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

IZDAVAČ
Uprava za vojno zdravstvo MO Srbije

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Osmog marta širom sveta obeležva se Dan žena. To je prilika da se ženama oda priznanje za postignute uspehe u svim sferama života, ali i istaknu problemi sa kojima se one sučavaju. Jedan od njih je i pomanjkanje odgovarajuće zdravstvene zaštite u ključnim periodima njihovog života, još uvek prisutan u mnogim zemljama sveta. Povodom ovogodišnjeg Dana žena, Uredništvo časopisa Vojnosanitetski pregled poziva sve zdravstvene radnike da u svojim sredinama učine sve što je u njihovoj moći da poboljšaju i unaprede zdravlje žena, od njihovog rođenja do starosti.

The International Women's Day is marked on March 8 worldwide. This is an opportunity to acknowledge women's achievements in all spheres of life, but also to highlight the problems they are coped with. One of them is the lack of adequate health care in the key periods of their lives still present in many countries worldwide. On the occasion of this year's Women's Day the Editorial Board of the *Vojnosanitetski pregled* appeals to all health care professionals to do everything in their communities to improve and promote the health of women from birth to older age.

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

Priznanje Autoru i Recenzentu godine Vojnosanitetskog pregleda za 2012.

The Author and the Reviewer of the Year 2012 award by the *Vojnosanitetski Pregled*

Silva Dobrić

Institut za naučne informacije, Vojnomedicinska akademija, Beograd, Srbija
Institute for Scientific Information, Military Medical Academy, Belgrade, Serbia

Ostvarivanje kvaliteta naučnog rada cilj je i obaveza svakog autora i normalno je da za postizanje tog cilja priznanje pripada autoru. Pisanje naučnog članka, kao i sve etape u nastajanju naučnog dela, kreativan je posao koji od autora zahteva dodatno znanje i veštinu. Često se zaboravlja, međutim, da u nastajanju konačne verzije jednog naučnog članka ulogu igra i recenzent – ekspert za određenu oblast – čiji je zadatak da proceni vrednost naučnog saopštenja podnesenog časopisu za objavljivanje. Na osnovu njegove procene, urednik časopisa donosi odluku o objavljivanju ili ne podnetog rukopisa, dok se autorima daju sugestije da li i na koji način da poboljšaju i unaprede svoj rad. Na taj način recenzent aktivno učestvuje u podizanju kvaliteta radova objavljenih u naučnim časopisima, te njegov doprinos poštuju i uredništva časopisa, i sami autori.

Imajući ovo u vidu Uredništvo i Izdavač časopisa "Vojnosanitetski pregled" (VSP) odlučili su da, ubuduće, pored priznanja koje dodeljuju autoru koji kao jedini ili prvi autor u prethodnoj godini objavi najviše radova na stranicama časopisa, dodele priznanje i recenzentu koji u toj godini uradi najviše recenzija.

Čin proglašenja Autora godine VSP ustanovljen je 1995. godine i obavlja se u sklopu proslave Dana Vojnomedicinske akademije (VMA), 2. marta, jer se još od davne 1961. godine Redakcija VSP nalazi pod krovom ove naše eminentne zdravstvene i naučnoobrazovne institucije. Izbor Autora godine VSP vrši se prema kriterijumima koji uzimaju u obzir broj i vrstu objavljenog članka, kao i redosled autora, pri čemu originalni članak i prvo mesto među autorima (ili jedino) donosi najveći broj bodova (Tabela 1).

Kada je u pitanju izbor Recenzenta godine u obzir se, pored broja urađenih recenzija u prethodnoj godini, uzima i njihov kvalitet (detaljan osvrt na svaki segment rada) i poštovanje zadatog roka za recenziju.

Top-quality scientific paper writing is the aim and obligation of each author, so for reaching this aim the author, of course, merits praise. Scientific research paper writing, complete with any stages of study development, is a highly creative project requiring an author to comprise additional knowledge and skills. For a scientific research paper to get its final version suitable for publication, however, a major role is often played by a reviewer, an expert in the field, who evaluates a scholarly paper submitted to a journal for publication. Considering his/her evaluation an editor makes a decision whether or not to publish a scholarly article, while the authors are suggested whether and how to improve it. In doing so, a reviewer actively takes part in improving the quality of papers published in scientific journals that is a contribution appreciated both by the editorial boards and the authors themselves.

For all these reasons, the Editorial Board and the Publisher of the *Vojnosanitetski pregled* (VSP) decided that for now on except for awarding the Author of the Year prize (a sole or the first author) of the most numerous and high-quality articles published in the Journal within the previous year) to also award the Reviewer of the Year prize (a reviewer who reviewed most articles in that year).

Awarding the Author of the Year prize by the VSP was established in 1995. It takes place on the Day of the Military Medical Academy, that is on March 2, due to the fact that the Editorial Staff of the VSP has been 'under the same roof' with this eminent Serbian health care and scientific and educational institution ever since 1961. The Author of the Year 2012 award by the VSP selection was done in compliance with criteria including the number and category of the published article, and the author's order in the byline, implying that original articles and the first or a sole author provide the highest score (Table 1).

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Tabela 1
Table 1

Kriterijumi za bodovanje autora i članaka u VSP / Criteria for author and article scoring in the *Vojnosanitertski Pregled*

Kategorija rada/ Article category	Broj bodova/ Score		
	prvi autor/ first author	drugi autor/ second author	treći autor/ third author
Originalni članak/ Original article	12	6	3.6
Prethodno saopštenje/ Preliminary report	5	2.5	1.5
Pregledni članak/ General review	10	5	3
Aktuelna tema ili Seminar praktičnog lekara/ Current topic or Practical advice for physicians	8	4	2.4
Kazuistika/ Case report	4	2	1.2
Istorija medicine/ History of medicine	5	2.5	1.5
Uvodnik/ Editorial	5	2.5	1.5

U skladu sa napred navedenim, kriterijumima za izbor Autora godine VSP, u 2012. godini najviše radova iz kategorija koje se boduju objavila je prof. dr Aneta Lakić iz Klinike za neurologiju i psihijatriju dece i omladine Kliničkog centra Srbije, inače vanredni profesor Medicinskog fakulteta Univerziteta u Beogradu. Njoj su kao jedinom, odnosno prvom autoru, u toku prošle godine u VSP-u objavljena četiri rada: jedan originalni članak, jedan prikaz bolesnika i dva saopštenja iz kategorije Aktuelna tema, odnosno Seminar praktičnog lekara (Tabela 2). Zahvaljujući tome, ona je osvojila ukupno 26 bodova i titulu Autora godine VSP za 2012. godinu.

Od recenzenata koji su prošle godine bili angažovani u proceni rukopisa podnetih za objavljivanje u časopisu VSP, najviše recenzija urađenih prema gorenavedenim kriterijumima izvršio je prof. dr Slobodan Obradović iz Klinike za urgentnu medicinu VMA, vanredni profesor interne medicine na Medicinskom fakultetu VMA Univerziteta odbrane u Beogradu. On je u toku 2012. izvršio ukupno 23 recenzije, zbog čega mu, s pravom, pripada titula Recenzenta godine VSP za 2012. godinu. Treba istaći da je on i u 2011. godini bio recenzent sa najvećim brojem urađenih recenzija, što još jednom potvrđuje da je ovo priznanje došlo u prave ruke.

U ime Izdavača, Uređivačkog odbora i Redakcije časopisa čestitam prof. dr Aneti Lakić i prof. dr Slobodanu Obradoviću na postignutim rezultatima kao Autoru, odnosno Recenzentu godine VSP za 2012. godinu, sa željom da nastave sa ovakvim uspesima i ubuduće. Istovremeno, zahvaljujem im na odanosti našem časopisu i uloženom trudu u podizanju njegovog kvaliteta i renomea.

Koristim priliku da zahvalim i svim ostalim autorima i recenzentima koji su u protekloj godini dali svoj značajan doprinos razvoju VSP sa nadom da ćemo još dugo sarađivati na obostrano zadovoljstvo.

Regarding the Reviewer of the Year award, except for the number of reviews their quality (a detailed comment on each part of the paper), and not expiring the time limit were also considered.

According to the above said, most papers of the categories which are scored were written by Prof. Dr. Aneta Lakić, the Clinic for Child and Adolescent Neurology and Psychiatry, Clinical Center of Serbia, Assoc. Prof at the Faculty of Medicine, University of Belgrade. As a sole or the first author, Prof. Dr. Aneta Lakić published four scientific research papers in the VSP last year: one original article, one case report, and two reports from the category Current Topic and Practical Advice for Physicians (Table 2). Prof. Dr Lakić scored 26 scores and won the Author of the Year 2012 title awarded by the VSP.

Out of the reviewers involved in manuscripts evaluation submitted to the VSP last year, according the above mentioned criteria the highest number of papers were reviewed by Prof. Dr. Slobodan Obradović, Clinic for Urgent Medicine, Military Medical Academy, Assoc. Prof. of Internal Medicine at the Faculty of Medicine, Military Medical Academy, University of Defense, in Belgrade. Namely, Prof. Dr. Slobodan Obradović reviewed 23, the highest number of scholarly papers in 2012 and won, by right, the Reviewer of the Year 2012 title awarded by the VSP.

In the name of the Publisher, Editorial Board and Editorial Staff, it is my pleasure to congratulate to Prof. Dr. Aneta Lakić and to Prof. Dr. Slobodan Obradović for the achieved results and winning the Author and the Reviewer of the Year 2012 by the VSP, respectively wishing them to keep on with such success. Also, I thank to them for being loyal to the VSP and for their effort put in improving the quality and visibility of the VSP.

I also take this occasion to thank to all the other authors and reviewers that significantly contributed to the VSP last year, expecting them to further cooperate with us to our mutual satisfaction.

Tabela 2
Table 2

Radovi prof. dr Anete Lakić u Vojnosanitetskom pregledu u 2012.
Articles of Prof. Aneta Lakić, PhD, MD, published in the *Vojnosanitetski Pregled* in 2012

Broj/ Number	Kategorija rada/ Article category	Autori i naziv rada / Authors and title of article
1	Kazuistika/ Case report	*Lakić A*. Depressive symptoms as a side effect of the sustained release form of methylphenidate in a 7-year-old boy with attention-deficit hyperactive disorder. VojnosanitPregl 2012; 69(2):201-4.
2	Aktuelna tema ili Seminar praktičnog lekara/ Current topic or Practical advice for physicians	*Lakić A.* Screening, identification and evaluation of autism spectrum disorders in primary health care. Vojnosanit Pregl 2012; 69(5):437-43.
3	Aktuelna tema ili Seminar praktičnog lekara/ Current topic or Practical advice for physicians	*Lakić A.* Quality of life in childhood and adolescence: from concept to practice. Vojnosanit pregl 2012; 69(3):257-9.
4	Originalni članak/ Original article	*Damnjanović M, Lakić A, Stevanović D, Jovanović A, Jančić J, Jovanović M, Leposavić Lj.* Self-assessment of the quality of life of children and adolescents in the child welfare system of Serbia. Vojnosnit Pre gl 2012; 69(6):469-74.

