliteta primenom laparoskopije i klasične laparotomije. **Metode.** Urađena je retrospektivno-prospektivna studija na 66 žena operativno lečenih od infertiliteta tuboperitonealnog porekla. Za retrospektivnu analizu korišćeni su podaci iz istorija bolesti operisanih žena (prethodno dijagnostikovanje uzroka infertiliteta, spermogram, histerosalpingogram, laparoskopija, utvrđivanje ovulacije, hormonsko ispitivanje), dok je prospektivna studija kojom su dobijeni podaci o rezultatima operativnog lečenja peritonealnog infertiliteta (laparoskopijom i klasičnom laparotomijom) urađena metodom ankete. U statističkoj analizi primenjen je neparametarski χ^2 test. Za nivo statističke značajnosti uzeto je $p < 0,05$. **Rezultati.** U periodu od 1996. do 1997. godine, 34 žene operisane su klasičnom laparotomijom (grupa I), a u periodu od 1999. do 2000. godine 32 žene operisane su laparoskopski (grupa II). Dobijeni su sledeći rezultati: ukupan broj nastalih trudnoća bio je 16 (24%), a od toga sedam u grupi I (20,6%) i devet u grupi II (28,1%). Bilo je 13 bolesnica sa po jednom trudnoćom, tj. šest u grupi I (17,6%) i sedam u grupi II (22%). Po dve trudnoće imale su tri žene u grupi I (2,9%) i dve u grupi II (6,2%). Što se tiče ishoda trudnoće, pet bolesnica imalo je spontani pobačaj, dve u grupi I (5,9%) i tri u grupi II (9,4%); dve bolesnice imale su vanmateričnu trudnoću, obe u grupi I (5,9%); tri prevremeni porođaj, jedna u grupi I (2,9%), i dve u grupi II (6,2%); terminski porođaj imalo je šest bolesnica dve u grupi I (5,9%), i četiri u grupi II (12,5%). Statističkom obradom podataka nađeno je da između ove dve grupe nema statistički značajne razlike u broju nastalih trudnoća. **Zaključak.** Hirurško lečenje tuboperitonealnog infertiliteta, bez obzira na to da li je izvedeno klasičnom operacijom ili laparoskopski, dovelo je do velikog broja trudnoća. Prednosti ovih metoda u odnosu na *in vitro* fertilizaciju, kao poslednju mogućnost u lečenju tuboperitonealnog infertiliteta, velike su i ne smeju biti zanemarene.

Ključne reči:
neplodnost, žene; laparotomija; laparoskopija; hirurgija, ginekološka, procedure; lečenje, ishod; trudnoća; abortus, spontani; porođaj.

Abstract

Background/Aim. A modern approach to surgical treatment of tuboperitoneal infertility is based on laporascopic techniques. The aim of this study was to compare results of tuboperitoneal infetility freatment by the use of laparoscopy and classical laparotomy. **Methods.** A retrospective-prospective study on 66 women treated operatively form tuboperitoneal infertility was performed. Data from patient's anemnesis and those related to the surgical treatment results, obtained by the use of an inquiry, were used in retrospective and prospective analysis, respectively. Chi-square test was used in statistical analysis. *P* value < 0.05 was considered singificant. **Results.** Classical laparotomy was used on 34 women in a period from 1996 to 1997, while 32 women were operated laparoscopically in a period from 1999 to 2000. The results were as follows: a total number of conceived women was 16 (24%), seven in the group I (20.6%) and nine in the group II (28.1%); 13 women were with one pregnancy, six in the group I (17.6%) and seven in the group II (22%). Twice pregnant were three women, one in the group I (2.9%) and two in the group II (6.2%). The resulting pregnancies were: five women with abortion spontaneous, two in the group I (5.9%) and three in the group II (9.4%); two women with extrauterine pregnancy in the group I (5.9%); three with pretemporal birth, one in the group I (2.9%) and two in the group II (6.2%), while six women were with the temporal birth, two in the group I (5.9%) and four in the group II (12.5%). Statistical analysis showed that there was no significant difference in the results between these two groups. **Conclusion.** Surgical treatment of tubeperitoneal infertility, regardless of the used methods (classical laparotomy or laparoscopy) was successful in a great number of women. These methods have a great advantage over *in vitro* fertilization, and they should not be ignored.

Key words:
infertility, female; laparotomy; laparoscopy; gynecologic surgical procedures; treatment, outcome; pregnancy; abortion, spontaneous; parturition.

Correspondence to: Drenka Turjačanin-Pantelić, Medicinski fakultet, Institut za medicinsku fiziologiju, Višegradska 26/2, 11 000 Beograd, Srbija. Tel.: +381 11 3611 278. E-mail: drenkaturjacanin@yahoo.com

Uvod

Laparoskopija čvrsto je integrisani deo svakodnevne ginekološke dijagnostičke i terapeutske prakse. Danas smo u svakom trenutku u stanju da vizuelno pregledamo unutrašnje genitalne organe žene, bez naročitog fizičkog opterećenja bolesnice [1]. Do šezdesetih godina ginekološka laparoskopija imala je više teoretsko značenje i primenjivana je retko, samo u pojedinim klinikama. Svoje izuzetno širenje i uvođenje u kliničku praksu laparoskopija zahvaljuje tehničkim dostignućima, i to u prvom redu automatskim aparatima za stvaranje veštačkog pneumoperitoneuma s CO_2, uvođenjem tzv. hladne svetlosti i poboljšanjem transporta slike u optičke instrumente [2–6]. Uvođenjem visokofrekventne struje omogućena je intraabdomenska koagulacija krvnih sudova, a samim tim i hemostaza, što je otvorilo vrata i sprovođenju manjih hirurških zahvata. Visokofrekventna struja omogućila je i koagulaciju jajovoda u svrhu sterilizacije, pa je laparoskopija sa sterilizacijom jajovoda postala najčešće primenjivana laparoskopska operacija u pojedinim zemljama. Potpunim ovladavanjem krvarenja nastalog za vreme laparoskopije i laparoskopskih operacija uz pomoć koagulacije visokofrekventnom strujom, endokoagulacijom ili specijalno konstruisanim omčama otvaraju se nove mogućnosti za mnogobrojne hirurške zahvate. To je presecanje adhezija u gornjem i donjem abdomenu, fimbrioplastika i salpingostomija kod tubarnog steriliteta, operativna korekcija tubarnog graviditeta, koagulacija endometritičkih žarišta, punkcija ovarijskih cista i resekcija njihovih zidova, punkcija folikula s aspiracijom ovuluma, enukleacija suspenzornih miomatoznih čvorića [7–18]. To teoretsko i praktično znanje iz ginekološke laparoskopije dobar je osnov i za endoskopsku abdomensku hirurgiju [9–21].

Cilj ovog rada bio je poređenje efikasnosti laparoskopije i klasične laparotomije u lečenju tuboperitonealnog infertiliteta.

Metode

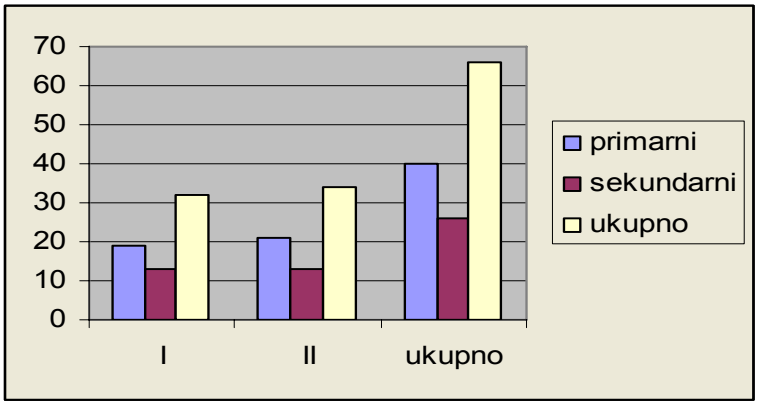
Za istraživanje korišćeni su podaci o bolesnicima operisanim klasičnom laparotomijom u periodu 1996–1997. god, kao i o bolesnicama operisanim laparoskopskim putem 1999–2000. god. u Ginekološko-akušerskoj klinici „Narodni front“. Urađena je retrospektivno-prospektivna studija. Za retrospektivnu analizu korišćeni su podaci iz istorija bolesti operisanih žena (prethodno dijagnostikovanje uzroka infertiliteta, spermogram, histerosalpingogram, laparoskopija, utvrđivanje ovulacije, hormonsko ispitivanje), dok je prospektivna studija kojom su dobijeni podaci o rezultatima operativnog lečenja peritonealnog infertiliteta (laparoskopijom i klasičnom laparotomijom) urađena metodom ankete, u periodu od aprila do juna 2003. god. Istraživanje je započeto na 169 žena kojima su poslate ankete, međutim, povratnu informaciju o nastalim trudnoćama dobili smo od samo 66 žena, i to od 32 laparoskopski operisane i 34 žene operisane klasičnom laparotomijom. Statistička analiza urađena je na kompjuteru primenom programa za obradu statističkih podataka SPSS. Statistička analiza obuhvatila je određivanje deskriptivnih parametara; aritmetičke sredine, standardne devijacije, kao i učestalosti pojedinih obeležja. U statističkoj analizi primenjen je neparametarski χ^2 test. Za nivo statističke značajnosti uzeto je $p < 0,05$.

Rezultati

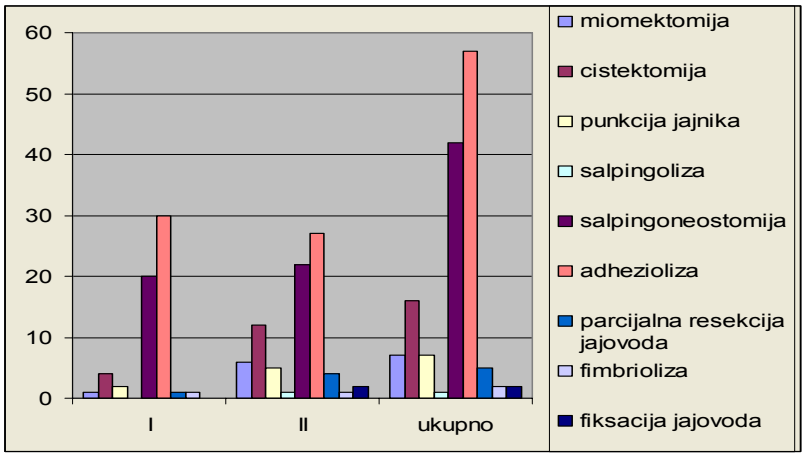
Od 66 žena 32 (48%) operisane su laparoskopski – prva grupa, dok je kod 34 (52%) urađena klasična laparotomija – druga grupa. Bolesnice operisane laparoskopski bile su uglavnom iz gradova i sela u unutrašnjosti, dok su bolesnice operisane klasičnom laparotomijom bile uglavnom iz Beograda. To pokazuje da napredak laparoskopije i upućenost u samu operaciju putem sredstava medija utiče na povećanje broja bolesnica iz unutrašnjosti, a naročito iz sela. U prvoj grupi prosečno životno doba žena bilo je 30 god, a u drugoj 32 god. Nije postojala statistički značajna razlika u godinama života između ove dve grupe ($p = 0,41$). Od ukupnog broja operisanih 62 (94%) bilo je u braku prvi put, a četiri (6%) drugi put. Nije postojala statistički značajna razlika između ove dve grupe ($p = 0,332$). Devet (13%) žena bilo je u braku tri godine, 14 (21%) četiri godine, 16 (24%) pet godina, osam (12%) sedam godina, tri (4%) osam godina, jedna (1%) devet godina, dve (2%) 10 godina, jedna (1%) 14 godina, dve (2%) 15 godina, jedna (1%) 17 godina i jedna (1%) 18 godina. Nije postojala statistički značajna razlika u dužini braka između ove dve grupe operisanih žena ($p = 0,399$). Prosek godina provedenih u braku u ove dve grupe operisanih žena bio je oko šest godina. Svih 66 žena (100%) pre operacije imalo je u anamnezi dijagnostikovano neko ginekološko oboljenje. Četrnaest žena (22%) od ukupnog broja operisanih imalo je u anamnezi neku ginekološku operaciju. Deset žena (16%) bilo je iz grupe laparoskopski operisanih, a četiri (6%) iz grupe operisanih klasičnom laparotomijom. Bez obzira što nije postojala statistički značajna razlika ($p = 0,052$), ona je ipak bila na granici značajnosti što pokazuje da se većina žena odlučila na ponovnu operaciju i to laparoskopsku, zbog prethodno iznesenih prednosti ove metode. Od ukupnog broja operisanih žena 62 (93%) imale su u anamnezi urađenu apendektomiju – u grupi laparoskopski operisanih bilo je 28 (42%), dok je u grupi operisanih klasičnom laparotomijom bilo 34 žena (51%). Postojala je statistički značajna razlika u broju prethodno urađenih apendektomija kod ove dve grupe operisanih žena ($p = 0,033$). Od ukupnog broja operisanih, devet žena (14%) imalo je u anamnezi porođaj sa živorođenom decom. Sedam žena (11%) koje su prethodno imale porođaj bilo je u grupi laparoskopski operisanih, a dve (3%) u grupi operisanih klasičnom laparotomijom. Nije postojala statistički značajna razlika u anamnezi prethodnih porođaja između ove dve grupe ($p = 0,058$). Od ukupnog broja operisanih žena, 57 (86%) nije imalo namerne prekide trudnoće, sedam (12%) imalo je jedan namerni prekid trudnoće, jedna (1%) imala je dva namerna prekida trudnoće i jedna (1%) tri namerna prekida trudnoće u anamnezi. Četiri žene (7%) imale su namerne prekide trudnoće u grupi laparoskopski operisanih, a pet (7%) u grupi operisanih klasičnom laparotomijom. Nije postojala statistički značajna razlika u broju namernih prekida trudnoće u anamnezi operisanih žena u ove dve grupe

($p = 0,551$). Od ukupnog broja operisanih žena, 56 (86%) nije imalo spontani pobačaj, osam (12%) jeste imalo jedan spontani pobačaj, a dve (2%) imale su dva spontana pobačaja. Po grupama: četiri žene (6%) u grupi laparoskopski operisanih imalo je spontani pobačaj, i šest žena (8%) u grupi operisanih klasičnom laparotomijom. Nije postojala statistički značajna razlika u anamnezi spontanih pobačaja između ovu dve grupe operisanih žena ($p = 0,378$).

Od ukupnog broja operisanih, 40 žena (61%) bilo je sa dijagnozom primarnog, a 26 (39%) sa dijagnozom sekundarnog infertiliteta (slika 1). U grupi žena operisanih klasičnom laparotomijom, 21 žena (32%) bila je sa dijagnozom primarnog infertiliteta, a 13 (20%) sa dijagnozom sekundarnog infertiliteta. Nije postojala statistički značajna razlika u dijagnozama primarnog i sekundarnog infertiliteta između laparoskopski i laparotomijski operisanih žena ($p = 0,842$). Sve operacije, izvedene kod bolesnica I i II grupe, prikazane su slikom 2. Od ukupnog broja operisanih, sedam žena (10%) imalo je dijagnostikovan miom uterusa, i to dve (3%) u grupi laparoskopski operisanih, dok je pet bilo (7%) u grupi operisanih klasičnom laparotomijom. Nije postojala statistički značajna razlika u učestalosti mioma u ove dve grupe operisanih žena ($p = 0,163$). Od ukupnog broja operisanih žena, dijagnozu ciste na jajnicima imalo je 13 (20%), i to tri (5%) u grupi laparoskopski operisanih i 10 (15%) u grupi operisanih klasičnom laparotomijom. Postojala je statistički značajna razlika u dijagnozi cista na jajnicima ($p = 0,040$). Od ukupnog broja operisanih žena, četiri (6%) su imale dijagnozu mikrocistične degeneracije jajnika (sve četiri žene bile su iz grupe operisanih klasičnom laparotomijom). Postojala je statistički značajna razlika u dijagnozi mikrocistične degeneracije jajnika između ove dve grupe operisanih žena ($p = 0,045$). Od ukupnog broja operisanih žena, dve (2%) su imale dijagnozu policistični ovarijum (PCO) u grupi operisanih klasičnom laparotomijom, dok u grupi laparoskopski operisanih nijedna žena nije imala ovu dijagnozu. Nije postojala statistički značajna razlika u dijagnozi PCO između ove dve grupe operisanih žena ($p = 0,163$). Od ukupnog broja operisanih žena dve (2%) su imale dijagnozu paraovarijalnih cisti, po jedna u svakoj od ovih grupa. Nije postojala statistički značajna razlika u dijagnozi paraovarijalnih cisti između ove dve grupe ($p = 0,96$). Od ukupnog broja operisanih žena, tri (4%) imale su dijagnozu salpingitisa, sve iz druge grupe. Nije postojala statistički značajna razlika u dijag-



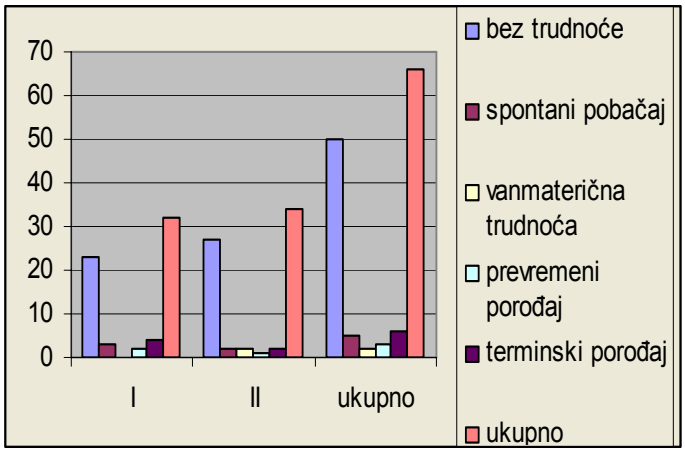
Sl. 1 – Prikaz učestalosti primarnog i sekundarnog infertiliteta kod žena operisanih laparoskopijom (grupa I) i klasičnom laporotomijom (grupa II)



Sl. 2 – Prikaz broja laparoskopskih (bolesnice grupe I) i klasičnih laparotomijskih (bolesnice grupe II) operacija

nozi salpingitisa između ove dve grupe ($p = 0,085$). Od ukupnog broja operisanih žena samo jedna (1%) imala je dijagnozu saktosalpinks i to žena iz druge grupe. Nije postojala statistički značajna razlika u dijagnozi saktosalpinksa između ove dve grupe ($p = 0,328$). Od ukupnog broja operisanih žena, 39 (59%) imalo je dijagnozu hidrosalpinks, i to 17 (26%) u prvoj grupi i 22 (33%) u drugoj grupi. Nije postojala statistički značajna razlika u dijagnozi hidrosalpinksa između ove dve grupe ($p = 0,085$). Od ukupnog broja operisanih žena, pet (8%) imalo je dijagnozu subokluzije jajovoda, a od toga tri (5%) iz prve grupe i dvoje (3%) iz druge grupe. Nije postojala statistički značajna razlika u dijagnozi subokluzije jajovoda između ove dve grupe ($p = 0,59$). Od ukupnog broja imala je dijagnozu adhezije, sedam (11%) iz prve i 14 (21%) iz druge grupe. Nije postojala statistički značajna razlika u dijagnozi adhezije između ove dve grupe ($p = 0,092$). Od ukupnog broja operisanih žena pet (8%) imalo je dijagnozu endometrioza, tri (5%) iz prve i dve (3%) iz druge grupe. Nije postojala statistički značajna razlika u dijagnozi salpingitisa između ove dve grupe ($p = 0,592$).

U ukupnom broju operacija drenaža *cavum Douglasi* izvedena je kod 41 žene (62%), 29 (44%) iz prve grupe i 12 (18%) iz druge grupe, što je predstavljalo statistički značajnu razliku ($p = 0,000$). Od ukupnog broja operisanih žena, trudnoća je začeta kod njih 16 (24%) i to kod devet (28,1%) žena iz prve grupe i sedam (20,16%) žena iz druge grupe. Nije po-



Sl. 3 – Prikaz ishoda trudnoće nastalih nakon operacije zbog tuboperitonealnog infektiliteta kod bolesnica operisanih laparoskopskim (grupa I) i klasičnim (grupa II) putem

operisanih žena, 17 (26%) imalo je dijagnozu okluzije leve tube, i to pet (8%) iz prve i 12 (18%) iz druge grupe. Nije postojala statistički značajna razlika u dijagnozi okluzije leve tube između ove dve grupe ($p = 0,0678$). Od ukupnog broja operisanih žena dijagnozu okluzije desne tube imalo je 12 žena (18%), i to pet (8%) u prvoj i sedam (10%) u drugoj grupi. Nije postojao statistički značajna razlika u dijagnozi okluzije desne tube između ove dve grupe ($p = 0,601$). Od ukupnog broja operisanih žena, dve (2%) bile su sa dijagnozom konglutinacije fimbrija jajovoda i to obe iz druge grupe. Nije postojala statistički značajna razlika u dijagnozi konglutinacije fimbrija između ove dve grupe ($p = 0,163$). Od ukupnog broja operisanih žena, jedna (1%) imala je dijagnozu aplazije jajovoda, i to iz druge grupe. Nije postojala statistički značajna razlika u dijagnozi aplazije jajovoda između ove dve grupe ($p = 0,328$). Od ukupnog broja operisanih žena 40 (60%) imalo je dijagnozu hroničnog periadneksitisa, i to 19 (29%) iz prve i 21 (31%) iz druge grupe. Nije postojala statistički značajna razlika u dijagnozi hroničnog periadneksitisa između ove dve grupe ($p = 0,842$). Od ukupnog broja operisanih žena, devet (14%) imalo je dijagnozu hronični pelveoperitonitis, šest (10%) iz prve i tri (4%) iz druge grupe. Nije postojala statistički značajna razlika u dijagnozi hroničnog pelveoperitonitisa između ove dve grupe ($p = 0,240$). Od ukupnog broja operisanih žena, 21 (32%) stojala statistički značajna razlika u broju nastalih trudnoća između ove dve grupe ($p = 0,475$). Od ukupnog broja operisanih žena, jednu trudnoću imalo je 13 (20%) žena, a dve trudnoće tri žene (4%) u prvoj grupi, sedam (22%) sa jednom trudnoćom i dve (6,2%) sa dve trudnoće; u grupi II šest (17,6%) sa jednom trudnoćom i jedna (2,9%) sa dve trudnoće. Nije postojala statistički značajna razlika u broju trudnoća između ove dve grupe ($p = 0,715$).

Ishod nastalih trudnoća (slika 3) bio je sledeći: pet (7%) završilo se spontanim pobačajem, tri (9,4%) iz prve grupe i dva (5,9%) iz druge grupe; dva (5,9%) vanmaterničnom trudnoćom, obe u grupi II; prevremeni porođaj kod tri (4%) i to dva (6,2%) u grupi I i jedan (2,9%) u grupi II; terminski porođaj kod šest (10%), i kod četiri (12,5%) u prvoj grupi i dva (5,9%) u drugoj grupi. Broj vanmaterničnih trudnoća bio je veći u drugoj grupi, a terminskih porođaja u prvoj grupi.

Diskusija

Operacije zbog tuboperitonealnog infertiliteta apsolutno ne dolaze u obzir ako je žena starija od 39 godina, ima verifikovanu tuberkulozu, aktivni nespecifični upalni proces, masivni i čvrsti adhezivni proces u maloj karlici, obostrane tuboovarijalne ciste, skleroatrofične jajovode, ili teže bipolarne ili unipolarne promene na jajovodima [22–25]. Posle medi-

kamentozne terapije za upalni proces na adneksima potrebna je pauza od šest meseci pre eventualnog hirurškog zahva. Nakon bilo kakve operacije ili manipulacije na genitalnom aparatu operacija se odgađa za 1–2 meseca. Neprikladnom i prevremenom operacijom mogu biti uništene sve mogućnosti za uspeh. Iz psiholoških razloga ne operišu se bolesnici kada se zna da neće ozdraviti. Ovim bolesnicama savetuje se vantelesna oplodnja [26–30]. Mnoge od kontraindikacija za operativno lečenje danas predstavljaju indikaciju za vantelesnu oplodnju. Uspeh operativnog lečenja tuboperitonealnog infertiliteta zavisi od operativne tehnike, a u najvećoj meri od stepena raširenosti oštećenja jajovoda i okoline [31–34]. Dijagnoza stepena i obima oštećenja jajovoda i okoline zbog toga je od bitnog značaja za uspeh operacije [35–39]. Najvažniji pregledi u dijagnostici tuboperitonealnog uzroka infertiliteta su histerosalpingografija i laparoskopija. Pored tih pregleda uvek se zahteva i spermogram, postkoitalni test, bazalna temperatura, biopsija endometrijuma i eventualno hormonske analize [40–42]. Na osnovu toga može se postaviti realna prognoza o mogućnosti operativnog lečenja. Operacija se savetuje ukoliko je mogućnost za uspeh veća od 20 %, a ukoliko je 10–20% ne savetuje se, osim kada se bračni par odluči za operaciju. Ukoliko je mogućnost za uspeh manja od 10% operacija se ne preporučuje niti radi. Tamo gde postoje uslovi i znanje, neke mikrohirurške operacije danas se mogu endoskopski uraditi [43–47].

Danas postoje dva uspešna načina lečenja tuboperitonealnog infertiliteta: rekonstruktivno hirurško lečenje i vantelesna oplodnja. Slažemo se s autorima koji smatraju da su mikrohirurgija i fertilizacija *in vitro* komplementarne metode lečenja tuboperitonealnog steriliteta. Laparoskopska operativna hirurgija tuboperitonealnog infertiliteta poslednji je stepenik u lečenju infertiliteta pre primene IVF. Žene mogu zatrudneti više puta posle jedne operacije. U našem ispitivanju od 34 žene operisane laparoskopskom hirurškom tehnikom, zatrudnelo je devet (28,1%), dok je od 32 žene operisane klasičnom operativnom tehnikom zatrudnelo je sedam žena (20,6%). Nije postojala statistički značajna razlika u broju nastalih trudnoća između ove dve grupe operisanih žena.

Dobijeni rezultati sugerišu da uspeh operativnog lečenja tuboperitonealnog infertiliteta zavisi pre svega od rasprostranjenosti patološkog procesa, a zatim od primenjenog operativnog metoda, iskustva hirurga, raspoložive opreme, starosti bolesnice kao i od dužine braka. Bolesnice operisane laparoskopskom hirurškom tehnikom imaju veći procenat nastalih intrauterinih trudnoća (28,1%) u odnosu na bolesnice operisane klasičnom metodom (20,6%), ali ipak ta razlika nije statistički značajna. Ektopične trudnoće nastale su samo kod dve žene operisane klasičnom hirurškom tehnikom. Žene mogu posle jedne operacije zatrudneti više puta. Laparoskopija izaziva manji metabolički odgovor na stres, zbog manje operativne destrukcije tkiva, eliminiše abdominalnu inciziju, štedi dijafragmalnu funkciju, štedi plućnu funkciju, smanjuje postoperativni ileus, obezbeđuje minimalnu nepokretnost žene, ekonomičnija je u odnosu na klasičnu laparotomiju i IVF, omogućuje preciznije operisanje zbog povećanja slike. Laparoskopijom se postiže bolja hemostaza zahvaljujući boljoj opremi, manje je gnječenja tkiva i oštećenja sluznice i izbegava se nepotrebna tamponada creva. Posle laparoskopskih operacija oporavak je brži i manje je bolan i ostaje manje ožiljaka na koži i u operativnom polju. Brža je mobilizacija bolesnica, manji je rizik od tromboembolije i tromboze, a oporavak kraći. Rezultati potvrđuju da ginekološka mikrohirurgija s pravom zauzima prvo mesto kada je u pitanju lečenje tuboperitonealnog infertiliteta, ali rezultati ponovo potvrđuju da su napretku hirurgije postavljene granice, kako u dijagnostici, tako i u operativnoj tehnici. Postoji relativno visok broj inoperabilnih bolesnica, a osim toga dobra rekonstrukcija ne znači uvek i dobru funkciju.

Zaključak

Hirurško lečenje tuboperitonealnog infertiliteta, bez obzira na to da li je izvedeno klasičnom operacijom ili laparoskopski, dovelo je do velikog broja trudnoća. Prednosti ovih metoda u odnosu na *in vitro* fertilizaciju, kao poslednju mogućnost u lečenju tuboperitonealnog infertiliteta, velike su i ne smeju biti zanemarene.

L I T E R A T U R A

1. *Šimunić V*, ed. Gynecology. Medicinska Knjiga Zagreb: 2001; 298–303.
2. XXV Basic course of laparoscopic surgery with theoretical and practical lectures. Belgrad Juen, Vojnomedicinska akademija Beograd, 20–21. Septembar 2002: 3–26. (Serbian)
3. *Wallwiener D, Meyer A, Bastert G.* Carbon dioxide laser tissue welding: an alternative technique for tubal anastomosis? J Clin Laser Med Surg 1997;15(4): 163–9.
4. *Nedeucker J, Saurland S, Neugebauer E.* the E.A.E.S. clinical practice gydeline on the pneumoperitoneuem for laparoscopic surgery. Helad at ninth International congress of the European Association for Endoscopy Surgery (E.A.E.S), Maastricht. June 13-June 15, 2001: p. 56.
5. *Mage G, Bruhat MA.* Pregnancy following salpingostomy: comparison between CO2 laser and electrosurgery procedures. Fertil Steril 1983; 40(4): 472–5.
6. *Daniel JF, Brown DH.* Carbon dioxide laser laparoscopy: Initial experience in experimental animals and humans. Obstet Gynecol 1982; 159–61.
7. *Wallwiener D, Maleika A, Rimbach S, Homann G, Rabe T, Gauwerky J, Bastert G.* The value of laparoscopic and laser-assisted techniques in reconstruction of distal fallopian tube pathology. Zentralbl Gynakol 1996; 118(2): 66–72. (German)
8. *Volk M, Obermaier W, Tabatabai K, Ernet E, Berndt D.* Transposition of the fallopian tube as a therapeutic possibility in special cases of tubal sterility. Geburtshilfe frauenheilkd 1994; 54(9): 515–8. (German)
9. *Sekine Y, Takai Y, Nishii O, Kudaka N, Onozawa A, Arai H,* et al. The participation of pharmacists in a team to introduce a clinical pathway to laparoscopic cystectomy in obstetrics and gynecology. Yakugaku Zasshi 2001; 121(12): 995–1004.
10. *Saleh WA, Dlugi AM.* Pregnancy outcome after laparoscopic fimbrioplasty in nonocclusive distal tubal disease. Fertil Steril 1997; 67(3): 474–80.
11. *Penzias AS, DeCherney AH.* Is there ever a role for tubal surgery? Am J Obstet Gynecol 1996; 174(4): 1218–21; discussion 1221–3.