Kratka biografija Autora godine VSP za 2012. godinu

Prof. dr Aneta Lakić (Slika 1), doktor medicinskih nauka, specijalista neuropsihijatrije, dečje psihijatrije i supspecijalista forenzičke psihijatrije, vanredni je profesor Medicinskog fakulteta Univerziteta u Beogradu.

The Author of the Year 2012 by the VSP – short biography

Prof. Dr. Aneta Lakić, PhD MD, (Figure 1), Specialist in Child Neuropsychiatry, Subspecialist in Forensic Psychiatry is an Associate Professor at the Faculty of Medicine, University of Belgrade.

Sl. 1 – Prof. dr Aneta Lakić, Autor godine Vojnosanitetskog Pregleda za 2012.
Fig. 1 – Assoc. Prof. Aneta Lakić, PhD, MD, the Author of the Year 2012 by the *Vojnosanitetski Pregled*

Diplomirala je na Medicinskom fakultetu Univerziteta u Beogradu 1975. godine sa srednjom ocenom 9,15. Na istom fakultetu 1980. godine odbranila je magistarski rad („Neki imunološki aspekti SSPE"), a 1986. godine i doktorsku disertaciju („Uticaj neuroleptika na kretanje prolaktina u pacijenata obolelih od shizofrenije").

Graduated from the Faculty of Medicine, University of Belgrade in 1975, with the average mark of 9.15, Prof. Dr. Aneta Lakić defended her master thesis "Some immunological aspects of SSPE" in 1980, and her doctorial dissertation "Impact of Neuroleptics on Prolactin Flow in Patients with Schizophrenia" from the same Faculty in 1986.

Specijalistički ispit iz neuropsihijatrije položila je 25.06. 1981. sa odličnom ocenom, a supspecijalistički rad iz sudske psihijatrije pod nazivom "Drugostepeno veštačenje dodele dece na dalju brigu i staranje u/po razvodu braka" odbranila je 01.12.1994. na Medicinskom fakultetu Univerziteta u Beogradu. Rešenjem Medicinskog fakulteta Univertziteta u Beogradu br. 3457/16 od 08.01.2007. a na osnovu odluke Ministarstva zdravlja Republike Srbije br 153-06-1403/05-02 od 29.09. 2006. dodeljeno joj je zvanje specijaliste dečje psihijatrije.

Profesionalnu karijeru započela je 1978. godine u Neuropsihjatrijskoj klinici u Beogradu, Odeljenje za neuropsihijatriju za decu i omladinu (sada Klinika za neurologiju i psihijatriju za decu i omladinu), gde se i sada nalazi. Od 1989. godine je načelnik Službe za psihijatriju na Klinici za neurologiju i psihijatriju za decu i omladinu, a u novembru 2012. postavljena je na mesto v.d. direktora te klinike.

U aprilu 1989. godine izabrana je prvi put za asistenta na Medicinskom fakultetu Univerziteta u Beogradu za predmet neuropsihijatrija. Trenutno se nalazi u zvanju vanrednog profesora (reizbori 2006. i 2011) za predmet psihijatrija.

Svoje aktivnosti na Fakultetu usmerila je, ne samo na rad sa studentima i specijalizantima kroz predavanja i mentorstva, već je jedan od začetnika i osnivača nove specijalizacije – Dečje i adolescentne psihijatrije, što je omogućilo školovanje novih stručnjaka i, posredno, unapredilo stepen zdravstvene zaštite mentalnog zdravlja ove vulnerabilne populacije u našoj zemlji Prvi je nastavnik na Medicinskom fakultetu Univerziteta u Beogradu za oblast dečje i adolescentne psihijatrije.

U njenom stručnom i naučno-istraživačkom opusu mogu se izdvojiti četiri celine: oblast zaštite mentalnog zdravlja dece i omladine i kvaliteta života u razvojnom periodu, oblast socijalne psihijatrije u razvojnom dobu, oblast forenzičke psihijatrije razvojnog doba i istraživanje bioloških mehanizama i fenomena kod poremećaja u razvojnom dobu. Iz okvira ovih tema objavila je 160 naučnih saopštenja, od kojih šest u časopisima indeksiranim u *Current Contents-u* (CC), a osam u *Science Citation Index Expanded* (SCIe) bazi naučne publicistike. Takođe, autor je, odnosno koautor četiri udžbenika/monografije i 21 poglavlja u monografskim publikacijama posvećenim neuropsihijatrijskim problemima dece i omladine.

Osim u domenu stručnonaučnog i pedagoškog rada, prof. dr Aneta Lakić izuzetno je aktivna i u radu mnogih strukovnih udruženja. Sekretar/predsednik (2 mandata) je Sekcije za dečju neuropsihijatriju Srpskog lakarskog društva, član stručnog sa veta Centra za autizam, predsednik Komisije za razvrstavanje dece višestruko ometene u razvoju, predsednik Etičkog komiteta Klinike za neurologiju i psihijatriju za decu i omladinu i zamenik rukovodioca nacionalne ekspertske grupe Ministarstva zdravlja Srbije za zaštitu mentalnog zdravlja mladih i član pod grupe za zaštitu mladih od zanemarivanja i zlostavljanja od 09.07. 2003, te član sudskopsihijatrijskog odbora Medicinskog fakulteta u Beogradu.

Treba istaći i to da je prof. dr Aneta Lakić bila jedan od osnivača Društva za dečju i adolescentnu psihijatriju i srodne struke Srbije i Crne Gore (DEAPS) i da je predsedavala osnivačkom Skupštinom tog udruženja.

Ovoj bogatoj profesionalnoj karijeri, 2. marta 2013. godine, prof. dr Aneta Lakić dodaće još jedno priznanje – titulu Autora godine „Vojnosanitetskog pregleda“ za 2012. godinu.

Prof. Dr. Aneta Lakić passed the specialist's examination on June 25, 1981 with honors. The specialist's paper on forensic psychiatry titled "Secondary testimony on allocating children to further bringing in/after divorce" Prof. Dr. Lakić defended from the Faculty of Medicine, University of Belgrade on December 1, 1994. The Faculty of Medicine, University of Belgrade by the act No. 3457/05-2 dated January 8, 2007, based on the decision of the Ministry of Health of the Republic of Serbia No. 153-06-1403/05-02 dated September 29, 2006 Prof. Dr. Aneta Lakić was granted the title Pediatric Psychiatry Specialist.

Her professional career Prof. Dr. Lakić started in 1978 in the Clinic for Neuropsychiatry, Belgrade, where she still works. Starting from 1989 Prof. Dr. Lakić is the Head of the Department for Psychiatry, Clinic for Neurology and Pediatric and Adolescent Psychiatry, while in November 2012 Prof. Dr. Lakić was appointed Acting Director in the same clinic. In April 1989 Prof. Dr. Lakić was firstly chosen to be Assistent at the Faculty of Medicine, University of Belgrade, while presently she is Assoc. Prof. of Psychiatry.

Prof. Dr. Aneta Lakić is not only occupied with her students and specialisants, but one of the devoted creators of a new specialization – namely Pediatric and Adolescent Psychiatry so making possible additional training for new experts, and, indirectly, improving mental health care of this vulnerable population in Serbia. Prof. Dr. Aneta Lakić is the first professor for the field of Pediatric and Adolescent Psychiatry at the Faculty of Medicine, University of Belgrade.

Regarding professional and scientific research engagement of Prof. Dr. Aneta Lakić there are four major fields: the field of pediatric and adolescent mental health care and the quality of life in the period of development, the field of social psychiatry in the period of development, the field of forensic psychiatry in the period of development and the field of scientific research of biological mechanisms and phenomenon in disorders in the period of development. The result are a total of 160 scientific articles and six of them in the journals indexed by Current Contents, eight in Science Citation Index Expanded (SCIe). Prof. Dr. Aneta Lakić is a sole first author or first co-author of four textbooks / monographs and 21 chapters in monographic publications on neuropsychiatric disorders in children and adolescents.

In addition, Prof. Dr. Aneta Lakić is a member of numerous professional associations, a Secretary/ President of the Section for Pediatric Psychiatry, Serbian Medical Society (2 mandates), a member of the Center for Autism, President of the Board for Screening Children with Multiple Disorder, President of Ethical Committee, Clinic for Neurology and Pediatric and Adolescent Psychiatry, Deputy Head of the National Experts Group, Ministry of Health Care of the Republic of Serbia, member of Forensic Psychiatry Board, Faculty of Medicine, University of Belgrade.

To this highly rich professional career on March 2, 2013 Prof. Dr. Aneta Lakić adds one award – the Author of the Year 2012 by the VSP. Sincere congratulations!

Kratka biografija Recenzenta godine VSP za 2012. godinu

Prof. dr Slobodan Obradović (Slika 2) vanredni profesor interne medicine na Medicinskom fakultetu VMA Univerziteta odbrane u Beogradu, diplomirao je na Medicinskom fakultetu Univerziteta u Beogradu 1994. godine sa prosečnom ocenom 9.74. U periodu 1995–1999. specijalizirao je internu medicinu na VMA. Supspecijalizaciju iz kardiologije završio je 2002. godine.

The Reviewer of the Year 2012 by the VSP – short biography

Prof. Dr. Slobodan Obradović (Figure 2), Assoc. Prof. of Internal Medicine at the Faculty of Medicine, Military Medical Academy, University of Defense, Belgrade, graduated from the Faculty of Medicine, University of Belgrade in 1994 with the average mark of 9.74, in a period 1995–1999 specialized in internal medicine in the Military Medical Academy, Belgrade, and in 2002 specialized in cardiology.

Sl. 2 – Prof. dr Slobodan Obradović, Recenzent godine VSP za 2012. godinu
Fig. 2 – Assoc. Prof. Slobodan Obradović, PhD, MD, the Reviewer of the Year 2012 by the *Vojnosanitetski Pregled*

Od kraja 1999. godine do danas zaposlen je na Klinici za urgentnu medicinu VMA gde obavlja složene procedure u okviru interventne kardiologije i leči najkompleksnije vitalno ugrožene internističke bolesnike.

Magistrirao je i doktorirao na VMA iz oblasti hemostaze u akutnom koronarom sindromu i perkutanoj koronarnoj intervenciji. Za docenta iz predmeta Interna medicina na VMA izabran je 2004. godine, a za vanrednog profesora 2011. godine.

U periodu 2008–2012. rukovodio je projektom „Matične ćelije u lečenju ishemijske bolesti srca“ iz koga je objavljeno nekoliko naučnih radova, a 2011. godine i poglavlje „*Stem Cell Therapy in Myocardial Infarction*” u knjizi „*Stem Cells in Clinic and Research*“ (Gholamrezanezhad A, editor. Rijeka: In Tech). Takođe, rezultati ovih istraživanja ušli su u metaanalizu koja će biti usmeno saopštena na Američkom kongresu kardiologa 2013. godine.

Mentor je više doktorata iz oblasti kardiologije, i, kao takav, izuzetno aktivan u podizanju naučnoistraživačkog podmlatka. Zajedno sa dr Sinišom Rusovićem i pro-

Since the end of 1999, Prof. Dr. Slobodan Obradović has been working at the Clinic for Urgent Medicine, Military Medical Academy, actively involved in complex procedures for interventional cardiology and treatment of patients with life-threatening internal disorders.

Prof. Dr. Slobodan Obradović defended both his master’s thesis and PhD dissertation in the Military Medical Academy, the field of hemostasis in acute coronary syndromes and percutane coronary intervention. Prof. Dr. Slobodan Obradović was chosen for Assist. Prof. and Assoc. Prof. of Internal Medicine in 2004 and 2011, respectively (Military Medical Academy).

Prof. Dr. Slobodan Obradović was a 3-year (2008–2012) leading investigatior of the project “Stem Cells in Ischemic Heart Disease Treatment” on which he published a few scholarly papers including a chapter in the book „Stem Cells in Clinic and Research“ (Gholamrezanezhad A., editor, Rijeka: In Tech; 2011). The results obtained in that project are included in the meta-analysis planned to be orally presented at the American Congress of Cardiologists in 2013.

fesorom Brankom Gligićem autor je monografije "Plućna tromboembolija kroz prikaze slučajeva" koja je objavljena 2011. godine. U njoj su prikazana 32 bolesnika lečena na Klinici za urgentnu medicinu VMA, uz navođenje najvažnijih dijagnostičkih i terapijskih postupaka u ovom stanju.

Objavio je veći broj radova iz oblasti hemostaze, perkutane koronarne intervencije, akutnog koronarnog sindroma i transplantacije matičnih ćelija u kardiologiji. U periodu 2009–2011. bio je predsednik radne grupe za trombozu i hemostazu Udruženja kardiologa Srbije. Član je uredništva VSP-a od 2010. godine.

O izvanrednoj stvaralačkoj energiji prof. dr Slobodana Obradovića govori i podatak da on, uprkos veoma zahtevnom stručnom i naučno-istraživačkom radu, nalazi vremena i za pisanje, ali ne samo naučnih članaka i recenzija, već kratkih priča i pesama. U njima često obrađuje teme iz svakodnevne lekarske prakse. Ovom prilikom čitaocima časopisa VSP poklanjamo jednu njegovu pesmu, posvećenu dežurnom lekaru:

ZA DEŽURNOG DOKTORA

Uči... Razmišljaj...
Budi hrabar... Osećaj strah...
Sabiraj iskustva...
Ne budi sujetan...
Sumnjaj, proveravaj, idi napred...
Traži pomoć...
Uradi sve što možeš...
Piši...Podeli...
UČI... U nedogled!
Ti si poslednja linija odbrane...

Put za smrt vodi kroz tvoje neznanje, kukavičluk, lenjost, sujetu...
Sam si.
Dolazi bolesnik, teško mu je...
Ohrabri ga. Pronađi u njemu snagu...
Ako ti nije stalo idi…
Nagrade nema….
Nagrada je jutro…. Za tebe i za još nekog...
Sam si.
Deo poslednjeg trenutka, nekog nepoznatog, a bliskog.
Moraš da se odmoriš malo.
Pred tobom je dug put.....
Život je vreme, kratko sećanje, najdublji trag u pesku…
Veličanstvena iskra!
Ničega drugog nema!

Prof. Dr. Slobodan Obradović has been doctorial dissertation advisor / mentor of numerous PhD students in cardiology, being very active in advising young researchers. With Siniša Rusović, MD, and Prof. Dr. Branko Gligić, Prof. Dr. Slobodan Obradović is an author of the monograph "Pulmonary thromboemboly – case reports" published in 2011 reporting on 32 cases treated in the Clinic for Urgent Medicine, Military Medical Academy and accounting for the major diagnostic and therapeutic procedures in this condition.

Prof. Dr. Slobodan Obradović published numerous scientific articles on hemostasis, percutane coronary intervention, acute coronary syndrome and stem cells transplantation in cardiology. A period of 2009–2011 was marked by presidency of Prof. Dr. Slobodan Obradović in the Group for Thrombosis and Hemostasis, Serbian Association of Cardiologists. Also, it is worth to mention, Prof. Dr. Slobodan Obradović has been a member of the VSP Editorial Board since 2010.

Exceptional creative ability of Prof. Dr. Slobodan Obradović is supported by a simple fact that in spite of very demandable professional and scientific research engagement he finds time to write, not only scholarly articles and reviews, but also short stories and lyric usually on everyday medical practice. This is the one of the poems about the physician on duty for the readers of VSP:

TO THE PHYSICIAN ON DUTY

Study... Contemplate...
Be brave... Feel fear...
Pile up experience...
Do not let vanity come over you...
Doubt, check, go ahead...
And ask for help...
But do anything you can....
Write... Share it with others...
STUDY... Endlessly!
You are the ultimate line of defense...

A path to death hyphenates cross your ignorance, cowardice, laziness, vanity...
You are all alone.
A patient comes, harboring his despair ...
Motivate him. Arouse strength in him...
If you do not care, just go away...
No reward...
Daybreak is a prize... For you and for some of the others
You are all alone.
A particle of the last moment of someone unknown, but close.
You need rest a little.
A long, long road is in front of you...
Life is just time, a short recollection, the deepest imprint in sand...
A magnificent spark!
Nothing else left!

ORIGINAL ARTICLES

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Analysis of intracranial hemorrhage grade in preterm singleton pregnancies delivered vaginally or by cesarean section

Analiza stepena intrakranijalnih hemoragija kod preterminskih monofetalnih trudnoća završenih vaginalnim putem ili carskim rezom

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Abstract

Background/Aim. Preterm birth is the leading cause of neonatal mortality. Periventricular hemorrhage–intraventricular hemorrhage (PVH–IVH) remains a significant cause of both morbidity and mortality in infants prematurely born. The aim of the study was to evaluate the perinatal outcome regarding IVH of premature babies according to the mode of delivery. **Methods.** A total of 126 women in preterm singleton pregnancies with vertex presentation and 126 neonates weighted from 750 g to 1,500 g at birth were enrolled. The outcomes of 64 neonates born vaginally were compared to 62 neonates born by cesarean section. **Results.** There was no significant difference in the incidence of IVH among both groups. **Conclusion.** Our data is consistent with the hypothesis that the mode of delivery does not influence IVH and consenquently perinatal outcome in preterm neonates.

Key words:
intracranial hemorrhages; infant, premature delivery, obstetric; cessareon section; mortality.

Apstrakt

Uvod/Cilj. Preterminski porođaj je vodeći uzrok neonatalnog mortaliteta. Kod prerano rođenog deteta periventrikularna – intraventrikularna hemoragija (PVH–IVH) je značajan uzrok morbiditeta i mortaliteta. Cilj rada bio je da se analizira perinatalni ishod preterminske novorođenčadi u pogledu nastanka IVH u odnosu na način završavanja porođaja. **Metode.** Ovom studijom bilo je obuhvaćeno 126 bolesnica u preterminskoj monofetalnoj trudnoći, sa prezentacijom glavom i 126 neonatusa telesne težine između 750 g i 1 500 g. Poređeni su perinatalni ishodi 64 neonatusa rođeni vaginalnim putem i 62 neonatusa rođena carskim rezom. **Rezultati.** Nije bilo statistički značajne razlike u incidenciji IVH između grupa vaginalno rođenih i grupe prematurusa rođenih carskim rezom. **Zaključak.** Rezultati dobijeni i u ovoj studiji u saglasnosti su sa hipotezom da način porođaja nema uticaja na IVH i, posledično, na perinatalni ishod preterminskih neonatusa.

Ključne reči:
krvarenje, intrakranijalno; nedonošće; porođaj; carski rez; mortalitet.

Introduction

Premature birth is one of the most delicate conditions in reproductive medicine. It is responsible for a large percentage of early neonatal death and early and/or late neonatal morbidity. Problems that may occur in premature born babies are related to organic immaturity and directly to gestational age. The most significant morbidity includes respiratory distress syndrome, persistent ductus arteriosus, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, retinopathy, hiperbilirubinemy and neonatal sepsis. In contrast to the period two decades ago, when the survival of these children was accompanied by a significant rate of disability (blindness, cerebral palsy or mental retardation), today the risk for disabilities exists in newborns weight below 1,500 g and lower gestational age [1, 2].

Statistically, the percentage of premature births has not significantly decrease in recent decades, despite drug therapy, cerclage application or bed rest. Despite the known risk factors for preterm birth: socioeconomic status, preterm membrane rupture, infection, maternal medical or obstetric complications, a large percentage of women can be classified into a group of patients with so-called idiopathic preterm labor [3, 4]. The pathophysiology of preterm labor initiation is unknown, but there are three possible theories: progesterone theory, the theory considering oxytocin initiating factor and

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the theory of organic communication, based on the fact that amniotic fluid contains many substances (prostaglandins, arachidonic acid, platelet activating factor and cytokines) whose activation initiates labor [5, 6].

Different authors make different risk-scoring systems in order to identify the risks for preterm birth [7–9]. Despite the applied criteria for the detection of preterm delivery, the diagnosis remains difficult. Cervical dilatation, as one of the important clinical signs, may not be accompanied by registered uterine activity and *vice versa*. More than 80% of women treated for premature delivery, gave birth at term, because uterine activity (Braxton-Hicks contractions) was not accompanied by cervical changes [10]. The use of tocolytic therapy, which may be applied in 17–20 weeks of gestation in women at high risk for preterm delivery, is widespread in the last 3–4 decades. Different agents are used to inhibit preterm delivery: beta-agonists, prostaglandin inhibitors, nitric oxide donor drugs, etc. For many of these agents there are data on their benefits in terms of extending the duration of gestation, but the accuracy of such data is questionable because it is difficult to make the diagnosis of premature birth. There is also a lack of data on the possible impact of these agents to the rate of perinatal morbidity and mortality. Many reports talk about the metabolic complications of prematurity: maternal hypokalemia and hyperglycemia and neonatal hypoglycemia [11].

Prematurity is an important predisposing factor for the occurrence of cerebral damage in the neonatal period and neurological sequelae are three times more frequent than in term neonates. A damage is caused by anatomical and physiological events in the brain, depending on the degree of maturation. Brain state blood vessels, cerebral tissue specificity and cerebrovascular autoregulation are the basis for understanding hemorrhage and hypoxic-ischemic cerebral changes in neonates.

Subependimal germinative matrix, formed between 10 and 20 weeks of gestation, is located lateral to the chamber system, proliferates in fetus during pregnancy and is responsible for the maturation of fragile blood vessels [12]. In early gestation the endothelium of blood vessels is thin, the vessels are prone to rupture. Over 80% of periventricular-intraventricular hemorrhage (PVH-IVH) can be explained by developments in the germinative matrix. The structure of arteries in the premature brain is responsible for hypoxic-ischemic changes. A relative resistance of the cerebral cortex to the development of hypoxic-ischemic stroke can be explained by rich anastomosis between meningeal arteries.

The pathogenesis of PVH-IVH is multifactorial and refers to intravascular, vascular and extravascular factors: cerebral blood flow disorder, increased cerebral venous pressure, coagulation disorder, fragile germinative vascular matrix, increased fibrinolytic activity and possible reduction of extravascular tissue pressure. Intrapartal asphyxia is relatively common and follows a high rate of incidence of neonatal cardiorespiratory problems.