12. *Mecke H, Semm K, Lehman Wilenbrock E, Stojanov M, Freys I.* Pelviscopic salpingostomy with everted suture. Zentralbl Gynekol 1995; 1178: 413–6. (German)
13. *Parker WH, Rodi IA.* Patient selection for laparoscopic myomectomy. J Am Assoc Gynecol Laparosc 1994; 2(1): 23–6.
14. *Bašić D, Grgić F, Ćorušić A, Dijaković A.* Laparoscopic enucleatiru of the intrammural mujoma. Gynaecol Perinatol 2000; 9: 35–8. (Croation)
15. *Gomel V.* Operative laparoscopy: time for acceptance. Fertil Steril 1989; 52(1): 1–11.
16. *Gomel V, Taylor PJ.* Diagnostic and operative gynecologic laparoscopy. St. Louis, Mosby, 1995.
17. *Carey M, Brown S.* Infertility surgery for pelvic inflammatory disease: succes rates after salpingolysis and salpingostomy. Am J Obstet Gynecol 1987; 156(2): 296–300.
18. *Audebert AJM.* Ovarian surgery: why expect more problems from laparoscopy than from laparotomy? Gynaecol Endose 1995; 4: 1–2.
19. *Bruhat MA, Manhes H, Mage G, Pouly JL.* Treatment of ectopic pregnancy by means of laparoscopy. Fertil Steril 1980; 33(4): 411–4.
20. *Vasquez G, Boeckx W, Brosens I.* Prospective study of tubal mucosal lesions and fertility in hydrosalpinges. Hum Reprod 1995; 10(5): 1075–8.
21. *Reddick EJ, Saye BW, Corbitt JD*, eds. Atlas of Laparoscopic Surgery. New York Raven Press 1993. p. 21.
22. *Audebert AJM.* The role of microlaparoscopy for safer wall entry: incidence of umbilical adhesiones according to past surgical history. Gynaecol Endosc 1999; 8(6): 363–7.
23. *Semm K.* Pro and contra: pelviscopy and microsurgery of the fallopian tube. Arch Gynecol Obstet 1995; 257(1–4): 302–10. Review. (German)
24. *Frangenheim H.* Indikationen Technik und Komplikationen der Laparoskopie und Kuldoskopie in der Gynekologie. Geburtsh Rauenheilk 1962; 7: 997. (German)
25. *Felberbaum R, Diedrich K.* Current aspects of diagnosis and therapy of tubal sterility. Arch Gynecol Obstet 1995; 257(1–4): 310–9. (German)
26. *Tomazević T, Ribić-Pucelj M, Omahen A, Colja B.* Microsurgery and in-vitro fertilization and embryo transfer for infertility resulting from pathological proximal tubal blockage. Hum Reprod 1996; 11(12): 2613–7.
27. *Gocial B.* Primary therapy for tubal disease: surgery versus IVF. Int J Fertil Menopausal Stud 1995; 40(6): 297–302.
28. *Sueoka K, Asada H, Tsuchiya S, Kobayashi N, Kuroshima M, Yoshimura Y.* Falloposcopic tuboplasty for bilateral tubal occlusion. A novel infertility treatment as an alternative for in-vitro fertilization? Hum Reprod 1998; 13(1): 71–4.
29. *Shelton KE, Butler L, Toner JP, Oehninger S, Muasher SJ.* Salpingectomy improves the pregnancy rate in in-vitro fertilization patients with hydrosalpinx. Hum Reprod 1996; 11(3): 523–5.
30. *Andersen AN, Lindhard A, Loft A, Ziebe S, Andersen CY.* The infertile patient with hydrosalpinges IVF with or without salpingectomy? Hum Reprod 1996; 11(10): 2081–4.
31. *Marana R, Rizzi M, Muzii L, Catalano GF, Caruana P, Mancuso S.* Correlation between the American Fertility Society classifications of adnexal adhesions and distal tubal occlusion, salpingoscopy, and reproductive outcome in tubal surgery. Fertil Steril 1995; 64(5): 924–9.
32. *Breznik R, Borko E, Dolenec N.* Microsurgical treatment of tubal infertility. Jugosl Ginekol Perinatol 1985; 25(1–2): 17–20. (Croatian)
33. *Akhan SE, Baysal B.* Laparotomy or laparoscopic surgery? Factors affecting the surgeons choice for the treatment of ectopic pregnancy. Arch Gynecol Obstet 2002; 266(2): 79–82.
34. *Kozlowski D, Luciano AA.* Bilateral atresia of the proximal ampullary segment of the fallopian tubes. J Am Assoc Gynecol Laparosc 1995; 3(1): 99–101.
35. *Aubriot FX, Chapron C, Morice P, Dubuisson JB.* Hydrosalpinx and sterility: indications for salpingectomy. Contracept Fertil Sex 1995; 23(11): 670–3. (French)
36. *Cittadini E, Flaming C, Foleo R, Sbiroli C.* Microchirurgia della tuba. In: *Cittadini E, Famingi c, Forleo R, Sbiroli C*, eds. Palermo: Cofese 1986; 325–64.
37. *Cognat M, Audebert A, Disant D.* Chirurgie tubaire iterative pour sterilite. Gynecologie 1982; 33: 557–42. (French)
38. *Dieterle S, Mesrogli M, Triebler B, Wollenhaupt J, Nettelnbreker E, Schlösser HW.* Is there a correlation between tubal occlusions in chronic salpingitis and urogenital chlamydia infections? Geburtshilfe Frauenheilkd 1994; 54(8): 455–9. (German)
39. *Duepree HJ, Senagore AJ, Delaney CP, Marcello PW, Brady KM, Falcone T.* Laparoscopic resection of deep pelvic endometriosis with rectosigmoid involvement. J Am Coll Surg 2002; 195(6): 754–8.
40. *Chapron C, Dubuisson JB, Chavet X, Morice P.* Treatment and causes of female infertility. Lancet 1994; 344(8918): 333–4.
41. *De Angelis C, Santoro G, Re ME, Cavalieri AP, Zichella L.* Ultrasonographic and biochemical screening of adnexal masses before operative laparoscopy. Minerva Ginecol 2002; 53–7.
42. *Semm K.* Pro and contra: pelviscopy and microsurgery of the fallopian tube. Arch Gynecol Obstet 1995; 257(1–4): 302–10.
43. *Frangenheim H.* Laparoscopie und die Kuldoscopie in der Gynakologie. Stuttgart: Thieme 1959; 2: 26. (German)
44. *Martin RG, Corfman RS.* Laser surgery. In: *Wallach EE, Zacur HA*, eds. Reproductive Medicine and Surgery. St. Louis Mosby, 1995; 1067–73.
45. *Dubuisson JB, Chapron C.* Is there still a role for laparotomy in tubal infertility surgery? Contracept Fertil Sex 1997; 25(9): 688–93. (French)
46. *Korell M, Strowitzki T, Hepp H.* Possibilities and limits of endoscopic fallopian tube surgery. Zentralbl Gynakol 1995; 117(12): 663–9. (German)
47. *Kratochwill A.* Die Bedeutung der Laparoskopie in der Sterilitatdiagnostik. Wien Klin Wschr 1986; 80: 581. (German)

Rad primljen 24. VI 2008.

C A S E R E P O R T UDC: 616.411-006.31-091.8

Atipical immunophenotype in a littoral cell angioma

Atipični imunofenotip kod angioma litoralnih ćelija

Radoje Čolović*, Nada Suvajdžić†, Nikica Grubor*, Nataša Čolović†, Tatjana Terzić‡

Clinical Center of Serbia, *Institute for Digestive Diseases, †Institute of Haematology, **Belgrade; School of Medicine,** ‡Institute of Pathology, **Belgrade**

Abstract

Background. Littoral-cell angioma (LCA) is a recently described benign vascular tumor of the spleen, whose imaging and pathologic characteristics have been discussed only by a few authors. The tumor is characterized by a mixture of papillary and cystic areas lined by neoplastic cells deriving from normal splenic lining – littoral cells. The neoplastic LCA cells express both endothelial and histiocytic antigens associated with CD8 negativity, compared with the normal endothelium of the venous sinuses of the spleen red pulp that only expresses endothelial antigens and CD8 positivity. Therefore, the typical and characteristic immunohistochemical pattern of the LCA is as follows: CD31, CD68, CD163, CD21, FVIII antigen positive; CD34, CD8 negative. **Case report.** We reported a 60-year-old male with moderate nodular splenomegaly with one large hypoechogenic solid lesion and mild thrombocytopenia in whom the diagnosis of LCA was made after the elective splenectomy. Namely, histopathological and immunohistochemical data allowed a final diagnosis of classical LCA in spite of CD21 negativity. As far as we know this is the first reporeted CD21-negative LCA patient. Histological specimens were presented and differential diagnoses discussed. **Conclusion.** Littoral-cell angioma is a very rare benign splenic neoplasm that should be considered in the differential diagnosis of multinodular splenomegaly, particularly if the patient has the signs of hypersplenism.

Key words:
splenic neoplasms; immunohistochemistry; histology; antigens, CD; splenectomy.

Apstrakt

Uvod. Angiom litoralnih ćelija (ALĆ) nedavno je opisan benigni tumor slezine vaskularnog porekla o čijim patohistološkim i radiološkim karakteristikama ima malo podataka u medicinskoj literaturi. Tumor se odlikuje prisustvom papilarnih i cističnih tvorevina sastavljenih od tumorskih ćelija koje vode poreklo od litoralnih ćelija slezine koje oblažu venske sinuse crvene pulpe. Za razliku od normalnih litoralnih ćelija slezine koje eksprimiraju samo endotelne antigene, ćelije ALĆ eksprimiraju istovremeno endotelne i histiocitne antigene uz odsustvo bojenja na CD8 koje je inače prisutno kod normalnih litoralnih ćelija. Stoga, imunofenotipski profil ALĆ jedinstven je i karakterističan: CD31, CD68, CD163, CD21, FVIII antigen pozitivni; CD34, CD8 negativni. **Prikaz bolesnika.** Prikazan je bolesnik, star 60 godina, sa umereno uvećanom, nodularno infiltrisanom slezinom i blagim stepenom trombocitopenije, kod koga je dijagnoza bila ALĆ, postavljena posle elektivne splenektomije. Patohistološki nalaz, dopunjen imunohistohemijom pokazao je da se radi o klasičnom obliku ALĆ, uprkos odsustvu eskpresije CD21 antigena. Koliko nam je poznato ovo je prvi slučaj ALĆ bez ekspresije CD21 antigena u medicinskoj literaturi. Prikaz bolesnika diskutovan je u svetlu patohistološkog nalaza i diferencijalne dijagnoze. **Zaključak**. Smatra se da je ALĆ redak, benigni tumor slezine koji može biti uzrok splenomegalije, pogotovo ako se radi o slezini sa nodusima i pridruženim hipersplenizmom.

Ključne reči:
slezina, neoplazme; imunohistohemija; histologija; antigeni, CD; splenektomija.

Introduction

Littoral-cell angioma (LCA) is a very rare primary tumor of the spleen arising from normal endothelial cells lining the venous sinuses of the splenic red pulp (littoral cells) [1]. The neoplastic LCA cells express both endothelial and histiocytic antigens, compared with the normal endothelium of the venous sinuses that only expresses endothelial antigens [1]. Therefore, the immunophenotypic signature of CD31, CD68, CD163, FVIII antigen and CD21 on the lining cells of the LCA is unique to this tumor. Typically, CD34 and CD8 are negative. The tumor is considered benign, though the litera-

Correspondence to: Nada Suvajdžić, Clinical Center of Serbia, Institute of Haematology, Dr. Koste Todorovića 2, 11 000 Belgrade, Serbia. Tel: + 381 64 2776227; E-mail: nvukovic@Eunet.yu

ture has described a patient with disseminated disease and an apparent response to the therapy, and two other cases have shown histological atypia, though without fully malignant histological features [1–3].

Case report

A 60-year-old male was referred to our institute in December 2006 due to spleen tumor. He complained of intermittent blunt pain of moderate intensity under his left costal margin lasting for a few years but it was not before November 2006 that the abdominal ultrasound (US) scan was perfomed revealing an enlarged spleen of 15.5 cm with a large hypoechogenic solid lesion. Computerized tomography (CT) without contrast confirmed splenomegaly (17 × 12.4 cm), nonhomogenous and hypodense without clear delineation of tumor.

Physical examination identified an enlarged, firm, nontender spleen extending 3 cm below the left costal margin. The patient's medical history besides arterial hypertension was unremarkable. He was not aware of any familial related diseases and had not recently visited a foreign country. The patient had been constitutionally well and denied suffering from fever, weight loss or night sweats. All hematological values were normal except for a mild thrombocytopenia (60–70 × 10^9/L). Clotting tests were within normal limits, excluding a disseminated intravascular coagulopathy. No biochemical or immunological abnormalities were found and viral serological tests were negative.

For diagnostic purposes the patient underwent splenectomy. The 900-gram resected spleen (16 × 13 × 8.7 cm) had an intact and sturdy capsule (Figure 1). Splenic tissue was

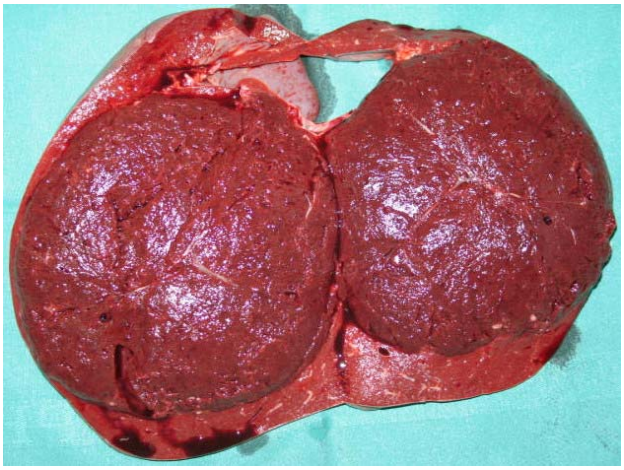


Fig. 1 – 900g-resected spleen specimen measuring 19 × 13 × 8.7 cm. Splenic tissue was almost completely, except the poles, replaced by the nodular tumor of 11.5 × 10 × 8.5 cm

completely replaced by a solitary nodular lesion of spongy appearance measuring 11.5 × 10 × 8.5 cm. Microscopically, the lesion consisted of dilated anastomozing vascular channels, with multiple papillary projections and cyst-like spaces (Figure 2). These channels were lined with tall endothelial cells positive for FVIII antigen, CD68 (Figure 3), CD3l (Figure 4) and lysozyme showing their mixed endothelial-

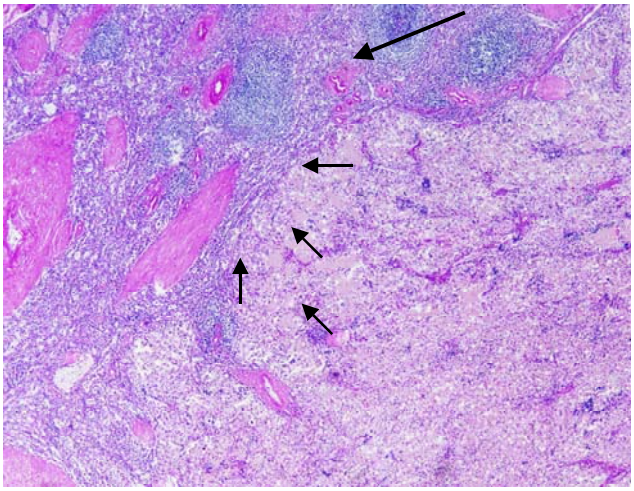


Fig. 2 – The spleen. Anastomosing blood filled vascular channels in the red pulp with irregular lumina forming cyst-like spaces indicated by shorts arrows; long arrow indicates a regular spleen tissue (H&E, original magnification, × 40)

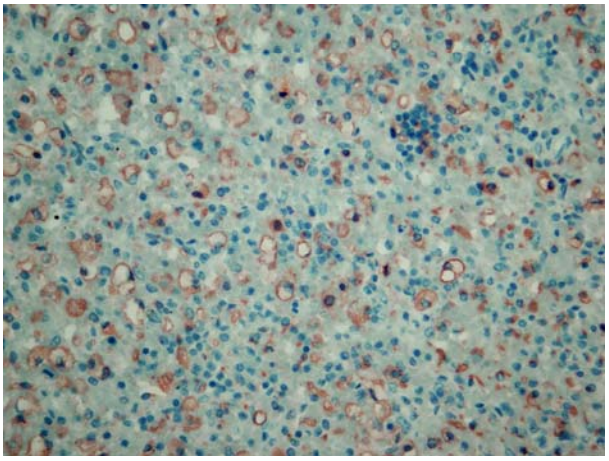


Fig. 3 – Immunohistochemical stains of the original tumor. Most littoral-cell angioma lining cells express membranous staining for CD68 (original magnification, × 400)

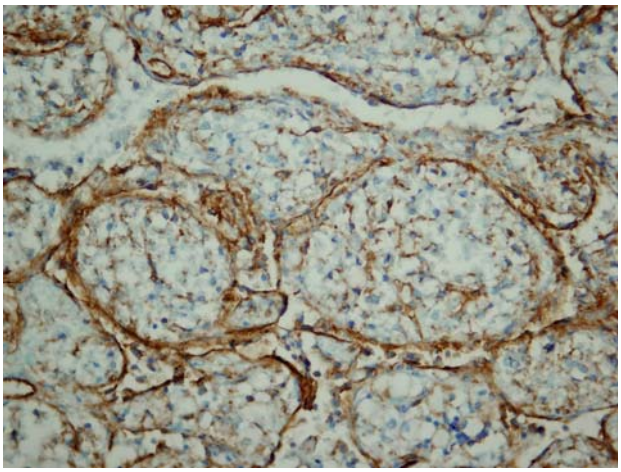


Fig. 4 – Immunohistochemical stains of the original tumor. Some littoral-cell angioma lining cells express cytoplasmic staining for CD31 (original magnification, × 400)

histiocyte phenotype. The endothelial cells were CD21, CD34 and CD8 negative. Littoral cells exhibited hemophagocytosis and an intracellular hemosiderin. Additional feature was a focus of extramedular hematopoiesis. No atypical cells or mitotic figures were seen. Although the endothelial cells in our patient lack CD21 positivity, which is typically at least focal in LCA, the pathohystological finding in our case is consistent with the immunophenotype of a classical LCA. Bone marrow and liver biopsies were normal. The patient recovered well from surgery and his platelet count normalized. Six months after the surgery, the patient remains asymptomatic.

Discussion

Littoral-cell angioma represents a rare and distinct clinico-pathological benign tumor of the spleen [1]. It is a lesion unique to the spleen and always situated within the splenic red pulp. It is seen throughout a wide age range and occurs equally in the sexes. The clinical presentation can include splenomegaly, hypersplenism with thrombocytopenia and/or anemia as in our case, pyrexia of unknown origin or could be an incidental finding. Littoral-cell angioma has been associated with synchronous malignancies (colorectal, renal and pancreatic adenocarcinoma, ovarian cancer and seminoma and lymphoma), autoimmune (aplastic anemia, Crohn's disease) and Gaucher's disease indicating a possible altered function of the immune system as a possible pathophysiological association [4–8]. Neither clinical signs nor symptoms of either malignant disease or any other disease were detected during the 18-month follow-up of the patient. The combination of morphologic and immunohistochemical analyses showing a hybrid endothelial-histiocytic phenotype established the diagnosis of LCA in the patient in spite of CD21 negativity.

Primary tumors of the spleen other than lymphoid and hematological tumors are quite rare, and LCA should be considered in the differential diagnosis of multinodular splenomegaly [9–13]. The most difficult differential diagnosis from which to distinguish LCA is angiosarcoma. LCA, however, lacks the irregular growth pattern of the anastomosing vessels, nuclear atypia, increased mitotic activity and necrosis seen in angiosarcoma. Radiological diagnosis is difficult as the findings on US, CT and ^{99}Technitium scanning are fairly nonspecific.

Conclusion

Littoral-cell angioma itself is a rare benign splenic neoplasm that should be considered in the differential diagnosis of nodular splenomegaly, particularly if the patient has clinical symptoms of hyperplenism.

Acknowledgements

The study was supported by the grant No 145061 from the Ministry of Science and Environmental Protection of Serbia.

R E F E R E N C E S

1. *Falk S, Stutte HJ, Frizzera G.* Littoral cell angioma. A novel splenic vascular lesion demonstrating histiocytic differentiation. Am J Surg Pathol 1991; 15(11): 1023–33.
2. *Rosso R, Paulli M, Gianelli U, Boveri E, Stella G, Magrini U.* Littoral cell angiosarcoma of the spleen. Case report with immunohistochemical and ultrastructural analysis. Am J Surg Pathol 1995; 19(10): 1203–8.
3. *Ben-Izhak O, Bejar J, Ben-Eliezer S, Vlodavsky E.* Splenic littoral cell haemangioendothelioma: a new low-grade variant of malignant littoral cell tumour. Histopathology 2001; 39(5): 469–75.
4. *Arber DA, Strickler JG, Chen YY, Weiss LM.* Splenic vascular tumors: a histologic, immunophenotypic, and virologic study. Am J Surg Pathol 1997; 21(7): 827–35.
5. *Steensma DP, Morice WG.* Littoral cell angioma associated with portal hypertension and resected colon cancer. Acta Haematol 2000; 104(2-3): 131–4.
6. *Chatelain D, Bonte H,Guillevin L, Balladur P, Flejou JF.* Small solitary littoral-cell angioma associated with splenic margional zone lymphoma and villous lymphopcyte leukaemia in a patiesnt with hepatitis C infection. Histopathology 2002; 41(5): 473–5.
7. *Tholouli E, Roulson JA, Byers R, Burton I, Liu Yin JA.* Littoral-cell angioma of the spleen in a patient with severe aplastic anemia. Haematologica online 2003; 88(11): e149–e150.
8. *Gupta MK, Levin M, Aguilera NS, Pastores GM.* Littoral cell angioma of the spleen in a patient with Gaucher disease. Am J Hematol 2001; 68(1): 61–2.
9. *Barshack I, Perelman M, Many A, Goshen E, Zwas ST, Kopolovic J.* Littoral cell angioma: a vascular tumor mimicking a solid tumor on a Tc-99m-red blood cell spleen scan. Isr J Med Sci 1997; 33(10): 677–80.
10. *Bisceglia M, Sickel JZ, Giangaspero F, Gomes V, Amini M, Michal M.* Littoral cell angioma of the spleen: an additional report of four cases with emphasis on the association with visceral organ cancers. Tumori 1998; 84(5): 595–9.
11. *Oliver-Goldaracena JM, Blanco A, Miralles M, Martin-Gonzalez MA.* Littoral cell angioma of the spleen: US and MR imaging findings. Abdom Imaging 1998; 23(6): 636–9.
12. *Suvajdzić N, Cemerikić-Martinović V, Saranović D, Petrović M, Popović M, Artiko V,* et al. Littoral-cell angioma as a rare cause of splenomegaly. Clin Lab Haematol 2006; 28(5): 317–20.
13. *Szpor J, Dyduch G.* From hamartoma to splenic hemangioma. Pol J Pathol 2008; 59(1): 33–41.

The paper received on July 10, 2008.

C A S E R E P O R T

UDC: 616–002.182–036.12–091.8

Kimura's disease in a young Balkan male

Bolest Kimura kod dečaka sa Balkana

Maja Jovičić Milentijević, Marin Basić, Aleksandar Petrović

University of Niš, School of Medicine, Institute of Pathology, **Niš, Serbia**

Abstract

Introduction. Kimura's disease is a rare, chronic inflammatory disorder of unknown cause, mainly seen in young Asian men. To our knowledge it has not been reported previously in persons from the Balkan countries. **Case report.** We presented a 15-year-old male with Kimura's disease manifested as chronic left neck mass. The diagnosis was based on the histopathological findings of the excised lesion. Peripheral blood eosinophilia and raised serum Immunoglobulin E (IgE) level supported the diagnosis. **Conclusion.** The presented patient confirmed the fact that Kimura's disease could occur in different ethnic groups. Histopathological examination, should be performed prior to making the definitive diagnosis.

Key words:
lymph nodes; neck; diagnosis; biopsy; immunohistochemistry; eosinophilia; diagnosis, differential; angiolymphoid hyperplasia with eosinophilia; adult.

Apstrakt

Uvod. Kimura bolest redak je hronični inflamatorni poremećaj nepoznate etiologije, koji se najčešće sreće kod mlađih muškaraca iz Azije. Prema našim saznanjima, do sada nije opisan nijedan slučaj Kimura bolesti na Balkanu. **Prikaz bolesnika.** Prikazan je bolesnik, dečak star 15 godina, sa hroničnim otokom na vratu, sa leve strane. Dijagnoza Kimura bolesti postavljena je na osnovu patohistološke analize ekstirpirane promene. Eozinofilija u perifernoj krvi i povišeni nivo serumskog imunoglobulina E (IgE) išli su u prilog postavljenoj dijagnozi. **Zaključak.** Treba imati u vidu da se Kimura bolest može javiti u različitim etničkim grupama i na našim prostorima. Definitivna dijagnoza postavlja se isključivo na osnovu patohistološke analize.

Ključne reči:
limfne žlezde; vrat; dijagnoza; biopsija; imunohistohemija; eozinofilija; dijagnoza, diferencijalna; angiolimfoidna hiperplazija sa eozinofilijom; odrasle osobe.

Introduction

Kimura's disease (KD) is a rare, chronic inflammatory condition of unknown cause. It was initially described in Chinese literature and it became known as KD after its publication by Kimura et al. [1] of similar cases in Japan [2]. It mainly affects young Asian men, although it occurs sporadically in other areas and ethnic groups [3–5]. To our knowledge it has not been reported previously in persons from Balkan countries. Kimura's disease occurs predominantly as a unilateral manifestation in the head and neck and it is frequently associated with regional lymphadenopathy with or without involvement of salivary glands [6]. Other unusual sites of involvement include the auricle, scalp and orbit [7, 8]. We report a case of KD in a young Serbian male. We present this unusual case to increase awareness of KD in different ethnic groups and to elucidate the pitfalls in its diagnosis.

Case report

A 15-year-old male was presented to the University Clinical Center in Niš for evaluation of a left neck palpable mass (4.5 × 3.5 × 3 cm) of 6-month duration. The patient was treated with antibiotics, but the tumor persisted. There was no history of pain, fever, or weight loss and he seemed well. No redness was noted on the overlying skin. Neither axillary or inguinal lymphadenopathy nor hepatosplenomegaly was noted. Laboratory findings revealed an eosinophilia in the peripheral blood and elevated serum Immunoglobulin E (IgE) level. Clinically, the differential diagnosis included infectious lymph node enlargement (tuberculosis, toxoplasmosis), although neoplastic conditions (Hodgkin's disease and non-Hodgkin's lymphoma) were the first diagnoses considered and an open biopsy was recommended. Stains and cultures for bacteria, fungi and mycobacteria were negative.

Correspondence to: Maja Jovičić Milentijević, University of Niš, School of Medicine, Institute of Pathology, Novoprojektovana bb, 18 000 Niš, Serbia. Tel.: +381 63 104 58 31. E-mail: majajm@eunet.yu

In March 2007, the patient underwent an open biopsy of the left neck mass with excision of cervical lymph nodes and salivary gland. The obtained tissue was fixed, embedded in paraffin and stained with hematoxylin-eosin (H&E). Immunohistochemical analysis was performed on paraffin sections with the alkaline phosphatase anti-alkaline phosphatase (APAAP) technique, using antibodies against CD20, CD3, CD45, CD15, CD34, S100 protein and alpha-smooth muscle actin (DAKO, Copenhagen, Denmark).

The sections stained with H&E showed diffuse, dense, lymphoid and eosinophilic infiltrates forming eosinophilic microabscesses (Figure 1). The inflammatory infiltrates involved the salivary gland and perinodal adipose tissue. Histopathology of the lymph nodes revealed a follicular lymphoid hyperplasia with focal eosinophilic infiltration within the paracortex and interfollicular region. Mitoses were confined to the reactive germinal centers. The lesion was markedly of vascular type; the thin-walled blood vessels were numerous with plump endothelial cells. There was no evidence of atypia. Large caliber arteries were rarely seen. Although plasma cells and histiocytes were present, no epithelioid cells and multinucleated giant cells were seen.

Immunohistochemical findings: CD20 highlighted the follicle center B-cells; CD3 and CD45 demonstrated numerous interfollicular T-cells; stains for CD15 and S100 protein were negative. There was a strongly positive reaction to CD34 on the endothelial lining cells of proliferating blood vessels. The majority of the vessels showed prominent perithelial cells, which were distinctly demonstrable by alpha-smooth muscle actin antibody (Figure 2). The diagnosis of KD was made based on histopathological findings after surgical excision. Peripheral eosinophilia and elevated serum IgE level further supported the diagnosis.

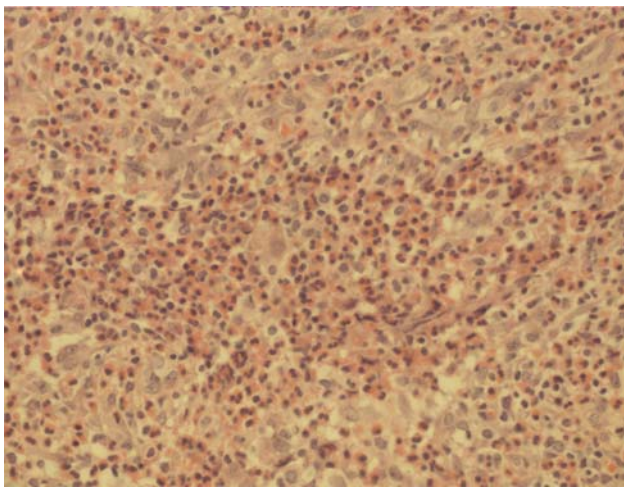


Fig. 1 – Section showing dense infiltration of eosinophils forming eosinophilic microabscesses (H&E 400 ×)

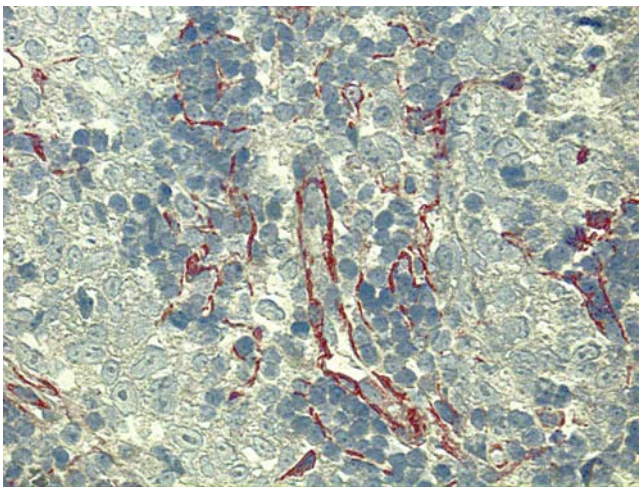


Fig. 2 – Perithelial cells in thin-walled blood vessel demonstrated by immunohistochemistry using alpha-smooth muscle actin (alkaline phosphatase anti-alkaline phosphatase, 630 ×)

Discussion

The etiology and pathogenesis of KD is unclear, although it might be a self-limited allergic or autoimmune response triggered by an unknown stimulus. A viral or parasitic trigger may alter T-cell immunoregulation or induce an IgE-mediated type 1 hypersensitivity resulting in the release of eosinophiliotrophic cytokines [5, 9]. Activated CD4 cells of the Th2 phenotype can release cytokines such as interleukin (IL)-4, IL-5 and IL-13, which in turn would act in B-cells favoring the production of antigen-specific IgE. T helper 2 (Th) cell proliferation and the overexpression of cytokines would play an essential role in the development of KD [10]. The prognosis of KD is excellent, and the disease has no potential for malignancy [11]. Prior to biopsy, we did not consider the diagnosis of KD in our patient because of its a rarity in this region. Patients with KD are often extensively evaluated for other disorders, such as Mikulicz's disease, eosinophilic granuloma, salivary gland tumors and lymphoma [5]. Although the intense eosinophilia are suggestive of a parasitic infection, no parasites have been identified. The morphological and immunohistochemical features excluded Hodgkin's disease and non-Hodgkin's lymphoma. The thin-walled blood vessels were prominent, but there was no true vasculitis, so that systemic vascular disease was unlikely. Kimura's disease can also be confused with angiolymphoid hyperplasia with eosinophilia (ALHE). In the past, KD and ALHE often were considered to be the same disease. Despite subtle clinical and histological similarities, KD and ALHE now are considered to be separate entities [6]. Angiolymphoid hyperplasia with eosinophylia is a vascular malformation resulting from an arteriovenous shunt, typically presenting in women during early to mid-adult life. Lymphadenopathia and salivary gland involvement are uncommon in ALHE; eosinophilia in the peripheral blood is frequently absent, as well as the levels of IgE which are normal [11]. Angiolymphoid hyperplasia with eosinophylia is characterized by dilated blood vessels which have irregular shapes, in addition to enlarged epithelioid-appearing endothelial cells with prominent vacuoles in the cytoplasm. These vacuoles are not present in KD [6, 11]. Additional morphologic features present in our case and characteristic of KD include the noncircumscribed inflamma-

tory infiltrates within extranodal tissues associated with reactive germinal center formation and eosinophilic microabscesses (Figure 1). The immunohistochemistry of the lesion demonstrated prominent perithelial cells by alpha-smooth muscle actin antibody in the majority of the blood vessels (Figure 2). A previous study suggested the table of differential histopathological features between ALHE and KD in which the absence of smooth muscles in blood vessel wall is a characteristic feature of KD [6]. Nevertheless, in our opinion the alpha-smooth muscle actin could be very useful diagnostic marker of KD.

Conclusion

Clinicians and pathologists may be unfamiliar with the clinical presentation and histopathology of this rare disease. Early diagnosis of KD may spare a patient from potentially harmful and unnecessary invasive diagnostic procedures. A definitive diagnosis can be made only by histopathological examination of the excised lesion, demonstrating the role of the surgical pathologist in the detection of this uncommon chronic inflammatory disorder.

Acknowledgement

We thank Professor Basić H. (University of Niš, Serbia) for his expert histological opinion in this case.

R E F E R E N C E S

1. *Kimura T, Yoshimura S, Ishikawa E.* On the unusual granulation combined with hyperplastic changes of lymphatic tissues. Trans Soc Pathol Jpn 1948; 37: 179–80.
2. *Kimm HT, Szeto C.* Eosinophilic hyperplastic lymphogranuloma, comparison with Mikulicz's disease. Proc Chin Med Soc 1937; 1: 329–31.
3. *Zhang JZ, Zhang CG, Chen JM.* Thirty-five cases of Kimura's disease (eosinophilic lymphogranuloma). Br J Dermatol 1998; 139(3): 542–3.
4. *Jaber K.* Kimura's disease in an Arab female. Histopathology. 1996; 29(1): 76–8.
5. *Shetty AK, Beaty MW, Mc Guirt WF, Woods CR, Givner LB.* Kimura's disease: a diagnostic challenge. Pediatrics 2002; 110(3): e39.
6. *Briggs PL.* Kimura disease is not angiolymphoid hyperplasia with eosinophilia: clinical and pathological correlation with literature review and definition of diagnostic criteria. An Bras Dermatol 2006; 86(2): 167–73.
7. *Buggage RR, Spraul CW, Wojno TH, Grossniklaus HE.* Kimura's disease of the orbit and ocular adnexa. Surv Ophtalmol 1999; 44(1): 79–91.
8. *Chan KM, Mok JS, Ng NG, Abdullah V.* Kimura's disease of the auricle. Otolaryngol Head Neck Surg 2001; 124(5): 598–9.
9. *Armstrong WB, Allison G, Pena F, Kim JK.* Kimura's disease: two case reports and literature review. Ann Otol Rhinol Laryngol 1998; 107(12): 1066–71.
10. *Tsukadaira A, Kitano K, Okubo Y, Horie S, Ito M, Momose T,* et al. A case of pathophysiological study in Kimura's disease: measurement of cytokines and surface analysis of eosinophils. Ann Allergy Asthma Immunol 1998; 81(5 Pt 1): 423–7.
11. *Hejmadi RK, Van Pittius DG, Stephens M, Chasty R, Braithwaite M.* Angiolymphoid hyperplasia with eosinophilia (epithelioid haemangioma) occurring within multiple deep lymph nodes and presenting with weight loss and raised CA-125 levels. Virchows Arch 2006; 448(3): 366–8.

The paper received on July 28, 2008.