Unconjugated hyperbilirubinemia of newborns with a deposit of bilirubin in the basal ganglia (kernicterus) can lead to microscopic neuronal destruction in the brain. Although not proven that previously determined risk factors: sepsis, asphyxia, acidosis, hypoglycemia and hypoalbuminemia, may be the cause of kernicterus, it cannot be prevented and in premature infants it presents risk for cerebral damage.

Prevention of neonatal cerebral hemorrhage can be divided into: antepartal (prevention of prematurity, intrauterine transport and pharmacological therapy – phenobarbital and vitamin K), intrapartal and postpartal.

According to the literature, the mode of delivery does not affect the development of neurological sequelae in neonates below the weight of 1250 g [4]. Another study, for the same weight, indicates that the mode of delivery has no effect on neonatal mortality in vertex presentation, but also indicates that neonatal mortality is significantly lower after cesarean section in malpresentations [1]. The same study, for the neonatal weight of 1,250 g to 1,500 g indicates a higher neonatal mortality, but not significantly after cesarean section. Another study suggests that the method of delivery did not affect the incidence of IVH in the neonates under 2,500 g [13]. Other authors conclude that the duration of active phase of labor carries greater risk of PVH-IVH than the method of labor [14]. A long-term uterine activity is a mechanical force that can lead to cerebral venous pressure elevation. Also, uterine contractions lead to an increase in fetal blood pressure resulting in the simultaneous increase in cerebral flow of preterm fetus who has immature cerebral autoregulation.

A relation between the occurrence of neonatal intraventricular hemorrhage and the mode of delivery is controversial, according to numerous studies. According to some studies, the risk of PVH-IVH is significantly reduced in neonates born by cesarean section, while other authors believe that cesarean section should be done only in extreme prematurity (28 weeks or less). Considering specific factors in the etiopathogenesis of PVH-IVH, the mode of delivery is determined by individual and optimal procedure.

The aim of this study was to evaluate the perinatal outcome of preterm newborns, in terms of the occurrence of IVH, compared to the mode of delivery. The study excluded malpresentations, as well as women with fetal intrauterine growth retardation.

Methods

A total of 126 women in preterm singleton pregnancies with vertex presentation and 126 neonates weighted from 750 g to 1,500 g at birth were enrolled. The outcomes of 64 neonates born vaginally were compared to 62 neonates born by cesarean section. We analyzed the rate of neonatal IVH compared to the mode of delivery, women's age, gestational age, use of tocolytic therapy and dexamethasone use. Neonatal outcomes were monitored by the appearance of IVH.

The data from this study were statistically analyzed and presented as figures and tables.

Results

We analyzed the occurrence of neonatal IVH in relation to the mode of delivery and the results were presented in Table 1.

Table 1

Occurence of the intraventricular hemorrhage (IVH) in relation to the mode of delivery

Type of delivery	IVH [n (%)]		Total number of newborns (%)
	No	Yes	
Vaginal	20 (31.3)	44 (68.8)	64 (100.0)
Cesarean section	27 (43.5)	35 (56.5)	62 (100.0)
Total	47 (37.3)	79 (62.7)	126 (100.0)

There was no statistically significant difference in the incidence of IVH in newborns compared to the mode of delivery, but a slightly higher percentage of IVH in vaginally born neonates was found.

Figure 1 shows the incidence of IVH in newborns as compared to the age of mothers.

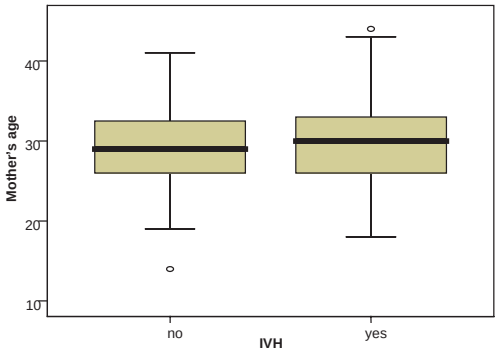

Fig. 1 –The incidence of intraventricular hemorrhage (IVH) compared to the age of the mnother

Mother's age not affect the incidence of IVH in neonates, regardless the mode of delivery.

The effect of the applied tocolytic therapy on the incidence of IVH is presented in Table 2.

Table 2

Tocolytic use and the incidence of the intraventricular hemorrhage (IVH)

Tocolytics use	IVH [n (%)]		Total number of newborns (%)
	No	Yes	
No	21 (30.9%)	47 (69.1%)	68 (100)
Yes	26 (44.8%)	32 (55.2%)	58 (100)
Total	47 (37.3%)	79 (62.7%)	126 (100)

In the monitored groups, there was no statistically significant difference regarding the use of tocolytic therapy and the incidence of IVH, regardles the mode of delivery.

Analysis of the dexamethasone use in relation to the incidence of neonatal IVH is presented in Table 3.

There was no statistically significant difference in the incidence of IVH in relation to the use of dexamethasone.

Analysis of the incidence of IVH in preterm newborns from vaginal deliveries and cesarean section in relation to the gestational age is presented in Table 4.

Table 4

Gestational age and the incidence of IVH

Type of delivery	IVH	gestational age		
		n	Median	SD
Vaginal	No	20	29.00	1.542
	Yes	44	30.00	1.875
	Total	64	29.50	1.826
Cessarom section	No	27	30.00	3.711
	Yes	35	32.00	2.435
	Total	62	32.00	3.098

n – number of newborns; SD – standard

There was no statistically significant difference in the incidence of IVH in the preterm newborns from vaginal deliveries and cesarean section in relation to the gestational age, but there was a higher incidence of IVH in vaginal delivery of lower gestations.

In relation to the newborns body weight the incidence of IVH was monitored according to the mode of delivery and the results were presented in Figure 2.

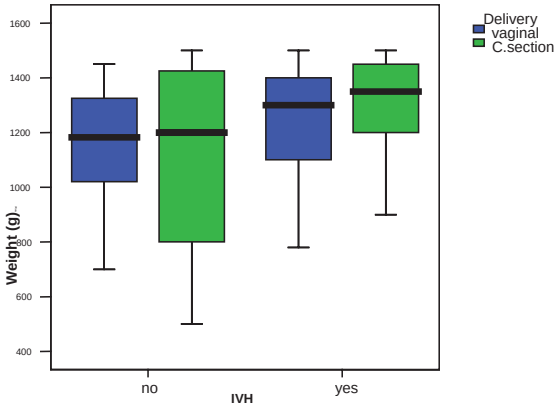

Fig. 2 – Body weight of the newborns and the incidence of intraventricular hemorrhage (IVH)

There was statistically significant difference in the incidence of IVH regarding the body weight of newborns.

Discussion

Prematurity is an important predisposing factor for the occurrence of cerebral damage in the neonatal period and

Table 3

The use of dexamethasone in relation to intraventricular hemorrhage (IVH)

Dexamethasone use	IVH [n (%)]		Total number of newborns (%)
	No	Yes	
No	38 (37.3%)	64 (62.7%)	102 (100)
Yes	9 (37.5%)	15 (62.5%)	24 (100)
Total	47 (37.3%)	79 (62.7%)	126 (100)

neurological sequelae are three times more frequent than in term neonates. A damage is caused by anatomical and physiological events in the brain, depending on the degree of maturation. Blood vessels state of the brain, cerebral tissue specificity and cerebrovascular autoregulation are the basis for understanding hemorrhage and hypoxic-ischemic cerebral changes in neonates.

The mode of delivery is one of major concerns in preterm birth modern obstetrics. It depends on obstetric indications, severity of maternal diseases and facility of hospital. Recommendations of mode of delivery in preterm birth still remain controversial and not yet clearly established. Some studies show a significant beneficial effect of cesarean delivery on neonatal mortality [11, 13]. Other studies report that mode of delivery affected very little adverse neonatal outcomes, either mortality or psychomotoric outcomes [4, 5]. There are limited studies evaluating the association between mode of delivery and neonatal outcomes in preterm birth.

The purpose of this study was to compare neonatal outcomes between modes of delivery in preterm births.

The main finding in this study is that the mode of delivery had no influence on the incidence of IVH in preterm neonates with vertex presentation. However, we registered a higher percentage of IVH at vaginal delivery compared to cesarean section at lower gestational age (from 29 to 31 weeks) and in relation to lower body weight of newborns that is consistent with the literature data.

Mother's age does not affect the incidence of neonatal IVH, regardless the mode of delivery.

Meta-analysis from Haas et al. [15] stated that administration of β-mimetics may facilitate a 48 h delay in delivery in comparison with no treatment/placebo, but do so at the cost of placing both the mother and fetus/neonate at greater risk of unwanted side effects than other types of tocolytics. It is also stated that the use of β-mimetic agents has been associated with an increased risk of many neonatal side effects including neonatal intraventricular hemorrhage. However, our study failed to confirm these data, since the results indicate that the tocolytic use (beta agonists) did not affect the incidence of IVH.

Our study indicates that the use of corticosteroid therapy has no effect on reducing the occurrence of IVH, despite some studies showing that corticosteroids reduce the incidence of IVH.

Although the majority of premature children had a low degree of IVH (I and II level), long-term prognosis is unpredictable.

We think that the mode of delivery in preterm birth should be determined by individual and optimal procedure.

Conclusion

Our data is consistent with the hypothesis that mode of delivery does not influenc IVH and consequently perinatal outcome in preterm neonates.

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ORIGINAL ARTICLE

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Measuring the osteochondral connection of the femoral head and neck in patients with impingement femoroacetabular by determining the angle of 2α in lateral and anteroposterior hip radiographic images

Merenje osteohondralnog spoja glave i vrata femura kod bolesnika sa femoroacetabularnim *impingement*-om određivanjem ugla 2α na lateralnim i anteroposteriornim radiografskim snimcima kuka

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Abstract

Background/Aim. Femoroacetabular impingement, a pathophysiological mechanism of small morphological changes of the hip leads to early arthritic changes. The aim of this study was to present a simple method for the quantification of femoral head and neck junction in patients with cam form of femoroacetabular impingement, in standardized anteroposterior and profile DUNN 90 radiograms of the hips. **Methods.** In standardized anteroposterior and profile DUNN 90 images of the hips we determined the angle of 2 alpha, defined by our own original method. We tested 141 hips in 81 patients without clinical signs of femoroacetabular impingement, and 153 hips in 76 patients with clinically clear signs of femoroacetabular impingement. **Results.** The value of the angle 2 alpha in anteroposterior hip radiograms was on average 113.7° for the patients with clinical symptoms of impingement, and 84.2° for the control group of patients ($p \leq 0.0001$), and in DUNN 90 profile radiography of the hip, the value of 2 alpha angle in the patients group was 97.2°, and 74.6° in the control group ($p \leq 0.0001$). The proposed method of determining the angle 2 alpha showed a high level sensitivity (97.8%) and specificity (98.7) and positive predictive value (98.6%). It was false positive in only 1.3%, and false negative in 2.12% of patients. **Conclusion.** Using standardized anteroposterior and profile radiographs of the hips, and without determination of femoral neck axis in patients with femoroacetabular impingement with the cam effect at the junction of the femoral head and neck, we proposed the method of measuring joint abnormalities of femoral head and neck junction, very capable to predict the disease development in an asymptomatic risk group of patients and high sensitive in the diagnosis of the disease in the group of patients.