P R I K A Z S L U Č A J A UDC: 616.149–007.272:616.36–089

Mezoatrijalni šant kod *Budd – Chiari* sindroma

Mesoatrial shunt in Budd – Chiari syndrome

Darko Mirković*, Nebojša Stanković*, Miodrag Jevtić†, Miroslav Mitrović*, Milan Jovanović*

Vojnomedicinska akademija, *Klinika za abdominalnu i endokrinu hirurgiju, †Uprava, **Beograd**

Apstrakt

Uvod. Budd-Chiari sindrom (BCS) predstavlja parcijalnu ili potpunu okluziju hepatičnih vena sa ili bez istovremene opstrukcije donje šuplje vene (VCI). Simptomi ovog sindroma su: abdominalni bol, hepatomegalija, ascites, proširene vene trbušnog zida, ponekad krvarenje iz gornjih partija gastrointestinalnog trakta (GIT), otoci nogu i žutica. Primarni BCS relativno je retko stanje i javlja se kod 1/100 000 stanovnika u svetu. **Prikaz bolesnika.** Muškarac, star 25 godina, nakon ekstrakcije umnjaka razvio je akutnu formu BCS. Fizikalnim pregledom na prijemu uočena je sivobleda boja kože, pojačan venski crtež na grudnom košu i stomaku, ascites, uvećana jetra koja je prominirala 8 cm ispod desnog rebarnog luka, dok je sa desne strane postojao manji pleuralni izliv. Kod bolesnika dopler sonografijom i kompjuterizovanom tomografijom (CT) verifikovana je tromboza dubokih vena desne noge i prisustvo tromba u intrahepatičnom delu donje šuplje vene. Multislajsna kompjuterizovana tomografija (MSCT) vena jetre i donje šuplje vene pokazala je okluziju hepatičnih vena (sindrom *Budd-Chiari*) i trombozu donje šuplje vene u retrohepatičnom delu u dužini od 6 cm. Registrovane su povišene vrednosti transaminaza i gama GT sa nižim vrednostima albumina i serumskog gvožđa. Molekularnim ispitivanjem otkrivena je mutacija faktora V Leiden - heterozigot. Nakon preoperativne pripreme kreiran je mesenterikoatrijalni šant *Gore-Tex ring* graftom 12 mm. Intraoperativno, nađena je uvećana jetra, modra, sa skoro crnim zonama napete kapsule. Nakon kreiranja grafta došlo je do smanjenja kongestije jetre, što je bilo praćeno promenom boje i volumena. U postoperativnom toku došlo je do izrazitog poboljšanja metaboličke i sintetske funkcije jetre. **Zaključak.** Kod bolesnika koji imaju *Budd-Chiari* sindrom medikamentna terapija ne daje adekvatne rezultate, već dovodi do pogoršanja opšteg stanja. Pravovremeno izvedena operacija sprečava ireverzibilne promene na jetri, a dekompresija portnog sistema omogućava vremensko premošćenje do transplantacije jetre.

Ključne reči:
tromboza, hepatičke vene; faktor Va; dijagnoza; portosistemski šant, hirurški; lečenje, ishod.

Abstract

Background. Budd-Chiari syndrome (BCS) represents partial or total occlusion of the hepatic veins with or without simultaneous obstruction of vena cava inferior (VCI). The symptoms of BCS are abdominal pain, hepatomegaly, ascites, varices of the abdominal wall, sometimes bleeding from the upper part of gastointestinal tract (GIT), lower limbs swelling and jaundice. Primary BSC is a relatively rare condition occuring in one per 100 000 of the population worldwide. **Case report.** A male patient, 25-year-old, facing tooth postextraction complications, was presented with acute BCS. On admission, physical examination revealed pale-grayish complexion, more pronounced veins over the thorax and abdomen, ascites, enlarged liver rising 8 cm below the right costal arch and having a minor pleural effusion by the right side. The patient was submitted to Doppler sonography and computed tomography (CT) that verified the right leg deep veins thrombosis, as well as the presence of a thrombus in the intrahepatic portion of the VCI. Multislice computed tomography (MSCT) showed occlusion of hepatic veins (Budd-Chiari syndrome) and thrombosis of the VCI in the retrohepatic part 6 cm long. Also, increased values of transaminases and gamma GT and reduced values of albumines and serum ferrum were registered. Molecular examination revealed Factor V Leiden mutation – heterozygote. After preoperative preparations a mesocaval shunt was made using Gore-Tex ring graft of 12 mm. Intraoperatively, the blue enlarged liver was found with almost black zones of tense capsule. After a graft making, liver congestion decreased followed by the change of colour and volume. Within postoperative course metabolic and synthetic liver functions were obvious. **Conclusion.** In patients with BCS medicamentous treatment does not yield adequate results, but even causes worsening of general condition. Surgical therapy in the presented patient was performed timely regarding the stage of the disease due to which irreversible liver changes were prevented while decompression of the portal system provided time overbridging up to liver transplantation.

Key words:
hepatic vein thrombosis; factor Va; diagnosis; portosystemic shunt, surgical; treatment outcome.

Correspondence to: Milan Jovanović, Vojnomedicinska akademija, Klinika za abdominalnu i endokrinu hirurgiju, Crnotravska 17, 11040 Beograd, Srbija. Tel.: +381 62 26 41 40. E-mail: mibine@gmail.com

Uvod

Budd-Chiari sindrom (BCS) podrazumeva parcijalnu ili potpunu okluziju hepatičnih vena sa ili bez istovremene opstrukcije donje šuplje vene (VCI). Nazvan je po britanskom internisti George-u Budd-u, koji je prvi opisao tri slučaja tromboze hepatičnih vena 1845. godine i Hans-u Chiari-u, austrijskom patologu koji je prvi dao opis jetre sa obliterišućim endoflebitisom hepatičnih vena 1899. godine [1].

Primarni BCS relativno je retko stanje i javlja se kod 1/100000 stanovnika u svetu [2]. Odlikuje se geografskim varijacijama u pogledu etioloških i predisponirajućih faktora. U anglosaksonskoj literaturi kao uzroci okluzije hepatičnih vena najčešće se navode mijeloproliferativne bolesti, hiperkoagulabilnost krvi, primena kontraceptivnih pilula i tumori, dok se u azijskim zemljama, kao uzrok, kod 60% bolesnika navodi membranska opstrukcija donje šuplje vene, a zatim trudnoća i infekcija jetre [3, 4].

Simptomi kod BCS su abdominalni bol, distenzija trbuha, ponekad krvarenje iz gornjih partija gastrointestinalnog trakta (GIT) i žutica. Najvažniji znaci bolesti su hepatomegalija, ascites, proširene vene trbušnog zida i otoci nogu [5, 6]. Dijagnoza sindroma ranije se bazirala na kavogramu donje šuplje vene, funkcijskom hepatogramu ili biopsiji jetre, a sada su značajne dijagnostičke metode angiografija magnetnom rezonancijom (MRI), kompjuterizovana tomografija (CT), multislajsna kompjuterizovana tomografija (MSCT), ultrasonografija i pulsna dopler sonografija [7–10]. Kod bolesnika sa BSC kod kojih okluzija ili kompresija VCI onemogućavaju korišćenje standardnog portokavalnog šanta za dekompresiju vene porte, kreiranje mezoatrijalnog šanta, pored transplantacije jetre, predstavlja metodu izbora [11].

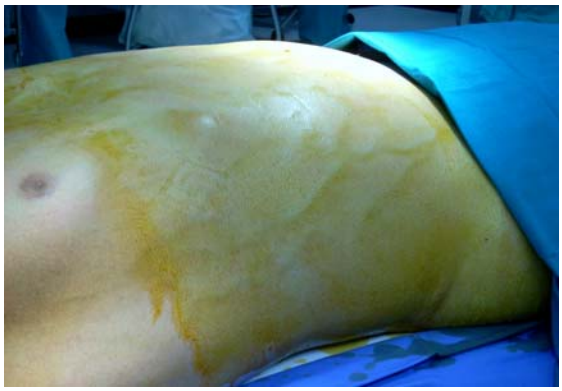
Kreiranje šanta vrši se upotrebom politetraflouroetilenskog grafta koji spaja gornju mezenteričnu venu i desnu pretkomoru [12].

Prikaz bolesnika

Bolesnik, star 25 godina, prve tegobe osetio je u maju 2007. godine, kada se javio zubaru zbog ekstrakcije zuba. Nekoliko dana nakon intervencije video je duple slike. Sa dijagnozom sinuzitisa, bolesnik je tri nedelje mirovao i uzimao antibiotike. Početkom jula iste godine, nekoliko dana pošto je prestao da koristi antibiotike, iznenada došlo je do otoka desne noge i malaksalosti, pri čemu nije imao bolove, a telesna temperatura bila je u granicama referentnih vrednosti. Uzimao je tablete aspirina nekoliko dana, zatim je hospitalizovan u bolnici u Čikagu, gde je uveden i enoksaparin, a zatim je preveden na varfarin. Registrovana je značajna mikrocitna, hiposideremijska anemija, hepatomegalija uz izrazito sniženje hemoglobina, kao i tromboza donje šuplje vene. Nakon povratka u Srbiju hospitalizovan je u Vojnomedicinsku akademiju, u Kliniku za urgentnu medicinu, kao hitan slučaj zbog znakova tromboze dubokih vena desne noge i hepatomegalije. Fizikalnim pregledom na prijemu uočena je sivobleda boja kože, pojačan venski crtež na grudnom košu i stomaku, ascites, uvećana jetra koja je prominirala 8 cm ispod desnog rebarnog luka, dok je sa desne strane postojao manji pleuralni izliv. Dopler sonografijom i CT verifikovana je tromboza dubokih vena desne noge i prisustvo tromba u intrahepatičnom delu donje šuplje vene.

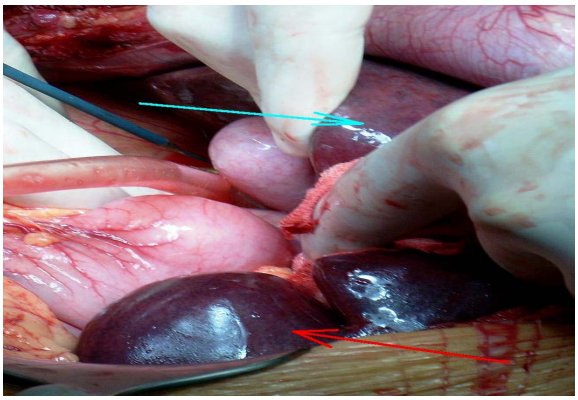
Metodom MSCT vena jetre i donje šuplje vene otkrivena je okluzija hepatičnih vena (BSC) i tromboza donje šuplje vene u retrohepatičnom delu u dužini od 6 cm. Kontrastnom flebografijom, pristupom iz leve noge, potvrđen je isti nalaz. Analiza tumorskih markera pokazala je da su vrednosti u granicama referentnih. Registrovane su povišene vrednosti transaminaza, gama GT sa nižim vrednostima albumina i serumskog gvožđa. Molekularnim ispitivanjem otkrivena je mutacija faktora V Leiden - heterozigot. Primenjena je konzervativna terapija: heparin, kibernin, albumini, diuretici, antibiotici, vitamini. Po primenjenoj konzervativnoj terapiji došlo je do delimičnog popravljanja kliničkog i laboratorijskog statusa, čime je bolesnik pripremljen za neophodnu hiruršku intervenciju koja je učinjena 16. avgusta 2007. godine (*Shunt mesoatrialis cum ringed Gore-Tex vascular grafti* N°12).

Operativni nalaz ukazivao je na distenziju trbuha bolesnika sa naglašenom kolateralnom venskom cirkulacijom preko trbušnog zida (slika 1).



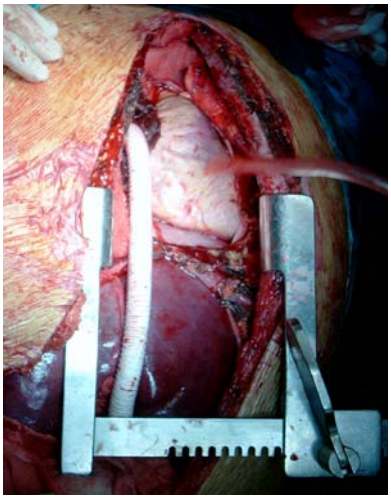
Sl. 1 – Naglašena kolateralna cirkulacija preko trbušnog zida

Operativna incizija izvršena je primenom sternotomije i medijalne laparotomije. Evakuisano je sedam litara ascitne tečnosti. Nađena je uvećana jetra, modra, sa skoro crnim zonama, napete kapsule. Desni lobus pružao se 8 cm ispod desnog rebarnog luka, a levi lobus 9 cm ispod levog rebarnog luka (slika 2). Za kreiranje šanta upotrebljen je ringovani po-



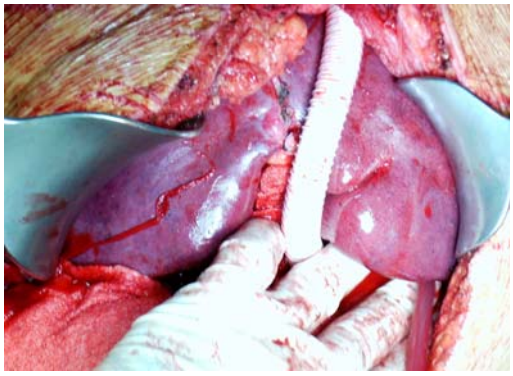
Sl. 2 – Uvećana, modra jetra, napete kapsule

litetrafluoroetilenski (*Gore-tex*) graft promera 12 mm koji je anastomoziran terminolateralno sa gornjom mezenteričnom venom promera 13 mm. Graft je plasiran kroz mezokolon i gastrokolični ligament, ispred jetre. Kreirana je terminolateralna anastomoza između grafta i aurikule (slika 3).



Sl. 3 – Operativno polje - položaj grafta

Po puštanju klema smanjila se kongestija jetre, sa promenom boje i volumena (slika 4). U postoperativnom toku došlo je do poboljšanja metaboličke i sintetske funkcije jetre.



Sl. 4 – Izgled jetre nakon plasiranja grafta

Kontrolnim snimcima MSCT i CT potvrđen je adekvatan položaj grafta i njegova funkcionalnost (slika 5).

Sl. 5 – Položaj grafta na snimku multislajsne kompjuterizovane tomografije

Diskusija

Sindrom BCS pokazuje varijacije u zavisnosti od geografskih karakteristika. U zapadnim zemljama dominantni uzroci su mijeloproliferativne bolesti, paroksizmalna noćna hemoglobinurija, genetska deficijencija antikoagulantnih faktora koji se prirodno nalaze u perifernoj cirkulaciji (poput proteina C, proteina S ili antitrombina III) i druge protrombogenske bolesti (poput mutacije protrombinskog gena). Abdominalna trauma, trudnoća, primena oralnih kontraceptivnih pilula na bazi estrogena predstavljaju faktore koji iniciraju trombogenezu [13–15]. Funkcionalnim i molekulskim ispitivanjima kao etiološki faktor koji je doveo do pojave tromboze hepatičnih vena kod prikazanog bolesnika dokazana je rezistencija na aktivirani protein C (APC) / mutacija faktora V Leiden. Prevalencija mutacije faktora V Leiden iznosi 5% kod zdrave populacije, a 25 – 31% kod bolesnika sa BCS [16]. Uloga faktora V u koagulaciji sastoji se u tome da aktivirani faktor V (FVa), u sadejstvu sa aktiviranim faktorom X (FXa), učestvuje u pretvaranju protrombina u trombin. Istovremeno sa procesom koagulacije, a kao zaštitni mehanizam od prekomerne koagulacije, odigrava se proces inhibicije. Dominantnu ulogu u inhibiciji procesa koagulacije imaju APC i aktivirani protein S. Oni se vezuju za FVa i sprečavaju dalju koagulaciju. Leiden mutacija faktora V dovodi do njegove rezistencije na dejstvo APC, a samim tim i izostanka inhibicije koagulacije. Bolesnici sa ovom mutacijom razvijaju tromboembolijske komplikacije u toku života uz sadejstvo potpomažućih faktora [17].

Postoje četiri metode lečenja BCS: medikamentna terapija, dekompresivna hirurgija, transjugularni portosistemski šant (TIPS) i transplantacija jetre. Nijedna od ovih metoda nije ključ za rešavanje problema kod BCS, ali njihova kombinacija omogućava dug period preživljavanja. Primena isključivo medikamentne terapije ima procenat smrtnosti od 86%. Zbog toga, portosistemski šant indikovan je što ranije kada se ova dijagnoza postavi [18].

Od Cameronovog opisa iz 1978. godine mezenterikoatrijalni šant koristi se za portosistemsku dekompresiju kod BCS kada je prisutna okluzija ili kompresija VCI (redukcija luminalnog dijametra > 75% ili gradijent pritiska u pretkomori i infrahepatičnom segmentu VCI > 15 mmHg) [19]. Početni rezultati bili su vrlo ohrabrujući [20].

U literaturi navode se četiri kliničke forme BCS: fulminantna, akutna, subakutna i hronična [21]. Transplantacija jetre kao opcija lečenja uzima se u obzir kod bolesnika sa fulminantnim oblikom opstrukcije jetrinih vena, ili kod onih bolesnika kod kojih postoji poslednji stadijum oštećenja jetre [22] .

Nakon transplantacije jetre petogodišnje preživljavanje bolesnika sa BCS je 89,4%, a nakon 10 godina 83,5%, što je slično, pa čak i bolje u odnosu na preživljavanje kod transplantacije jetre zbog drugih indikacija [23]. Akutna i subakutna forma posledica su totalne ili parcijalne opstrukcije hepatičnih vena uz reverzibilna oštećenja jetre i kod njih je dekompresivni šant metoda izbora. Dekompresivne procedure koje se danas najčešće koriste su laterolateralni (L-L) portokavalni šant, mezokavalni šant sa autolognim ili sintetskim graftom i mezoatrijalni šant. Ukoliko ne postoji tromboza donje

šuplje vene, najčešće se preporučuje metoda L-L portokavalnog šanta [24]. Drugi autori izbegavaju korišćenje portne vene za anastomozu i koriste gornju mezenteričnu venu, zato što se portna vena čuva za moguću transplantaciju jetre. Ukoliko postoji značajna disproporcija dijametra sintetskog grafta, koji treba da bude širok, i relativno uske vene mezenterike superior (VMS), mezoatrijalni šant se kreira u dva koraka: mezokavalnog i kavoatrijalnog šanta [25]. U literaturi se navodi da kod četiri od pet bolesnika sa portokavalnim ili mezokavalnim šantom dolazi do tromboziranja šanta ako postoji tromboza donje šuplje vene, te je zato neophodno kod njih kreirati mezoatrijalni šant [26].

Kod našeg bolesnika VMS bila je prečnika 13 mm, kvalitetnog zida, pogodnog za kreiranje anastomoze. Operacija je izvedena u subakutnoj fazi bolesti. Bolesnik je preoperativno, perioperativno i postoperativno dobijao antikoagulantnu terapiju koja se i dalje sprovodi, sa ciljem prevencije tromboze grafta i prevencije progresije duboke venske tromboze desne noge. Iako postoje radovi koji opisuju trombolitički medikamentni tretman delotvornost se može očekivati samo kod onih slučajeva gde je vrlo rano data terapija [27, 28]. U trenutku postavljanja dijagnoze kod velikog broja bolesnika tromb je organizovan i efektivna liza nije moguća, ali generalno je prihvaćeno da antikoagulansi imaju efekat u kasnijoj prevenciji širenja tromba [29].

Bolesnici sa BSC koji je izazvan mutacijom faktora V Leiden najčešće se javljaju lekaru kada im je život ugrožen razvojem bolesti i za njih je jedino pravo lečenje transplantacija jetre, zato što jetra donora stvara novi, nemutirani faktor V. U zemljama u kojima sistem donatorstva organa nije na adekvatnom nivou, operacije kreiranja šantova predstavljaju jedinu mogućnost za preživljavanje ovakvih bolesnika do transplantacije.

Na kontroli posle dvanaest meseci od operacije prikazani bolesnik subjektivno se dobro osećao, a objektivno bio je prisutan odličan Karnofski index, uvećao je telesnu masu za četiri kilograma, laboratorijske vrednosti bile su u granicama referentnih vrednosti.

Operacija je izvedena u najpovoljnijoj fazi bolesti čime su sprečene ireverzibilne promene na jetri a dekompresija portnog sistema omogućila je vremensko premošćenje do transplantacije jetre.

Zaključak

Kod bolesnika koji imaju *Budd-Chiari* sindrom medikamentna terapija ne daje adekvatne rezultate, već dovodi do pogoršanja opšteg stanja. Pravovremeno izvedena operacija sprečava ireverzibilne promene na jetri, a dekompresija portnog sistema omogućava vremensko premošćenje do transplantacije jetre.

L I T E R A T U R A

1. *Aydinli M, Bayraktar Y.* Budd-Chiari syndrome: etiology, pathogenesis and diagnosis. World J Gastroenterol 2007; 13(19): 2693−6.
2. *Valla DC.* The diagnosis and management of the Budd-Chiari syndrome: consensus and controversies. Hepatology 2003; 38: 793−803.
3. *Denninger MH, Chaït Y, Casadevall N, Hillaire S, Guillin MC, Bezeaud A*, et al.Cause of portal or hepatic venous thrombosis in adults: the role of multiple concurrent factors. Hepatology 2000; 31(3): 587−91.
4. *Okuda K.* Inferior vena cava thrombosis at its hepatic portion (obliterative hepatocavopathy). Semin Liver Dis 2002; 22(1): 15−26.
5. *Dilawari JB, Bambery P, Chawla Y, Kaur U, Bhusnurmath SR, Malhotra HS*, et al. Hepatic outflow obstruction (Budd-Chiari syndrome). Experience with 177 patients and a review of the literature. Medicine 1994; 73(1): 21−36.
6. *Kohli V, Pande GK, Dev V, Reddy KS, Kaul U, Nundy S.* Management of hepatic venous outflow obstruction. Lancet 199; 342(8873): 718−22.
7. *Erden A, Erden I, Karayalçin S, Yurdaydin C.* Budd-Chiari syndrome: evaluation with multiphase contrast-enhanced three-dimensional MR angiography. AJR Am J Roentgenol 2002; 179(5): 1287−92.
8. *Lupescu IG, Dobromir C, Popa GA, Gheorghe L, Georgescu SA.* Spirial computed tomography and magnetic resonance angiography evaluation in Budd-Chiari syndrome. J. Gastrointestin Liver Dis 2008; 17(2): 223−6.
9. *Hirooka K, Hirooka M, Kisaka Y, Uehara T, Hiasa Y, Michitaka K*, et al. Doppler waveform pattern changes in a patient with primary Budd-Chiari syndrome before and after angioplasty. Intern Med 2008; 47(2): 91−5.
10. *Bolondi L, Gaiani S, Li Bassi S, Zironi G, Bonino F, Brunetto M*, et al. Diagnosis of Budd-Chiari syndrome by pulsed Doppler ultrasound. Gastroenterology 1991; 100(5 Pt 1): 1324−31.
11. *Wang ZG, Zhung FJ, Li XQ, Meng QY.* Manegement of Budd-Chiari syndrome: what is the best approach? Gastroenterol and Hepatol 2004; 19(S7): S212−8.
12. *Cameron JL, Maddrey WC.* Mesoatrial shunt: a new treatment for the Budd-Chiari syndrome. Ann Surg 1978; 187(4): 402−6.
13. *Valla D, Le MG, Poynard T, Zucman N, Rueff B, Benhamou JP.* Risk of hepatic vein thrombosis in relation to recent use of oral contraceptives. A case-control study. Gastroenterology 1986; 90(4): 807−11.
14. *Khuroo MS, Datta DV.* Budd-Chiari syndrome following pregnancy. Report of 16 cases, with roentgenologic, hemodynamic and histologic studies of the hepatic outflow tract. Am J Med 1980; 68(1): 113−21.
15. *Mahmoud AE, Mendoza A, Meshikhes AN, Olliff S, West R, Neuberger J*, et al. Clinical spectrum, investigations and treatment of Budd-Chiari syndrome. QJM 1996 ; 89(1): 37−43.
16. *Mahmoud AE, Elias E, Bauchamp N,* et al. Prevalence of the factor V Leiden mutation in hepatic and portal vein thrombosis. Gut 1991; 40: 798−800.
17. *Piersigilli F, Auriti C, Seganti G.* Budd-Chiari syndrome and factor V Leiden in a neonate. N Engl J Med 2006; 355(5): 527−8.
18. *Ruh J, Malagó M, Busch Y, Lang H, Paul A, Verhagen R,* et al. Management of Budd-Chiari syndrome. Dig Dis Sci 2005; 50(3): 540−6.
19. *Slakey DP, Klein AS, Venbrux AC, Cameron JL.* Budd-Chiari syndrome: current management options. Ann Surg 2001; 233(4): 522−7.
20. *Haimovici H, Hoffert PW, Zinicola N, Steinman C.* An experimental and clinical evaluation of grafts in the venous system. Surg Gynecol Obstet 1970; 131(6): 1173–86.

21. *Bismuth H, Sherlock DJ*. Portasystemic shunting versus liver transplantation for the Budd-Chiari syndrome. Ann Surg 1991; 214(5): 581−9.
22. *Murad SD, Kamath PS*. Liver transplantation for Budd-Chiari syndrome: when is it really necessary? Liver Transplantation Society 2008; 14(2): 133−5.
23. *Urlich F, Pratschke J, Neuman U, Pascher A, Puhl G, Fellmer P,* et al. Eighteen years of liver transplantation experience in patients with advanced Budd-Chiari syndrome. Leiver Transplantation Society 2008; 14(2): 140−50.
24. *Orloff MJ, Daily PO, Orloff SL, Girard B, Orloff MS*. A 27-year experience with surgical treatment of Budd-Chiari syndrome. Ann Surg 2000; 232(3): 340−52.
25. *Jalleh RP, Smith PL, Habib NA*. Two step mesoatrial shunt in Budd-Chiari syndrome. Case report. Eur J Surg 1994; 160(3): 185−6.
26. *Ahn SS, Yellin A, Sheng FC, Colonna JO, Goldstein LI, Busuttil RW*. Selective surgical therapy of the Budd-Chiari syndrome provides superior survivor rates than conservative medical management. J Vasc Surg 1987; 5(1):28−37.
27. *Warren RL, Schlant RC, Wenger NK, Galambos JT*. Treatment of Budd-Chiari syndrome with streptokinase. Gastroenterology 1972; 62:200.
28. *Greenwood LH, Irizarry IM, Hallet JW, Scowille GS*. Urokinase treatment of Budd-Chiari syndrome. AJR 1983; 145: 1057−9.
29. *Emre A, Kalayci G, Ozden I, Bilge O, Acarli K, Kaymakoğlu S*, et al. Mesoatrial shunt in Budd-Chiari syndrome. Am J Surg 2000; 179(4): 304−8.

Rad primljen 11. IX 2008.

POVLAČENJE ČLANKA/ ARTICLE RETRACTION

Obaveštenje o povlačenju članka

Silva Dobrić, glavni i odgovorni urednik, Vojnosanitetski pregled

Članak "Prognostički značaj akutnog bloka grane kod bolesnika sa akutnim infarktom miokarda", autora Mijailović V, Mrdović I, Ilić M, Ašanin M, Srdić M, Rajić D [1] povlači se na zahtev urednika jer su autori prekršili profesionalni i etički kodeks podnoseći navedeni članak redakciji Vojnosanitetskog pregleda, iako se on najvećim delom preklapa sa člankom koji je već bio dostavljen i publikovan u časopisu ABC – časopis urgentne medicine [2].

1. *Mijailović V, Mrdović I, Ilić M, Ašanin M, Srdić M, Rajić D*. Prognostički značaj akutnog bloka grane kod bolesnika sa akutnim infarktom miokarda. Vojnosanit Pregl 2008; 65(10): 733–7.

2. *Mijailović V, Mrdović I, Ilić M, Peruničić J, Ašanin M, Lasica R, Savić L, Srdić M, Jozić T, Rajić D, Terzić B, Matić D, Matić M, Vasiljević Z.* Prognostički značaj akutnog bloka grane kod bolesnika sa akutnim infarktom miokarda. ABC – časopis urgentne medicine 2007; 7(2–3): 104–8.

Article retraction notice

Silva Dobrić, Editor-in-Chief, Vojnosanitetski pregled

The article „Prognostic significance of acute bundle branch block in patients with acute myocardial infarction" by Mijailović V, Mrdović I, Ilić M, Ašanin M, Srdić M, Rajić D [1] was retracted at the request of the editors because the authors had infringed the normal professional and ethical codes by submitting the above article to the Vojnosnitetski pregled after an article with substantial overlap of its content (patients, methods,results and conclusions) had been accepted for publication and published in another journal, ABC – časopis urgentne medicine [2].

1. *Mijailović V, Mrdović I, Ilić M, Ašanin M, Srdić M, Rajić D*. „Prognostic significance of acute bundle branch block in patients with acute myocardial infarction"Vojnosanit Pregl 2008; 65(10): 733–7. (Serbian)

2. *Mijailović V, Mrdović I, Ilić M, Peruničić J, Ašanin M, Lasica R, Savić L, Srdić M, Jozić T, Rajić D, Terzić B, Matić D, Matić M, Vasiljević Z.* „Prognostic significance of acute bundle branch block with patients suffering from myocardial infarction". ABC – časopis urgentne medicine 2007; 7(2–3): 104–8. (Serbian)

INDEKS RADOVA

VOJNOSANITETSKI PREGLED GODINA 2008.

KATEGORIJE I POTKATEGORIJE 2008. GOD.

ANATOMIJA

NERVNI SISTEM

Vladimir Živković, Natalija Stefanović, Tatjana Đurović-Filipović, Snežana Pavlović, Vesna Stojanović, Mirjana Bakić, Braca Kundalić, Miljana Pavlović
Oblici akumulacije lipofuscina u ganglijskim ćelijama gornjeg vratnog gangliona kod čoveka
2008; 65(10): 738-42.

EMBRIONSKE STRUKTURE

Snežana Pavlović, Dejan Zdravković, Natalija Stefanović, Miljana Pavlović, Mirjana Bakić, Vladimir Živković
Anatomohistološke karakteristike Mekelovog divertikuluma fetusa
2008; 65(8): 606-12.

BOLESTI

BAKTERIJSKE I GLJIVIČNE INFEKCIJE

Predrag Stojanović, Branislava Kocić
Dijareja izazvana *Clostridium difficile* kod bolesnika sa postoperativnim suphepatičnim apscesom
2008; 65(3): 249-54.

Gordana Mijović, Goran Lukić, Nebojša Jokmanović, Snežana Crnogorac, Nada Kuljić-Kapulica, Milan Gajić, Marija Kulauzov, Marina Bujko
Uticaj bakterijske vaginalne i cerviksne kolonizacije/infekcije na nastanak prevremenog porođaja
2008; 65(4): 273-80.

Biljana Miljković-Selimović, Zorica Lepšanović, Tatjana Babić, Branislava Kocić, Gordana Ranđelović
Primena analize plazmidskog profila u identifikovanju epidemijskih sojeva
2008; 65(4): 303-7.

Vesna Šuljagić
Bolničke infekcije izazvane multirezistentnim mikroorganizmima – kako ih pobediti
2008; 65(5): 341-2.

Ljiljana Petrović Jeremić, Nada Kuljić Kapulica, Veljko Mirović, Branislava Kocić
Mehanizmi rezistencije *Staphylococcsa aureus* na meticilin
2008; 65(5): 377-82.

VIRUSNE BOLESTI

Silva Dobrić
Dvadeset godina „svetskog rata“ protiv AIDS-a. Ima li izgleda za pobedu?
2008; 65(12): 867-8.

PARAZITNE BOLESTI

NEOPLAZME

BOLESTI MIŠIĆNO-SKELETNOG SISTEMA

Goran Plavec, Ilija Tomić, Sanela Bihorac, Gordana Kovačević, Ljiljana Pavlica, Gordana Cvetković, Stevan Sikimić, Rade Milić
Plućne manifestacije kod sistemskih bolesti vezivnog tkiva
2008; 65(9): 688-91.

BOLESTI DIGESTIVNOG SISTEMA

Milan Radojković, Miroslav Stojanović, Aleksandar Zlatić, Danijela Radojković, Ljiljana Jeremić, Predrag Kovačević, Biljana Stošić
Mikrocirkulacijski poremećaji u ishemijsko/reperfuzijskom oštećenju jetre
2008; 65(12): 913-8.

BOLESTI RESPIRATORNOG TRAKTA

Zorica Lazić, Ivan Čekerevac, Ljiljana Novković, Vojislav Ćupurdija
Efekat primene kiseonika na visinu kapnije kod bolesnika sa pogoršanjem hronične respiratorne insuficijencije
2008; 65(7): 521-4.

Zorica Ćirić, Ivana Stanković, Milan Rančić, Tatjana Pejčić, Milan Radović
Respiratorna rehabilitacija bolesnika sa hroničnom opstruktivnom bolešću pluća
2008; 65(7): 533-8.

Dragana Nikić, Dragan Bogdanović, Aleksandra Stanković, Maja Nikolić, Zoran Milošević
Uticaj aerozagađenja na učestalost hospitalizacije dece sa respiratornim oboljenjima
2008; 65(11): 814-9.

BOLESTI UVA, GRLA I NOSA

Aleksandar Perić, Dejan Gaćeša
Etiology and pathogenesis of chronic rhinosinusitis
2008; 65(9): 699-702.

BOLESTI NERVNOG SISTEMA

Dragana Obradović, Bela Balint, Evica Dinčić, Ranko Raičević, Slobodan Obradović, Gordana Tončev, Vladimir Kostić
Primena matičnih ćelija u lečenju neuroloških oboljenja – da li je budućnost već stigla?
2008; 65(6): 473-80.

Dejana R. Jovanović, Ljiljana Beslać-Bumbaširević, Ranko Raičević, Jasna Zidverc-Trajković, Marko D. Ercegovac
Etiology of ischemic stroke among young adults of Serbia
2008; 65(11): 803-9.

OČNE BOLESTI

Gordana Suvajac
Komplikacije nastale nošenjem mekog kontaktnog sočiva
2008; 65(1): 15-20.

Dušica Risović, Dragan Vicić
Alfabetski sindromi
2008; 65(1): 57-60.

Lepša Žorić, Natalija Kosanović-Jaković, Emina Čolak, Aleksandra Radosavljević, Vesna Jakšić, Snežana Stević
Oksidativni stres u sklopu faktora rizika od nastanka i razvoja senilne degeneracije makule
2008; 65(4): 313-8.

UROLOŠKE I MUŠKE GENITALNE BOLESTI

Dejan Petrović, Biljana Stojimirović
Proteinuria as a risk factor for the progression of chronic renal disease
2008; 65(7): 552-8.

Darko Laketić, Vesna Laketić
Nokturija i benigna hiperplazija prostate
2008; 65(10): 751-4.

GINEKOLOŠKE BOLESTI I POREMEĆAJI TRUDNOĆE

Emilija Jašović-Siveska, Vladimir Jašović
Povezanost kontrolisane hiperstimulacije ovarijuma kod bolesnica sa blagim oblikom endometrioze
2008; 65(2): 147-52.