Key words:
hip; osteoarthritis; diagnosis; methods; radiography.

Apstrakt

Uvod/Cilj. Femoroacetabularni *impingement* predstavlja patofiziološki mehanizam koji na terenu malih morfoloških promena u predelu kuka vodi do nastanka rane artroze kuka. Cilj rada bio je da se prikaže jednostavna metoda za kvantifikaciju morfoloških abnormalnosti na spoju femoralne glave i vrata kod bolesnika sa *cam* formom femoroacetabularnog *impingement*-a, na standardizovanim anteroposteriornim i profilnim DUNN 90 radiografskim snimcima kukova. **Metode.** Na standardizovanim anteroposteriornim i profilnim DUNN 90 snimcima kukova, određivali smo ugao 2 alfa. Testirali smo 153 kuka kod 81 bolesnika bez kliničkih znakova *impingement*-a, i 141 kuk kod 76 bolesnika sa jasnim kliničkim znacima femoroacetabularnog *impingement*-a. **Rezultati.** Vrednosti ugla 2 alfa na anterposteriornim radiografskim snimcima kukova je iznosila u proseku 113,7° za bolesnike sa kliničkim znacima *impingement*-a i 84,2° za kontrolnu grupu bolesnika ($p \leq 0{,}0001$), a na DUNN 90 profilnim radiografskim snimcima kukova, vrednost ulga 2 alfa u grupi bolesnika bila je 97,2° i u kontrolnoj grupi 74,6° ($p \leq 0{,}0001$). Predloženi metod određivanja ugla 2 alfa pokazao je visok nivo senzitivnosti (97,8%), specifičnosti (98,7%), te pozitivnu prediktivnu vrednosti od 98,6%; lažno je bio pozitivan kod svega 1,3%, a lažno negativan kod 2,12% bolesnika. **Zaključak.** Korišćenjem standardizovanih anteroposteriornih i profilnih radiografskih snimaka kukova, bez prethodnog određivanja osovine vrata butne kosti kod bolesnika koji imaju femoroacetabularni *impingement* sa *cam* osteohondralnom abnormalnošću na spoju femoralne glave i vrata, prikazali smo metodu merenja abnormalnosti spoja femoralne glave i vrata, sa visokom sposobnošću predviđanja razvoja bolesti u asimpomatskoj, rizičnoj grupi bolesnika, kao i sa visokim stepenom senzitivnosti u dijagnostici bolesti u grupi bolesnika.

Ključne reči:
kuk; osteoartritis; dijagnoza; metode; radiografija.

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Introduction

Femoroacetabular impingement (FAI) is a pathophysiological mechanism, manifested as a nonphysiological contact of the anterosuperior connection of the femoral head and neck on the anterior or anterosuperior edge of the acetabulum, as a consequence of the small, often hardly noticeable morphological changes at the proximal femur, acetabulum or in combination on the proximal femur and acetabulum at the same time. Given the primary localization of morphological changes, there are three basic forms of FAI [1]. First, Pincer, is the mechanism of FAI with primary morphological changes in the acetabulum in the form of localized overcoveradge of the femoral head, known as acetabulum retroversion or *coxa profunda* and *protrusio acetabuli*. Second, cam, is mechanism of FAI with morphological changes in proximal femur in the form of osteochondral abnormalities on the femoral head and neck connection (Figure 1), which reduces the space between the anterosuperior edge of the acetabulum and the anterolateral femoral head and neck connection. During movement or flexion, internal rotation and adduction of the thigh in the hip, this osteochondral prominence goes under the initially intact labrum, putting pressure on it, and then, lifts the labrum adjacent articular cartilage, from the subchondral bone [1–5]. The true reason for this osteohondral prominence occuring is unknown, but it is thought that it occurs in: silent forms of femoral head epiphysiolysis in adolescence (SLIP), in Leg Calve Perthes disease, in poorly healed fractures of the femoral neck, in avascular necrosis of the femoral head and others [4, 6–8]. Third, a mixed mechanism of FAI is a combination of the two previous morphotypes with changes in the acetabulum and in the femoral head and neck connection, and it appears most frequently in daily clinical work.

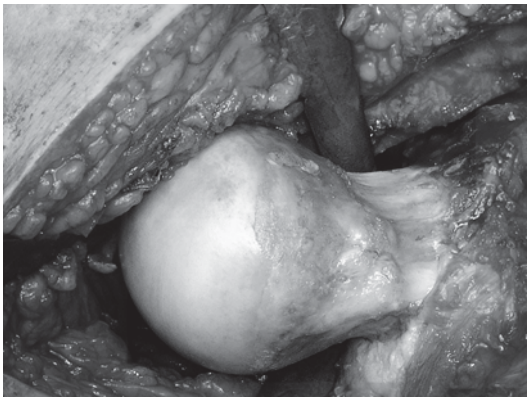

Fig. 1 – Osteochondral deformity at the anterosuperior side of the femoral head and neck junction

Cam FAI is more common among young people, often very active persons and it is manifested clinically as a feeling of jumping, snapping or groin pain [1], which can be reproduced by the so-called impingement test with the leg in internal rotation, hip in flexion ranged of 30°–90° and different values of thigh adduction. The appearance of the FAI and the consequent damage to the hip joint are already documented in the form of silent and subacute cases of femoral head epiphysiolysis in adolescents [4]. On the other hand, a number of studies suggest that mild, barely visible, anatomical changes in the hip joint, could be a significant cause of arthrosis in the hip in the latter ages of life [3, 9]. Stulberg at al. [9] describe the so-called "pistol grip" deformity, of the proximal femur, which is present in 40% of the patients who develop hip arthrosis.

In the literature and daily clinical practice descriptive the used terms that only describe the deformity at the femoral head and neck junction are "pistolgrip", "post-slip", "head tilt" which are easily observed on the standard hips anteroposterior (AP) radiographic records [6, 9–11] but cannot be used to quantify the severity of hip deformity. Goodman et al. [12] state that the basic deformity is a subclinical form of the femoral head epiphysiolysis in the adolescents (SLIP) in the sagittal plane, therefore on the anterior side of the femoral neck, and, if so, it is not necessary to be visible in AP hip images.

Radiological methods and criteria for quantification of morphological changes on the proximal femur and the acetabulum in patients with anterior impingement are described by several authors [13–17]. Nötzli et al. [13] in 2002 promoted the method of determining the angle α, which measures the osteohondral prominence at the junction of the head and neck of the femur in the nuclear magnetic resonance (NMR) cones. The imperative of this method is that the NMR images must precisely plot the femoral neck axis as the one of the arms of the angle α. The problem and disadvantage of the method is an insufficient precision in determining the angle α, given that there is no "gold standard" in determination of the femoral neck axis in the NMR images, as well as in standardized AP and lateral (cross table leg, Dunn 90, Dunn 45, frog-leg) radiographic hip records. It turned out that the method by which the femoral neck axis always passes through the center of rotation of femoral head is not reliable when it comes to hip morphology that is similar to cam FAI morphotype [6, 15, 16]. This suggests that neither the angle α values measured by this method in patients with FAI form of cam are not reliable enough [6, 9, 12].

Therefore, we defined the double angle α (2α), as the sum of two angles, the angle α defined in the literature, and the angle which sits on the angle α just opposite to the femoral neck axis and which is equal to the angle α, since the marked axes symmetrically divides the femoral neck into two equal halves in the healthy population. Then, we assumed that it is possible to numerically measure, without prior determination of the femoral neck axis, using this angle of 2 alpha, morphological changes on the anterolateral connection of the head and neck of the femur, on standardized radiographic AP and lateral recordings.

The aim of this paper was to show that in patients with clinical symptoms and signs of FAI and with morphological changes at the junction of the head and neck of the femur, an osteohondral abnormality at this junction can be measured using the classic, standardized AP and lateral radiographic records [16, 17] by determining the angle of 2 α, without prior determination of the femoral neck axis, and also that the angle 2 α values, obtained in a group of clinically symptomatic patients significantly differ from that of the control group of people with healthy hips. Also, we assumed that, due to

anatomical differences in the thickness of the femoral neck occur in AP and lateral radiographic records of the hip, and the difference in the values of the angle α in these two recordings occurs either, we suggested two upper limits for the normal values of the angle 2 α in AP and lateral radiographic records of the hips. To compare our method of determining the angle 2 α, with the method of measuring the angle α we determined in our material, at the same time, the angle α in AP and in lateral DUNN 90 radiographic hip records.

Methods

For this study we chose two groups of examinees. One group consisted of patients with positive clinical symptoms and radiological changes in the hips, which corresponded to the cam form of the FAI and the control group of healthy subjects. Criteria of inclusion patients with positive clinical findings were: groin pain, which lasted at least 3–18 months before setting suspicion to FAI, a positive impingement test [18], internal rotation of the symptomatic hip was less than 20° at the hip flexion on 90°, present radiographic signs of cam morphotype FAI and absent signs of radiographic changes in the morphology of the acetabulum. Within these radiographic criteria a normal acetabulum is meant the absence of *coxa profunda*, *protrusio acetabuli*, retroversion of the acetabuli and the value of center edge (CE) angle of 25°–35° on standardised AP radiographic recordings of the hips [16, 19]. Criteria for exclusion from the study were: previous history and/or surgery of the hip, posttraumatic conditions, the CE angle less than 25° or greater than 35°, clear signs of femoral head avascular necrosis, septic or rheumatoid arthritis and advanced osteoarthritis (Tönnis degree ≥ 2). The group of subjects with cam FAI form (patient group), consisted of 81 patients (49 men and 32 women), aged 30.3 years ± 8.3 years (range 19–55 years), where for the purposes of this study we examined 153 radiographic records of the hips of which there were 70 right hips and 83 left hips, and 9 hips were excluded from the study. The second group of subjects (control group) consisted of 76 subjects with asymptomatic, healthy hips with 40 men and 36 women, average age, 34 ± 5.8 years (range 21–54 years), in who we analyzed 141 hips, 68 right and 73 left. The study included subjects with saddle pain, lower back and ischialgic region pain with radiographic images made from differential diagnostic reasons. The criteria for inclusion in the control group were: asymptomatic, painless hip, internal rotation greater than 20° at 90° flexion of the leg in the hip, and negative impingement test. Eleven hips are excluded from the study because internal rotation of the hip was lower than 20°, and in four of the subjects groin pain during forced adduction of the thigh in the hip was present, with radiographic suspicion to Pincer FAI form. Internal rotation of the thigh in the hip in both tested groups was on average 32 ± 9° (range 20° to 40°) for the control group, and 9.4° ± 6.7° (range 0°–15°) for the group of patients.