Biljana Đorđević, Jelena Milošević, Zorica Stanojević
Zastupljenost i karakteristike polipa endometrijuma kod bolesnica sa patološkim uterusnim krvarenjem
2008; 65(5): 349-52.

Milan Trenkić, Marin Bašić, Maja Milentijević, Aleksandar Petrović, Vesna Živković, Viktor Lazarević
Immunohistohemical evidences of pregnancy in uterine curettage tissue by the use of a double immunocytochemical staining technique using cytokeratin 7 and vimentin antibodies
2008; 65(11): 810-3.

KARDIOVASKULARNE BOLESTI

Zorica Mladenović, Anđelka Angelkov-Ristić, Dimitra Kalimanovska-Oštrić, Zdravko Mijailović, Branko Gligić, Slobodan Obradović, Dragan Tavčiovski, Aleksandra Jovelić
Early predictors of left ventricular function improvement late after myocardial infarction
2008; 65(1): 9-14.

Radomir Matunović, Zdravko Mijailović, Dragan Tavčiovski, Zoran Ćosić, Zoran Tajić
Tipovi dijastolne disfunkcije u predikciji funkcijskog oporavka vijabilnog miokarda
2008; 65(2): 113-8.

Branislava Ivanović, Ivan Paunović, Đorđe Nikčević, Dane Cvijanović, Nevena Kalezić, Dragan Simić
Ambulatory arterial blood pressure monitoring in patients before and after thyroidectomy
2008; 65(2): 137-40.

Žarko Vučinić
Nova univerzalna definicija infarkta miokarda – šta je promenjeno
2008; 65(3): 239-44.

Nataša Savić, Ljiljana Gojković-Bukarica
Produženi QT interval: genetska osnova i uticaj lekova
2008; 65(4): 308-12.

Dragan Đorđević, Marina Deljanin Ilić, Ivan Tasić
Korelacija 24-časovnog profila krvnog pritiska i ventrikulskih aritmija i njihov prognostički značaj kod bolesnika sa arterijskom hipertenzijom
2008; 65(5): 353-8.

Ivana Burazor, Aristo Vojdani, Mirko Burazor
Interrelationship of interleukin 6, C-reactive protein and *Chlamydia pneumoniae* IgG antibodies in patients with acute coronary syndromes
2008; 65(6): 425-34.

BOLESTI KRVNOG I LIMFNOG SISTEMA

METABOLIČKE I NUTRICIONE BOLESTI

BOLESTI ENDOKRINOG SISTEMA

HEMIJSKE MATERIJE I LEKOVI

PESTICIDI, NOKSE I DRUGI ZAGAĐIVAČI ŽIVOTNE SREDINE

Stevan Đurić, Dragan Jovanović, Rajko Hrvačević, Zoran Kovačević, Marija Konjević
Asimptomatsko oštećenje bubrega kod osoba sa hroničnom profesionalnom ekspozicijom niskim koncentracijama elementarne žive
2008; 65(9): 670-5.

AMINO KISELINE, PEPTIDI I PROTEINI

Gordana Mandić, Ivanka Marković, Marija Ostojić, Tanja Stojković, Sonja Misirlić-Denčić, Tatjana Živanović-Radnić, Rodoljub Stefanović, Marko Bumbaširević, Elka Stefanova, Vladimir Kostić
Beta amiloidni i tau protein u cerebrospinalnoj tečnosti: biomarkeri Alchajmerove bolesti
2008; 65(12): 901-4.

SREDSTVA KOJA DELUJU NA CENTRALNI NERVNI SISTEM

Milan B. Lakočević, Nenad R. Rajšić
Hipokretinski neurotransmiterski sistem i narkolepsija
2008; 65(5): 393-6.

IMUNOLOŠKI I BIOLOŠKI FAKTORI

Neven Vavić, Ljiljana Ignjatović, Biljana Drašković, Rajko Hrvačević, Zoran Kovačević, Zoran Paunić
Efikasnost terapijskog monitoringa ciklosporina određivanjem C2 i $PIK_{0–4}$ tokom prva 24 meseca posle transplantacije bubrega
2008; 65(2): 119-27.

Hiroshi Kinoshita, Akira Kubota, Shogo Kasuda, Minori Nishiguchi, Harumi Ouchi, Takako Minami, Kiyoshi Matsui, Takehiko Yamamura, Hiroyuki Motomura, Nao Ohtsu, Shie Yoshida, Nobuyuki Adachi, Shigeru Aoki, Motoo Komeda, Shigeru Hishida
An autopsy case of asthmatic death – usefulness of biochemical examination
2008; 65(5): 404-6.

FARMACEUTSKI PREPARATI

Dušica Mirković, Mirjana Antunović, Vesna Putić, Dragana Aleksić
Ispitivanje stabilnosti smeše za totalnu parenteralnu ishranu koja se priprema u bolničkoj apoteci
2008; 65(4): 286-90.

Mirjana Antunović, Dragana Aleksić
Izrada i ispitivanje rastvora za perfuziju i prezervaciju organa pri transplantaciji
2008; 65(8): 596-600.

ANALITIČKE, DIJAGNOST. I TERAP. TEHNIKE I OPREMA

DIJAGNOSTIKA

Sanja Dugonjić, Boris Ajdinović, Dušan Stefanović, Ljiljana Jauković
Dijagnostički značaj dinamske scintigrafije pljuvačnih žlezda sa stimulacijom askorbinskom kiselinom kod bolesnika sa Sjögrenovim sindromom: poređenje sa testom nestimulisane ukupne sijalometrije
2008; 65(1): 41-6.

Branislav Baškot, Slobodan Obradović, Branko Gligić, Vjekoslav Orozović, Anđelka Ristić-Angelkov, Radosav Romanović, Robert Jung, Vladimir Ivanović, Miroslav Bikicki, Miodrag Pavlović
Adenozinski stres protokoli za perfuzionu scintigrafiju miokarda
2008; 65(1): 47-50.

TERAPIJSKE PROCEDURE

Slobodan Ćulafić, Robert Juszkat, Siniša Rusović, Dara Stefanović, Ljubodrag Minić, Milan Spaić
Endovaskularni tretman karotidno-kavernozne fistule tip A primenom platinskih spirala
2008; 65(12): 923-6.

ANESTEZIJA I ANALGEZIJA

Tatjana Vulović, Gordana Đorđević
Tenzijski pneumotoraks u jedinicama intenzivne nege
2008; 65(3): 245-8.

Tatjana Vulović, Gordana Đorđević
Principi reanimacije u zbrinjavanju povreda grudnog koša
2008; 65(4): 319-24.

Maja Šurbatović, Mirjana Kendrišić, Miodrag Jevtić, Nikola Filipović, Nada Popović, Zoran Slavković
Uticaj hijaluronidaze na raspodelu anestetika u retrobulbarnom prostoru nakon sub-Tenon anestezije
2008; 65(7): 525-32.

Jelena Martić, Borisav Janković, Predrag Minić, Aleksandar Sovtić, Ljubica Nikolić, Snežana Ristić, Adrijan Sarajlija
Primena mehaničke ventilacije kod pedijatrijskih bolesnika
2008; 65(12): 876-81.

OPERATIVNE HIRURŠKE PROCEDURE

Vlado Cvijanović, Vojkan Stanić, Aleksandar Ristanović, Bojan Gulić, Davor Stamenović, Nebojša Marić, Snežana Kovačević, Lidija Zolatarevski
Lečenje plućnog sekvestra
2008; 65(1): 33-40.

Vojkan Stanić, Tatjana Vulović, Marjan Novaković, Aleksandar Ristanović, Davor Stamenović, Vlado Cvijanović, Nenad Stepić, Gordana Đorđević
Radical resection of giant chondrosarcoma of the anterior chest wall
2008; 65(1): 64-8.

Miroslav Stojanović, Goran Stanojević, Milan Radojković, Aleksandar Zlatić, Ljiljana Jeremić, Branko Branković, Milan Jovanović, Miloš Kostov, Miodrag Zdravković, Dragan Milić
Bezbednost simultanih resekcija kolona i jetre u hirurškom lečenju karcinoma kolorektuma i sinhronih metastaza u jetri
2008; 65(2): 153-7.

Predrag Aleksić, Vladimir Bančević, Borislav Stijelja, Novak Milović, Perica Toševski, Zoran Čampara, Branko Košević, Dejan Mocović
Desetogodišnje iskustvo u primeni direktnih i antirefluksnih tehnika anastomoziranja uretera i ortotopske crevne neobešike nakon radikalne cistektomije
2008; 65(2): 163-6.

Vojkan Stanić, Tatjana Vulović, Davor Stamenović, Gordana Đorđević
Use of Marlex mesh with methylmethacrylate to repair large full-thickness defects after subtotal sternectomy caused by chondroma
2008; 65(2): 175-8.

Aleksandar Perić, Jelena Sotirović, Nenad Baletić, Ružica Kozomara, Dušan Bijelić, Dejan Rašić
Konha buloza i sindrom opstrukcije srednjeg nosnog hodnika
2008; 65(3): 255-8.

Dejan Vulović, Nenad Stepić
Značaj pravilnog inicijalnog lečenja srednje teških i teških opekotina
2008; 65(4): 281-5.

Biljana Anđelski-Radičević, Obrad Zelić, Silvija Mirković, Tatjana Todorović
Stanje tkiva periodoncijuma kod bolesnika sa dijabetesom melitusom u populaciji Beograda
2008; 65(11): 799-802.

Biljana Andonovska, Cena Dimova, Sašo Panov
Matrix metalloproteinases (MMP-1, -8, -13) in chronic periapical lesions
2008; 65(12): 882-6.

PSIHIJATRIJA I PSIHOLOGIJA

PONAŠANJE I MEHANIZMI PONAŠANJA

Silva Dobrić
Borba protiv pušenja
2008; 65(2): 111-2.

Darko Hinić, Goran Mihajlović, Željko Špirić, Slavica Đukić-Dejanović, Mirjana Jovanović
Excessive Internet use – addiction disorder or not?
2008; 65(10): 763-8.

MENTALNI POREMEĆAJI

Maja Simonović, Grozdanko Grbeša, Tatjana Milenković, Miša Radisavljević
Procena kliničke depresije udružene sa posttraumatskim stresnim poremećajem
2008; 65(3): 199-204.

Sanja S. Kocić, Časlav T. Milić, Gordana G. Grbić, Aleksandar H. Plašić, Zoran V. Tatić
Godine starosti kao faktor rizika od suicida
2008; 65(5): 371-6.

Petar Opalić, Sanja Nikolić
Procena kvaliteta života shizofrenih bolesnika
2008; 65(5): 383-92.

BIHEVIORALNE DISCIPLINE I AKTIVNOSTI

Zorka Lopičić, Tomislav Gajić, Goran Mihajlović, Branka Stamatović-Gajić
Dinamička farmakoterapija kao aspekt odnosa psihoterapije i leka
2008; 65(8): 639-44.

BIOLOŠKE NAUKE

ŽIVOTNA SREDINA I JAVNO ZDRAVSTVO

Branka Đurović, Vesna Spasić-Jokić, Branislav Đurović
Influence of occupational exposure to low-dose ionizing radiation on the plasma activity of superoxide dismutase and glutathione level
2008; 65(8): 613-8.

GENETIKA

Svetlana Dragojević, Branka Nikolić, Snežana Rakić, Vladimir Pažin, Srđan Dikić, Barbara Damnjanović
Ethical legal aspects in assisted reproductive technologies
2008; 65(2): 171-4.

Bojana Petrović, Aleksandar Ljubić, Ljubinka Nikolić
Aberacije hromozoma kao etiološki faktori intrauterusnog zaostajanja u rastu fetusa
2008; 65(3) 195-9.

ZDRAVSTVENA ZAŠTITA

KVALITET, PRISTUP I PROCENE ZDRAV. ZAŠTITE

ISTORIJA MEDICINE

RATNA MEDICINA

SANITETSKE JEDINICE I USTANOVE

INDEKS AUTORA

INDEKS DESKRIPTORA

ВОЈНОСАНИТЕТСКИ ПРЕГЛЕД
ВОЈНОМЕДИЦИНСКА АКАДЕМИЈА
Црнотравска 17, 11040 **Београд, Србија**
Тел/факс: +381 11 2669689
vmaini1@eunet.yu
vmaini2@eunet.yu

Позив на рекламирање у 2009. години

У прилици смо да вам понудимо могућност оглашавања и рекламирања производа и услуга у часопису „**Војносанитетски преглед**“ (ВСП). То је сигурно најбољи вид и најзаступљенији начин упознавања евентуалних корисника са вашим услугама и производима.

Часопис „**Војносанитетски преглед**“, званични орган лекара и фармацеута Војске Србије, научно-стручног је карактера и објављује радове из свих области медицине, стоматологије и фармације. Радове равноправно објављују стручњаци из војних и цивилних установа и из иностранства. Штампа се на српском и енглеском језику. Часопис излази непрекидно од 1944. године до сада. Једини је часопис у земљи који излази месечно (12 бројева), на око 100 страна А4 формата, а повремено се објављују и тематски додаци (суплементи). Путем размене или претплате ВСП се шаље у 23 земље света. Радове објављене у ВСП-у индексирају: *Science Citation Index Expended (SCIE)*, *Journal Citation Reports/Science Edition*, *Index Medicus (Medline)*, *Excerpta Medica (EMBASE), EBSCO* (преко ове базе ВСП је *on line* доступан од 2002. године у *pdf* формату) и *Biomedicina Serbica*.

Цене реклама и огласа у часопису „Војносанитетски преглед“ у 2009. години су:

1.	Оглас у црно-белој техници А4 формата за један број	20 000,00 динара
2.	Оглас у ц/б техници А4 формата за целу годину (11-12 бројева)	200 000,00 динара
3.	Оглас у боји А4 формата за један број	35 000,00 динара
4.	Оглас у боји А4 формата за целу годину (11-12 бројева)	330 000,00 динара
5.	Оглас у боји на корицама К3 за један број	50 000,00 динара
6.	Оглас у боји на корицама К3 за целу годину (11-12 бројева)	455 000,00 динара
7.	Оглас у боји на корицама К2 и К4 за један број	55 000,00 динара
8.	Оглас у боји на корицама К2 и К4 за целу годину (11-12 бројева)	530 000,00 динара

За сва објашњења, упутства и понуде заинтересовани контактирају редакцију часописа „Војносанитетски преглед“. Средства се уплаћују на жиро рачун код Управе јавних плаћања у Београду број: 840-941621-02 **ВМА (за Војносанитетски преглед или за ВСП)**, **ПИБ 102116082**. Уплатницу (доказ о уплати) доставити лично или поштом (писмом, факсом, *e-mail*-ом) на адресу: Војносанитетски преглед, Црнотравска 17, 11000 Београд; тел/факс: 011 2669 689, e-mail: vmaini1@eunet.yu или vmaini2@eunet.yu

UPUTSTVO AUTORIMA

Vojnosanitetski pregled (VSP) objavljuje radove koji ranije nisu nigde publikovani, niti predati za publikovanje redosledom koji određuje uređivački odbor. Uz rad, na posebnom listu, treba dostaviti: izjavu da rad do sada nije (ili je delimično) objavljen ili prihvaćen za štampu u drugom časopisu; potpise svih koautora; ime, tačnu adresu, brojeve telefona (fiksne, mobilne, faks), *e-mail* adresu, kao i kopiju dokaza o pretplati na časopis za sve autore (i koautore). Za objavljene radove VSP zadržava autorsko pravo.

Radove slati na adresu: Vojnosanitetski pregled Vojnomedicinska akademija, Institut za naučne informacije, Crnotravska 17, 11040 Beograd.

U VSP-u se objavljuju **uvodnici**, **originalni članci, prethodna** ili **kratka saopštenja**, revijski radovi tipa **opšteg pregleda**, **aktuelne teme** ili **metaanalize**, **kazuistika**, članci iz **istorije medicine**, lični stavovi, naručeni komentari, pisma uredništvu, izveštaji sa naučnih i stručnih skupova, prikazi knjiga, referati iz naučne i stručne literature i drugi prilozi.

Radove tipa opšteg pregleda Uredništvo će prihvatati samo ukoliko autori navođenjem najmanje 5 autocitata potvrde da su eksperti u oblasti o kojoj pišu.

Radovi se objavljuju na srpskom ili engleskom jeziku sa apstraktima na srpskom i engleskom, za radove tipa originalnih članaka, prethodnih ili kratkih saopštenja, metaanalize i kazuistike. Odabrani članci objavljuju se u celini na engleskom jeziku sa apstraktom na srpskom.

Rukopis se piše pomoću IBM-PC kompatibilnog računara, sa proredom 1,5. Štampa se na laserskom ili nekom drugom visokokvalitetnom štampaču, uredno i bez ispravki, na čistoj beloj hartiji formata A4, sa levom marginom od **4 cm**. Koristiti font veličine 12, a načelno izbegavati upotrebu **bold** i *italic* slova, koja su rezervisana za podnaslove. Originalni članci, opšti pregledi i metaanalize ne smeju prelaziti 16 stranica (sa prilozima); aktuelne teme – osam, kazuistika – šest, prethodna saopštenja – pet, a pisma uredniku, izveštaji sa skupova i prikazi knjiga – dve stranice.