For all the subjects of both groups radiographic hip images were made: one standardized AP radiographic image of the hip [15], with the patient lying on his back with feet in internal rotation of 15°, the distance between the focus of the X-ray apparatus and X-ray film was 120 cm, with central ray directed at the center line of the body on the half way between the bispinal line and pubic symphysis. In order to assess effects of pelvic rotation and tilt on the values of the angle 2 α on each recorded AP radiographic image of the hips, the distance from the top of the upper edge of the pubic symphysis to the middle of the sacrococygeal joint was measured, where the normal value of 3–5 cm in men and 2–3 cm in women [20] was taken, and the central axis of the body was going through the pubic symphysis. The second radiographic image that we used for this study was the lateral Dunn Ripstein Müller 90° (DUNN 90) radiographic record of the hip [7], which was made with a patient lying on his back, hips and knees flected at 90°, and upper thigh abducted on 20°, with the feet in neutral rotation. The distance focus of the X-ray apparatus X-ray cassette was 120 cm, and central X-rays was aimed at the middle of the pubic symphysis.

The method of determining the angle 2 α (Figure 2) was as follows: After making AP and lateral hip radiographs

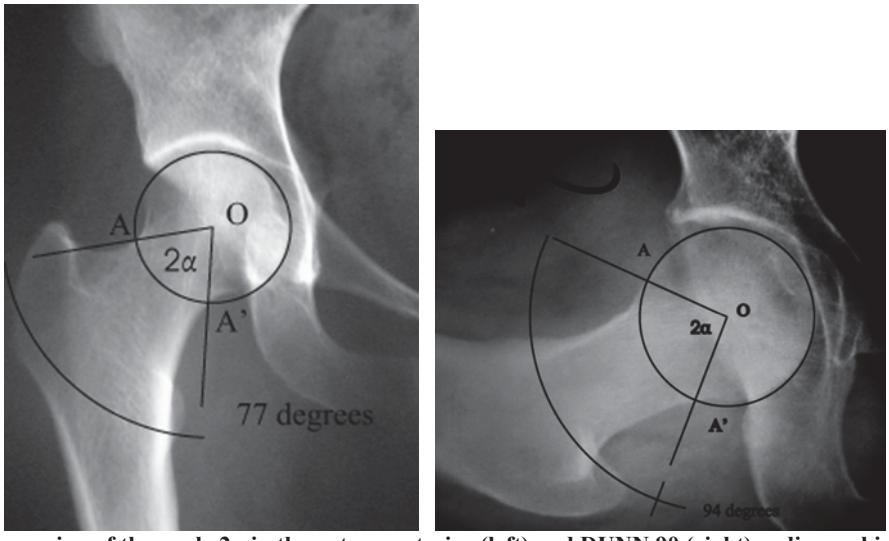

Fig. 2 – Measuring of the angle 2α in the anteroposterior (left) and DUNN 90 (right) radiographic images of the hips in the control group of the subjects (explanation of the method is given in the text)

(DUNN 90 in the control group, the angle 2 α was determined using Mosse concentric circles, the center of rotation of the femoral head (point O) was determined, using a compass, circular line was plotted on the edge of the femoral head, and the intersections of these lines with the edges of the femoral neck were plotted and marked as points A and A'. A ruler was used to draw lines connecting the center of rotation of the femoral head with points A and A', and then with protractors of the angle AOA' or angle 2 α was measured. The angle 2 α was determined in the same way in DUNN 90 or lateral radiographs of the hips. To determine this angle it was not necessary to determine the femoral neck axis. The method of determining the angle 2 α was the same in the group with clinically suspected to positive form of cam FAI (Figure 3), but the point A is marked in the place of circular line of the femoral head intersecting osteochondral prominence at the junction of the head and neck of the femur [13, 21, 22]. These points represent pathoanatomical end point of femoral head sphericity, ie. point up to which the femoral head slips below the labrum in the acetabulum, without touching the edge of the acetabulum with its osteochondral prominence present at the juncion of the femoral head and neck.

The angle α (Figure 4) was determined using the same method described by Nötzli et al. in 2002 [13]: after determining the femoral head rotation center O and the circular line marking the edge of the X-ray projection of the femoral head, the central point between two points in the narrowest part of the femoral neck was determined and marked as point B. The resulting middle point of the neck was connected with the center of rotation of the femoral head and thus the femoral neck axis was obtained and marked as OB. From the center of rotation of the femoral head a line was drawn passing through the point A. The angle between the line AO and the line of femoral neck axis OB is the angle α.

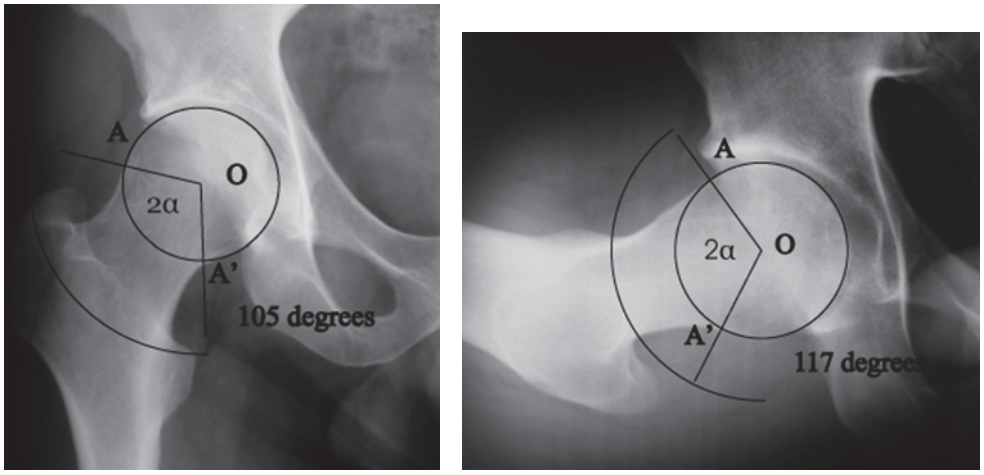

Fig. 3 – Measuring of the angle 2α in the anteroposterior (left) and DUNN 90 (right) radiographic images of the hips in patients with Cam form of impingement femoroacetabular (explanation of the method is given in the text)

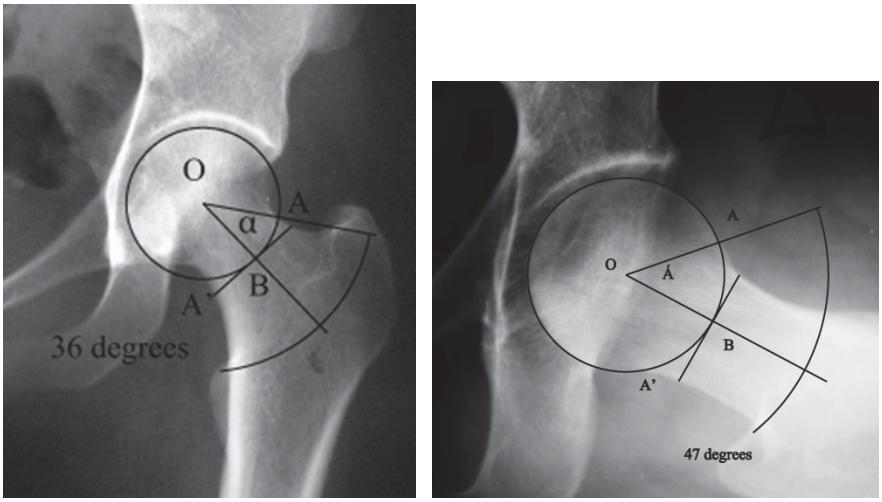

Fig. 4 – Measuring of the angle α by Nötzli method on the anteroposterior (left) and DUNN 90 (right) radiographic images of the hip in the control group of subjects (explanation of the method is given in the text)

For statistical processing of the obtained data, we used several statistical parameters. Normality of distribution of the obtained data was checked using the Kolmogorov-Smirnov test. Student's *t*-test was used to test the hypotheses and to test intra- and interobserver agreement. To determine

the intraobserver and interobserver agreement in the study, we included two independent orthopedic surgeons who, at a 3-week intervals, performed two measurements of the angle 2 α on standardized AP and lateral DUNN 90 radiographic images of the hip. To measure the validity of the test, ie. to determine the sensitivity, specificity and other parameters, we formed a contingency table. To correlate values of the angle 2 α, the angles α and α' the Pearson's correlation coefficient was used.

A confidence interval of 95% ($p < 0.05$) was taken. The statistical power of the test was greater than, or equal to 80%. Processing of graphics image was done in the video image processing Corell Draw 11 and all the data were processed in the computer statistical program SPSS 8.0 for Windows.

Results

Using the Kolmogorov Smirnov test we obtained a normal distribution of all measured values of the angle 2 α, the angle α, as in the standardized AP radiographic images of the hip, and in lateral DUUN 90 radiographic images of the hip in the control group and in the group of patients.

Before the study began, we had conducted a pilot study whith the aim to confirm the assumption that the angle 2 α in fact is a sum roughly equal to two angles that lie at the opposite sides of the femoral neck axis and goes from the center of rotation of the femoral head. We measured the angles α and its opposite angle α' in AP and DUNN 90 radiographic images of the hips in the control group of patients. We used 50 right and 50 left hips with AP and lateral DUNN 90 radiographic images. Statistical analysis showed that the mean value ($\bar{x}$) of the angle α in the AP recordings was 42.5° ± 3.42° with a standard error of the mean (SE) of 0.284° and of the angle α', $\bar{x}$ = 41.7° ± 3.29°, SE = 0,0273° and no significant difference in values between these angles was found ($p = 0.694$). The values of the angle α in the DUNN 90 radiographic recordings were similar to, $\bar{x}$ = 39.23° ± 4.69°, SE = 0.396°, and the angle α', $\bar{x}$ = 38.29° ± 3.57°, SE = 0.302°, and there was no significant difference, either, in the values of the two angles in DUNN 90 lateral radiographic images of hip ($p = 0.755$), suggesting that the angles α and α' are approximately equal angles, thus the summ of these two angles is the angle 2 α, which was the aim of this study.

The average value of the angle 2 α, in AP radiographic hip images of the control group of subjects (Table 1) was for the right hip $\bar{x}$ = 83.5° ± 5.7° (range 70°–95°), for the left hip for $\bar{x}$ = 84.3° ± 5.5° (range 72°–95°) while the difference was not found in the values of angle 2 α for the left and right hip ($p = 0.34$), and the average value for the left angle 2 α and right, cumulatively, in all 141 hips was $\bar{x}$ = 84.2° ± 5.6° (range 70°–95°), with SE = 0.471°. In the cam FAI group of subjects in standardized AP radiographic images of the hip angle 2 α values are (Table 1), collectively, for the left and right hip observed $\bar{x}$ = 113.7° ± 14.3° (range 85°–146°), with SE = 1.156°, where the values for the right hip were $\bar{x}$ = 114.5° ± 13.3°, and for the the left hip $\bar{x}$ = 113° ± 15.3°, with no significant differences in the values of the angle 2 α between the left and right sides ($p = 0.30$).