U celom radu obavezno je korišćenje međunarodnog sistema mera (SI) i standardnih međunarodno prihvaćenih termina.

Radove (tekst i grafičke priloge) treba slati na disketi (CD) i štampane u tri primerka (original i dve kopije). Autori konačnu verziju rukopisa i priloga prihvaćenih za publikovanje predaju u jednom štampanom primerku i na disketi od 3,5" (očišćenoj od „virusa“) ili na kompakt disku. Za obradu teksta koristiti program **Word for Windows** verzije 97, 2000, XP ili 2003, a samo izuzetno i neki drugi. Za izradu grafičkih priloga koristiti standardne grafičke programe za **Windows**, poželjno iz programskog paketa **Microsoft Office** (**Excel, Word Graph**). Kod kompjuterske izrade grafika izbegavati upotrebu boja i senčenja pozadine.

Prispeli radovi kao anonimni podležu uređivačkoj obradi i recenziji najmanje dva urednika/recenzenta. Primedbe i sugestije urednika/recenzenata dostavljaju se autoru radi konačnog oblikovanja. Otisak članka šalje se prvom autoru na korekturu, koji treba vratiti u roku od pet dana. Rukopisi radova prihvaćenih za štampu ne vraćaju se autoru.

Priprema rada

Delovi rada su: **naslovna strana, apstrakt sa ključnim rečima, tekst** i **literatura.**

1. ***Naslovna strana***

a) Naslov treba da bude kratak, jasan i informativan i da odgovara sadržaju rada. Podnaslove treba izbegavati.

b) Ispisuju se puna imena i prezimena autora.

c) Navode se puni nazivi ustanove i organizacijske jedinice u kojima je rad obavljen i mesta u kojima se ustanove nalaze, sa jasnim obeležavanjem odakle je autor, koristeći standardne znake za fus-note.

2. ***Apstrakt i ključne reči***

Na drugoj stranici nalazi se strukturisani apstrakt sa naslovom rada. Kratkim rečenicama na srpskom i engleskom jeziku iznosi se **uvod i cilj** rada, osnovne procedure - **metode** (izbor ispitanika ili laboratorijskih životinja; metode posmatranja i analize), glavni nalazi - **rezultati** (konkretni podaci i njihova statistička značajnost) i glavni **zaključak**. Naglasiti nove i značajne aspekte studije ili zapažanja. Strukturisani apstrakt (**250** reči) ima podnaslove: *uvod/cilj, metode, rezultati* i *zaključak*. Za apstrakte na engleskom dozvoljeno je i do **450** reči. Strukturisani apstrakt je obavezan za metaanalize (istog obima kao i za originalne članke) i kazuistiku (do 150 reči, sa podnaslovima *uvod, prikaz slučaja i zaključak*). Ispod apstrakta, pod podnaslovom „Ključne reči“ predložiti 3–10 ključnih reči ili kratkih izraza koji oslikavaju sadržinu članka.

3. ***Tekst članka***

Tekst sadrži sledeća poglavlja: **uvod**, **metode**, **rezultate** i **diskusiju**. **Zaključak** može da bude posebno poglavlje ili se iznosi u poslednjem pasusu diskusije. U **uvodu** ponovo napisati naslov rada, bez navođenja autora. Navesti hipotezu (ukoliko je ima) i ciljeve rada. Ukratko izneti razloge za studiju ili posmatranje. Navesti samo strogo relevantne podatke iz literature i ne iznositi opširna razmatranja o predmetu rada, kao ni podatke ili zaključke iz rada o kome se izveštava.

Metode. Jasno opisati izbor metoda posmatranja ili eksperimentnih metoda (ispitanici ili eksperimentne životinje, uključujući kontrolne). Identifikovati metode, aparaturu (ime i adresa proizvođača u zagradi) i proceduru, dovoljno detaljno da se drugim autorima omogući reprodukcija rezultata. Navesti podatke iz literature za uhodane metode, uključujući i statističke. Tačno identifikovati sve primenjene lekove i hemikalije, uključujući generičko ime, doze i načine davanja. Za ispitivanja na ljudima i životinjama navesti saglasnost etičkog komiteta.

Rezultate prikazati logičkim redosledom u tekstu, tabelama i ilustracijama. U tekstu naglasiti ili sumirati samo značajna zapažanja.

U **diskusiji** naglasiti nove i značajne aspekte studije i izvedene zaključke. Posmatranja dovesti u vezu sa drugim relevantnim studijama, u načelu iz poslednje tri godine, a samo izuzetno i starijim. Povezati zaključke sa ciljevima rada, ali izbegavati nesumnjive tvrdnje i one zaključke koje podaci iz rada ne podržavaju u potpunosti.

Literatura

Literatura se u radu citira kao superskript, a popisuje rednim brojevima pod kojima se citat pojavljuje u tekstu. Navode se svi autori, ali ako broj prelazi šest, navodi se prvih šest i dodaje et al. Svi podaci o citiranoj literaturi moraju biti tačni. Literatura se u celini citira na engleskom jeziku, a iza naslova se navodi jezik članka u zagradi. Ne prihvata se citiranje apstrakata, sekundarnih publikacija, usmenih saopštenja, neobjavljenih radova, službenih i poverljivih dokumenata. Radovi koji su prihvaćeni za štampu, ali još nisu objavljeni, navode se uz dodatak „u štampi“. Rukopisi koji su predati, ali još nisu prihvaćeni za štampu, u tekstu se citiraju kao „neobjavljeni podaci“ (u zagradi). Podaci sa *Interneta* citiraju se uz navođenje datuma.

Primeri oblika 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)

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

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

Tabele

Sve tabele štampaju se sa proredom 1,5 na posebnom listu hartije. Obeležavaju se arapskim brojevima, redosledom pojavljivanja, u desnom uglu (**Tabela 1**), a svakoj se daje kratak naslov. Objašnjenja se daju u fus-noti, ne u zaglavlju. Za fus-notu koristiti sledeće simbole ovim redosledom: ***, †, ‡, §, ||, ¶, **, ††, ...** Svaka tabela mora da se pomene u tekstu. Ako se koriste tuđi podaci, obavezno ih navesti kao i svaki drugi podatak iz literature.

Ilustracije

Slikama se zovu svi oblici grafičkih priloga i predaju se u tri primerka i na disketi (CD). Fotografije treba da budu oštre, na glatkom i sjajnom papiru, do formata dopisnice. Slova, brojevi i simboli treba da su jasni i ujednačeni, a dovoljne veličine da prilikom umanjivanja budu čitljivi. Na svakoj slici treba na poleđini, tankom grafitnom olovkom, označiti broj slike, ime prvog autora i gornji kraj slike. Slike treba obeležiti brojevima, onim redom kojim se navode u tekstu (**Sl. 1; Sl. 2** itd.). Ukoliko je slika već negde objavljena, obavezno citirati izvor.

Legende za ilustracije pisati na posebnom listu hartije, koristeći arapske brojeve. Ukoliko se koriste simboli, strelice, brojevi ili slova za objašnjavanje pojedinog dela ilustracije, svaki pojedinačno treba objasniti u legendi. Za fotomikrografije navesti unutrašnju skalu i metod bojenja.

Skraćenice i simboli

Koristiti samo standardne skraćenice, izuzev u naslovu i apstraktu. Pun naziv sa skraćenicom u zagradi treba dati kod prvog pominjanja u tekstu.

Detaljno uputstvo može se dobiti u redakciji.

INSTRUCTIONS TO AUTHORS

Vojnosanitetski pregled (VSP) publishes only previously neither published nor submitted papers in any other journals in the order determined by the Editorial Board. The following should be enclosed with the manuscript: a statement that the paper has not been submitted or accepted for publication elsewhere; a consent signed by all the authors that the paper could be submitted; the name, exact address, phone number, and e-mail address of the first author and co-authors. VSP reserves all copyrights.

Papers should be sent to: Military Medical Academy, Institute for Scientific Information, Crnotravska 17, 11040 Belgrade, Serbia & Montenegro, for "Editorial Board of VSP."

VSP publishes: **editorials, original articles**, **short communications**, **reviews**/**meta-analyses, case reports**, from the **medical history** (general or military), personal views, invited comments, letters to the editor, reports from scientific meetings, book reviews, extensive abstracts of interesting articles from foreign language journals, and other contributions. Papers are published in Serbian or English with abstracts in both languages, and the selected ones fully in English for original artic les, short communications, meta-analyses and case reports.

General review papers type will be accepted by the Editorial Board only if the authors prove themselves as the experts in the fields they write on by citing not less than 5 self-citations.

Papers should be written on IBM-compatible PC, using 12 pt font, and double spacing, and printed on the laser, or other high-quality printer without any corrections, on white bond paper ISO A4 (212×297 mm) with at least 4 cm left margin. **Bold** and *italic* letters should be avoided. Observational and experimental articles, reviews and meta-analyses, should not exceed 16 pages (including tables and illustrations); case reports – 6; short communications – 5; letters to the Editor, reports on scientific meetings and book reviews – 2.

All measurements should be reported in the metric system in terms of the International System of Units (SI). Standard, internationally accepted terms should be used. Papers should be submitted on a diskette (CD) in triplicate (original and two copies).

Authors are requested to submit the final version of manuscript approved for publishing with tables and illustrations on a 3.5" virus free diskette or a CD. **MS Word for Windows** (97, 2000, XP, 2003) is recommended for word processing; other programs are to be used only exceptionally. Illustrations should be made using standard **Windows** programs**.** Avoid the use of colors in graphs.

Papers are reviewed anonymously by at least two editors and/or invited reviewers. Remarks and suggestions are sent to the author for final composition. Galley proofs are sent to the first author for corrections that should be returned within 5 days. Manuscripts accepted for publication are not being returned.

Preparation of manuscript

Parts of the manuscript are: **Title page; Abstract with key words; Text; References**.

1. ***Title page***

a) The title should be concise but informative. Subheadings should be avoided;

b) full name of each author;

c) name and place of department(s) and institution(s) of affiliation, clearly marked by standard footnote signs.

2. ***Abstract and key words***

The second page should carry a structured abstract with the title for original articles, metanalyses and case reports. The abstract should state the purposes of the study or investigation, basic procedures (selection of study subjects or laboratory animals; observational and analytical methods), main findings (giving specific data and their statistical significance, if possible), and the principal conclusions. It should emphasize new and important aspects of the study or observations. S t r u c - t u r e d abstract should contain typical subtitles: *background/aim, methods, results* and *conclusion*. The abstract for metaanalyses and obrginal papers should have up to 450 words, and up to 150 words for case reports (with subtitles *background, case report, conclusion*). Below the abstract authors should provide, and identify as such, 3–10 key words or short phrases that will assist indexers in cross-indexing the article and will be published with the abstract.

3. ***Text***

The text of original articles is divided into sections with the headings: **Introduction**, **Methods**, **Results**, and **Discussion**. Long articles may need subheadings within some sections to clarify their content.

In the **Introduction** repeat the title of the article, excluding the names of authors. State the purpose of the article and summarize the rationale for the study or observation. Give only strictly pertinent references and do not include data or conclusions from the work being reported.

Methods. Describe your selection of the observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods. Identify precisely all drugs and chemicals used, with generic name(s), dose(s), and route(s) of administration. State the approvement of the Ethnics Committe for the tests in humans and enimals.

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 important 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

References should be superscripted and numbered consecutively in the order in which they are first mentioned in the text. **The references must be verified by the author(s) against the original document.** List all authors, but if the number exceeds 6, give 6 followed by et al. Do not use abstracts, secondary publications, oral communications, unpublished papers, official and classified documents. References to papers accepted but not yet published should be designated as "in press". Information from manuscripts not yet accepted should be cited in the text as "unpublished observations". References are cited according to the ***International Committee of Medical Journal Editors.*** *Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Ann Intern Med 1997; 126: 36–47. Updated October 2001.*

Examples of references:

Jurhar-Pavlova M, Petlichkovski A, TrajkovD, Efinska-Mladenovska O, Arsov T, Strezova A, et al. Influence of the elevated ambient temperature on immunoglobulin G and immunoglobulin G subclasses in sera of Wistar rats. Vojnosanit Pregl 2003; 60(6): 657–612.

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. 413-428.

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

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

Tables

Type each table double-spaced on a separate sheet. Number tables consecutively in the order of their first citation in the text in the upper right corner **(Table 1)** and supply a brief title for each. Place explanatory matter in footnotes, using the following symbols, in this sequence: ***, †, ‡, §, ||, ¶, **, ††, ...** Each table has to be mentioned in the text. If you use data from another source, acknowledge fully.

Illustrations

Figures are submitted in triplicate, and for the final version also on diskette/CD. Photos should be sharp, glossy black and white photographic prints, not larger than 203 × 254 mm. Letters, numbers, and symbols should be clear and even throughout and of sufficient size that when reduced for publication, each item will still be legible. Each figure should have a label on its back indicating the number of the figure, author's name, and top of the figure. If a figure has been published, acknowledge the original source.

Legends for illustrations are typed on a separate page, with arabic numerals corresponding to the illustrations. Identify and explain each one clearly in the legend symbols, arrows, numbers, or letters used to identify parts of the illustrations. Explain the internal scale and identify the method of staining in photomicrographs.

Abbreviations and symbols

Use only standard abbreviations. Avoid abbreviations in the title and abstracts. The full term for which an abbreviation stands should precede its first use in the text.

VOJNOSANITETSKI PREGLED
VOJNOMEDICINSKA AKADEMIJA
Crnotravska 17, 11040 **Beograd**, **Srbija**
Tel/Fax: +381 11 2669689
vmaini1@eunet.yu
vmaini2@eunet.yu

Časopis „Vojnosanitetski pregled“ izlazi godišnje u 12 brojeva.

Godišnja pretplata za 2009. godinu iznosi: 4 000 dinara za građane Srbije, 8 000 dinara za ustanove iz Srbije i 150 € za strane državljane i ustanove. Sredstva se uplaćuju na tekući račun Vojnomedicinske akademije Beograd kod Uprave za javna plaćanja u Beogradu broj: **840-941621-02 VMA (za Vojnosanitetski pregled ili za VSP)**, **PIB 102116082 ili na devizni račun kod Narodne banke broj: 54104-oznaka valute-549**. Uplatnicu (dokaz o uplati) dostaviti lično ili poštom (pismom, faksom, *e-mail*-om). Za zaposlene u MO i Vojsci Srbije moguća je i pretplata u 12 mesečnih rata putem trajnog naloga, tj. „odbijanjem od plate“. Popunjen obrazac poslati na adresu VSP-a.

PRIJAVA ZA PRETPLATU NA ČASOPIS „VOJNOSANITETSKI PREGLED“

Ime i prezime ili naziv ustanove	
Jedinstveni matični broj građana	
Poreski identifikacioni broj (PIB) za ustanove	
Mesto	
Ulica i broj	
Telefon / telefaks	

Pretplata na časopis „Vojnosanitetski pregled“ (zaokružiti):

1. Lično. Dokaz o pretplati dostavljam uz ovu prijavu.
2. Za pripadnike MO i Vojske Srbije: Dajem saglasnost da se prilikom isplate plata u Računovodstvenom centru MO iz mojih prinadležnosti obustavlja iznos mesečne rate (pretplate).
3. Virmanom po prijemu profakture.

Datum _____	Potpis _____

VOJNOSANITETSKI PREGLED
VOJNOMEDICINSKA AKADEMIJA
Crnotravska 17, 11040 **Beograd**, **Srbija**
Tel/Fax: +381 11 2669689
vmaini1@eunet.yu
vmaini2@eunet.yu

Časopis „Vojnosanitetski pregled“ izlazi godišnje u 12 brojeva.

Godišnja pretplata za 2009. godinu iznosi: 4 000 dinara za građane Srbije, 8 000 dinara za ustanove iz Srbije i 150 € za strane državljane i ustanove. Sredstva se uplaćuju na tekući račun Vojnomedicinske akademije Beograd kod Uprave za javna plaćanja u Beogradu broj: **840-941621-02 VMA (za Vojnosanitetski pregled ili za VSP)**, **PIB 102116082 ili na devizni račun kod Narodne banke broj: 54104-oznaka valute-549**. Uplatnicu (dokaz o uplati) dostaviti lično ili poštom (pismom, faksom, *e-mail*-om). Za zaposlene u MO i Vojsci Srbije moguća je i pretplata u 12 mesečnih rata putem trajnog naloga, tj. „odbijanjem od plate“. Popunjen obrazac poslati na adresu VSP-a.

PRIJAVA ZA PRETPLATU NA ČASOPIS „VOJNOSANITETSKI PREGLED“

Ime i prezime ili naziv ustanove	
Jedinstveni matični broj građana	
Poreski identifikacioni broj (PIB) za ustanove	
Mesto	
Ulica i broj	
Telefon / telefaks	

Pretplata na časopis „Vojnosanitetski pregled“ (zaokružiti):

1. Lično. Dokaz o pretplati dostavljam uz ovu prijavu.
2. Za pripadnike MO i Vojske Srbije: Dajem saglasnost da se prilikom isplate plata u Računovodstvenom centru MO iz mojih prinadležnosti obustavlja iznos mesečne rate (pretplate).
3. Virmanom po prijemu profakture.

Datum _____	Potpis _____