For lateral DUNN 90 X-ray shot of the hips, in the control group of patients (Table 1), the obtained values of the angle 2 α, for the right hip were $\bar{x}$ = 74.5° ± 6.3°, for the left hip $\bar{x}$ = 75.8° ± 5.8°; there was no difference in the value of angle 2 α between the left and right sides ($p = 0.13$), and the measured values of the angle 2 α for the left and right sides, cumulatively, were $\bar{x}$ = 75.3° ± 6.9° with SE = 0.581°. We found a significant difference ($p < 0.0001$) for values of the angle 2 α measured in AP and DUNN 90 radiographic recordings of the hip in the control groups. In the group with cam FAI in lateral DUNN 90 radiographs of the hips the average value of angle 2 α for the left and right hip, cumulatively, was $\bar{x}$ = 97.2° ± 11.8° (range 64° to 126°), with SE = 0.954, the values of the same angle for the right hip were $\bar{x}$ =

Table 1

The values of the angle α in the anteroposterior (AP) or DUNN 90 radiographic images in the control subjects and patients with clinical signs of Cam FAI

Angles	Radiographic images		Control group		Cam FAI group	
			Right side (n = 68)	Left side (n = 73)	Right side (n = 70)	Left side (n = 83)
2 α	AP	Range	70–95	72–95	93–142	90–146
		$\bar{x}$ ± SD	83.5 (± 5.7)	84.3 (± 5.5)	114.5 (± 13.3)	113.1 (± 15.3)
		SE	0.47			
α		Range	30–50	35–53	50–98	47–106
		$\bar{x}$ ± SD	42.3 (± 3.34)	42.3(± 3.2)	71(± 13.4)	70.6 (± 14.6)
		SE	0.291			
2 α	DUNN 90	Range	60–90	64–90	76–126	64–125
		$\bar{x}$ ± SD	74.5 (± 6.3)	75.8 (± 5.8)	97.8 (± 11.11)	96.6 (± 12.6)
		SE	0.581			
α		Range	30–49	31–51	48–89	34–90
		$\bar{x}$ ± SD	38.8 (± 2.2)	39.6 (± 2.0)	60.9 (± 10.5)	62.1 (± 10.4)
		SE	0.176			

DUNN 90 – Dunn Rippsetin Mueller radiographic image; Cam FAI – cam form of femoroacetabular impingement; $\bar{x}$ – mean; SD – standard deviation; SE – standard error of the mean

97.8° ± 11.11°, and for the left hip $\bar{x}$ = 96.6° ± 12.6°. A significant difference was found in the values of angle 2 α (p < 0.00001) measured in standardized AP radiographs of hips in the control group and cam FAI group of patients, as well as values obtained by the same angle in lateral DUNN 90 hip radiographs (p < 0.0001) of the control group and the group of patients.

The values of angle α, assesed by Nötzly method, in our recordings for the AP hip radiographic images in the control group of subjects (Table 1), were for both, left and right hip, $\bar{x}$ = 42.4° ± 3.28° with SE = 0.291°, which are almost identical values received by Nötzly et al. [13] (42.2° ± 2.2°), and the value of the same angle on the DUNN 90 radiographic images were for the control group, for both hips $\bar{x}$ = 39° ± 2° with SE = 0.176°. The average value of the angle α in the cam FAI group of patients was in average, for AP, $\bar{x}$ = 70.8° ± 14° with SE = 1.132°, and for DUNN 90 hip radiographs $\bar{x}$ = 61.54° ± 10.9° with SE = 0.88°, and with a significant difference compared to the control group of subjects (p < 0.001). Using comparative analysis of the value of angle α and 2 α using the Pearson's correlation coefficient, we obtained very high level of agreement in the values of these angles within the control and patient groups for the AP (r = 0.926, p < 0.01) and DUNN 90 (0.956, p < 0.01). radiographic recordings of hips.

To obtain the maximum and minimum limit value of the angle 2 α in our material, at the confidence interval of 95%, we enlarged the average value of angle 2 α in the control group of healthy subjects, for 2 standard deviations. So, we got the maximum value of the angle 2 α in AP radiographs of the hips of 94.6° and the minimum value of angle 2 α of 73°. The value of 95° was taken as maximum upper, marginal, normal, possible value of the angle 2 α in the group of healthy hips for standardized AP radiographic images of the hips. Limits for the angle 2 α on DUNN 90 radiographic images of the hips were determined in the same way, and amounted to 75.3° ± 13.8° (two standard deviations) with the minimum possible value of this angle of 61.5°, a maximum value up to 89.1°, so we have taken 90 degrees as the upper limit, normal value of angle 2 α, for the lateral DUNN 90 hip radiographic images of the control group of subjects.

These limit values of the angle 2 α were used to form a contingency table 2 × 2 and to determine the validity parameters of a diagnostic test measuring angle 2 α. A high ability of the resulting test to predict the disease in the group of patients (sensitivity test) was obtained 97.8% for AP and 97.4% for DUNN 90 radiographic images of the hips, as well as high capacity of the test to diagnose healthy persons in the control group of subjects (specificity test), 98.6% for the AP and 87.4% for DUNN 90 hip radiographs. The ability of the test to predict the disease was 98.6%, for AP radiographs of the hips and 96.5% for DUNN 90 radiographs of the hips, and the test was false positive in 1.3% for AP and 3.6% for DUNN 90 radiographs of the hips, and a false negative for AP 2.12% and 2.63% for DUNN 90 radiographic images of hips.

Intraobsever agreement of the received values showed no statistically significant differences in the measurement of the angle 2 α in the control group and the group of patients, within the same examiner, between the first and second measurements, with a delay of three weeks between the measurements (for the first examiner p = 0.2, for other examiners p = 0.14). Interobserver measurements showed no significant differences in the values obtained in the measurement of the angle 2 α between the examiners (p = 0.18 for the first measurement and p = 0.33 for the second measurement).

Discussion

A critical point beyond which the rest of the femoral head in the patients with cam FAI form cannot slip without resistance in the acetabulum during movements or flexion, adduction and internal rotation, and in doing this in which, the process of mechanical damage of the labrum and cartilage of acetabulum began, is a marked point A in the enclosed radiographic images of the angle 2 α measurements. In the patients cam type, there is osteohondral prominence at the junction of head and the neck of the femur as a consequence of morphological changes such as: wide neck, formation of osteophytes or posterior dislocation of the femoral head, which are the primary reasons for the angle 2 α to take on pathological values. On the other hand, some other FAI reasons such as acetabulum retroversion, *coxa profunda*, *protrusio acetabuli*, osteophytes of the acetabulum, will not influence the value of the angle 2 α, but can explain the existence of clinical signs of FAI such as groin pain, positive impingement test and the reduction of internal rotation of the hip in normal limits of the angle 2 α which is characteristic of Pincer FAI form.

Stulberg et al. [9] introduced the term "pistol-grip deformity" to describe the radiographic image abnormalities in the junction of the femoral head and neck in the standardized AP radiographic hip images. Although they found that the predominant deformity is present in young active men and in many patients with a so-called "idiopathic" arthrosis of the hip, they did not try to elucidate the pathological mechanism underlying this deformity. There were anatomical differences in the femoral neck diameter in the frontal and horizontal planes [23].

Structural abnormalities at the junction of the head and neck of the femur in mature skeletal individuals are associated with arthrosis of the hip [1, 2, 5, 9, 11, 24, 25],therefore, further exploration of the disorder etiology is imperative to determine the occurrence of abnormalities, the time of its origin, method of well-timed diagnosis, but not just to describe but also to quantify.

Nötzli et al. [13] described the angle α, and the index of offset as an excellent method for measuring abnormal femoral head and neck junctin in radial MRI hip cuts, and obtained the average value of angle α 42.2° ± 2.2° (range 33° –48°) which is almost identical to the value obtained in this study in the AP radiographic images of the hips in the control group measuring of the angle α. If the mean value of the angle α in the paper of Nötzli et al. [13] is multipled by 2 the value of Nötzli is received angle α two times multiply, which is 84.4° ± 4.4°. On the other hand, in our material, the mean 2 α angle value was 84.3° ± 5.5° (range 70°

to 98°). After Nötzli et al. [13] paper was published, many authors began to use this method of measuring osteohondral prominence at the junction of femoral head and neck, not only on NMR and CT images of the hips, but on the AP radiographic hip and lateral images of the hips [22, 26–29]. The measuring the angle α in these papers is not standardized, and thus the lack of precise determination of the femoral neck exists. All authors are setting up the axis through the center of rotation of femoral head and the midpoint of the femoral neck at its narrowest part. Unfortunately, this way of measuring the femoral neck axis is not accurate when it comes, at least, in a number of patients with cam FAI form, backward and/or downward sliding of the femoral head epyphysis, over the period of adolescence, which is one of the reasons for the femoral head center to relocate outside of the axis of the femoral neck and which also happens in patients with poorly healed femoral neck fractures [12, 23, 29, 30]. Murray [6] has determined in AP radiographic images the axis of the femoral neck using the midpoint between the top of the greater and lesser trochanter, on the one hand, and the midpoint of the narrowest part of the femoral neck, on the other, and then he determined the femoral head "ratio" to show that the femoral neck axis does not go always through the center of rotation of femoral head in a number of patients with already formed hip arthrosis [6, 10]. Using skeletal preparations Goodman et al. [12] showed epyphysiolysis, the deformity of femoral head and neck junction to be predominantly anteriorly positioned and 3-dimensional, and as the femoral head slides back and forth, than the center of rotation of femoral head is positioned further from the femoral neck axis. Therefore, they recommend the use of lateral radiographic image to describe the hip deformity in the axial plain in front of the femoral head and neck junction which indicates "anterior" edge mechanism known in the literature as FAI [12].

Measurements carried out and presented in this paper were aimed to propose a modified method of measuring the value of osteohondral prominence at the junction of the head to the neck of the femur, which is not a prerequisite for determining the femoral neck axis and the possible consequent inaccuracy. The results presented in this paper show a significant difference in the values of the angle 2 α on AP and DUNN 90 lateral hip radiographic images within the control group of subjects which is a consequence of anatomical differences in the thickness of the femoral neck, and not a consequence of structural abnormalities [23]. Also, we can concluded that there is a significant difference in the values of angle 2 α between the cam group of patients with FAI hip morphology and groups of asymptomatic individuals in AP and DUNN 90 radiographic images of the hips, as a consequence of structural and morphological osteochondral prominence at the junction of femoral head and neck as the only pathoanatomical substrate that was detected in this region. High degreee correlation of the presented method, with the already accepted method of determining angle α, indicates the applicability of the presented method in clinical practice.

In the absence of the gold standard, and analysing the value of angle 2 α in the control group of patients measured in AP and DUNN 90 radiographic hip images, we obtained the top, normal value of this angle for AP hips radiographs to be 95°, and for DUNN 90 hips images was 90° and that each measured value of the angle 2 α over proposed can be considered as pathological. This means that in the case of symptomatic patients with clinical signs of groin pain and positive impingement test, the values over the specified for the angle 2 α are considered as abnormal with high degree of sensitivity for the cam FAI form. If, however, there is an asymptomatic hip, in which, as noted incidental radiographic finding of the existence of values above the recommended angle 2 α, then the probability that a person will develop clinical form of FAI is 98.6% for AP, and 96.5% for the DUNN 90 radiographic images of the hips, with 1.3% probability for AP, and 3.6% for DUNN 90 radiographs of the hips, that the measured value gave a false positive result.

If a significant number of authors suggest the abnormality of the junction of femoral head and neck as a factor in the development of hip arthrosis, it is necessary to make efforts toward earlier detection and recognition of deformity, as to its earlier treatment and, if possible, which is most importantly, to its prevention [1, 4, 10, 11, 25, 31–34]. Unfortunately, so far, a generally accepted method for identification the risk group of hips has not been developed, and there are not yet defined radiographic criteria (lack of "gold standards") of the limit values for osteochondral prominence at the junction of the head and neck of the femur. The method of determining the angle 2 α [35] numerically quantifies the relationship between the lateral and anterior femoral head and neck using it for AP and DUNN 90 radiographs of the hips, and the technique of measuring angle 2 α is simple, which is confirmed by a high degree of intra- and interobserver agreement requiring no determination of the femoral neck axis as it is the case for the measurement of the angle α.

Conclusion

In this paper we proposed a relatively simple method and the limit values for measuring osteochondral prominence at the junction of the head and neck of the femur, which can be defined in the radiographic images and be used in everyday clinical practice.

This method has a high ability to predict disease development in an asymptomatic risk group of patients and a high sensitivity in the diagnosis of the disease in the group of patients.

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Adherence to depot versus oral antipsychotic medication in schizophrenic patients during the long-term therapy

Pridržavanje farmakoterapije šizofrenih bolesnika u fazi održavanja depo antipsihoticima u odnosu na peroralne antipsihotike

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Abstract

Background/Aim. There is a high rate of schizophrenic patients who do not adhere to their prescribed therapy, despite the implementation of antipsychotic long-acting injections and the introduction of atypical antipsychotics. The aim of this study was to investigate the differences in sociodemographic, clinical and medication adherence variables between the two groups of schizophrenic patients on maintenance therapy with depot antipsychotic fluphenazine decanoate and oral antipsychotics only as well as a correlation between the medication adherence and other examined variables. **Methods.** A total of 56 patients of both genders, aged < 60 years, with the diagnosis of schizophrenia (F20) (ICD-10, 1992) clinically stable for at least 6 months were introduced in this cross-sectional study. The patients from the depot group (n = 19) were on classical depot antipsychotic fluphenazine decanoate administering intramuscularly every 4 weeks (with or without oral antipsychotic augmentation) and the patients from the oral group (n = 37) were on oral therapy alone with classical or atypical antipsychotics, either as monotherapy or combined. The Positive and Negative Syndrome Scale (PANSS) was used to assess symptom severity. Item G12 of the PANSS was used to assess insight into the illness. The patients completed the Medical Adherence Rating Scale (MARS) was used to assess adherence to the therapy. A higher MARS score indicates behavior [Medical Adherence Questionnaire (MAQ subscale)] and attitudes toward medication [Drug Attitude Inventory (DAI subscale)] that are more consistent with treatment adherence. The exclusion criteria were determined. The Pearson's χ^2 test was used to compare categorical variables, Student's *t*-test to compare continuous variables and Pearson's correlation to test the correlation significance; $p = 0.05$. **Results.** Significant between-group differences in age, illness duration, chlorpromazine equivalents, PANSS score and DAI subscore were found. Item G12 of the PANSS subscore and MARS score correlated significantly negatively. A significant positive correlation between receiving depot antipsychotic and DAI subscore as well as between illness duration and both DAI subscore and MARS score were also found. **Conclusion.** Schizophrenic patients on classical depot antipsychotic maintenance therapy might present subpopulation of patients with significantly longer illness duration, more favorable medication attitude and outcome in relation to those on oral antipsychotics alone.

Key words:
schizophrenia; therapeutics; pharmaceutical preparations; antipsychotic agents; drug utilization; delayed-action preparations.

Apstrakt

Uvod/Cilj. Postoji visoka stopa šizofrenih bolesnika koji se ne pridržavaju propisane terapije uprkos primeni antipsihotika u obliku injekcija dugog dejstva i uvođenja atipičnih antipsihotika. Cilj ovog rada bio je da se ispitaju razlike u sociodemografskim, kliničkim i varijablama pridržavanja terapije između dve grupe šizofrenih bolesnika na terapiji održavanja depo antipsihotikom flufenazin-dekanoatom i samo oralnim antipsihoticima, kao i da se utvrdi korelacija između pridržavanja terapije i drugih ispitivanih varijabli. **Methode.** Ova studiju preseka obuhvatila je 56 bolesnika oba pola, starosti < 60 godina sa dijagnozom šizofrenije (F20) (MKB-10, 1992) koji su bili klinički stabilni najmanje šest meseci. Bolesnici depo grupe (n = 19) bili su na klasičnom depo antipsihotiku flufenazin-dekanoatu koji se daje intramuskularno na četiri nedelje (sa ili bez oralne augmentacije antipsihoticima), a bolesnici oralne grupe (n = 37) bili su samo na oralnoj terapiji klasičnim ili atipičnim antipsihotikom, bilo kao monoterapija ili u kombinaciji. Skala pozitivnog i negativnog sindroma (PANSS) korišćena je za procenu težine simptoma. Stavka G12 PANSS korišćena je za procenu uvida u bolest. Skala procene pridržavanja lečenja (MARS) koju popunjava bolesnik, upotrebljena je za procenu pridržavanja

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terapije. Viši MARS skor ukazuje na ponašanje [Upitnik pridržavanja lečenja (MAQ subskala)] i stavove prema terapiji [Inventar stavova prema terapiji (DAI supskala)] koji su više u skladu sa pridržavanjem lečenja. Kriterijumi isključivanja bili su određeni. Pearson-ov χ^2 test je korišćen za poređenje kategorijskih varijabli, Student-ov *t*-test za poređenje kontinuiranih varijabli, a Pearson-ova korelacija je korišćena za testiranje značajnosti korelacije; $p = 0,05$. **Rezultati.** Nađene su značajne razlike između grupa u starosti, dužini trajanja bolesti, ekvivalentima hlor-promazina, skoru PANSS i supskoru DAI. Supskor G12 stavke PANSS i skor MARS negativno su korelirali. Takođe, nađena je i značajna pozitivna korelacija između primanja depo antipsihotika i supskora DAI, kao i između dužine trajanja bolesti i supskora DAI i skora MARS. **Zaključak.** Šizofreni bolesnici na terapiji održavanja klasičnim depo antipsihotikom mogu predstavljati suppopulaciju bolesnika sa značajno dužim trajanjem bolesti, povoljnijim stavom prema lečenju i ishodom u odnosu na one bolesnike koji su samo na oralnim antipsihoticima.

Ključne reči:
shizofrenija; lečenje; lekovi; antipsihotici; lekovi, korišćenje; lekovi, produženo dejstvo.

Introduction

In the treatment of schizophrenia, adherence is identified as the most important modifiable risk factor [1]. Non-adherence patients have an average risk of relapse that is 3.7 times greater than that of good adherence patients [2]. Medication adherence behavior is a multifactorial phenomenon. Meta-analytical studies [3, 4] on risk factors for non-adherence to medication in patients with schizophrenia showed a consistent influence of certain variables (insight and therapeutical alliance, for example), while study results for other variables such as age, gender, marital status, duration of illness are too inconsistent to let drawing a conclusion regarding their influence on adherence behavior.

Depot formulations (long-acting injections) of classical (first-generation) antipsychotics were introduced in the 1960s to promote medication adherence. The use of classical depot antipsychotics is less frequent in the last decade, perhaps owing to the introduction of oral atypical antipsychotics. A prospective, observational study of the treatment for schizophrenia by Shi et al.[5] found that only 26% of patients were treated with depot formulations of typical antipsychotics at least once during the designated three-year period. Clinicians use long-acting antipsychotic injections to manage fewer than 1 in 5 patients with schizophrenia having episodes of medication non-adherence [6] despite treatment guidelines for schizophrenia recommend that clinicians strongly consider depot therapy for patients who may be non-adherent to antipsychotic treatment regimens [7].

Depot antipsychotics are unable to prevent relapse completely; even in clinical trials there are 20%–25% of patients who relapse, despite receiving depots. According to a large, prospective, observational study of schizophrenia patients treated in ten European countries, the European Schizophrenia Outpatient Health Outcomes (EU-SOHO), reported that more than 50% of patients who were initiated on classical depot antipsychotics or were switched to them were treated with depot formulations to help address problems of nonadherence, rather than for lack of efficacy or other reasons [8]. Systematic literature reviews of randomized controlled trials and observational studies of classical antipsychotic long-acting injections vs. oral antipsychotics in schizophrenia [9, 10] suggested that classical depot antipsychotics may improve outcome and significantly reduce relapse rate compared with oral antipsychotics.

Over the past decade, a substantial number of patients switched from classical depot antipsychotics to oral atypical antipsychotics. However, one number of patients remains on first- generation depot antipsychotic therapy long term.

The aim of this study was to investigate the differences in sociodemographic, clinical and medication adherence variables between the two groups of schizophrenic patients on maintenance therapy with depot antipsychotic fluphenazine decanoate (group D) and oral antipsychotics only (group O) as well as correlation between the medication adherence and other examined variables.

Methods

A cross-sectional assessment of patients with schizophrenia on maintenance treatment was undertaken. The patients recruited for this study were regular on scheduled outpatient visits for depot administration and/or prescription of oral antipsychotic therapy and remained covered by the same doses of antipsychotic drugs that had been applied at least 6 months before inclusion.

The inclusion criteria were that participants of both genders were aged < 60 years, fulfilled International Statistical Classification of Diseases and Related Health Problems, 10th Revision 1992 (ICD; World Health Organization) [11] criterion for schizophrenia (F 20), had been clinically stable for 6 months, were currently prescribed either classical depot antipsychotic therapy or oral antipsychotic therapy alone.

The sample consisted of 56 patients. The patients of the depot group (the group D) (n = 19) were receiving fluphenazine decanoate administering intramuscularly every 4 weeks with or without oral antipsychotic augmentation. The patients of the oral group (the group O) (n = 37) were using antipsychotics either as monotherapy or in combination.

The patients were prescribed oral classical antipsychotics (high potency-fluphenazine and low potency-chlorpromazine or levomepromazine) and atypical antipsychotics (risperidone and clozapine). Concomitant non-antipsychotic psychotropic therapy was administered to the patients included antidepressants or/and mood stabilizers to attain better symptom control, as well as anticholinergics for treating of extrapyramidal unwanted effects.

The dosage of each antipsychotic was converted to its chlorpromazine equivalents [12, 13].

Apart from the registration of both sociodemographic and clinical data from medical records, the Positive and Negative Syndrome Scale (PANSS) [14] was performed to assess symptom severity and the patients completing the Medical Adherence Rating Scale (MARS) [15] was used to assess adherence to medication.

The exclusion criteria were the following: a history of drug abuse, evidence of organic brain disorder including mental retardation, severe somatic disease.

Oral and written informed consent was obtained from all participants prior to the participation in the study.

The study was conducted at the Outpatient's Department of Clinic for Psychiatry, Clinical Centre of Serbia, Belgrade, Serbia, from 2008 to February 2011.

Assessment

The PANSS [14] is a 30-item (7 positive, 7 negative, and 16 general psychopathology symptom items) observer-rated scale. Each item is rated on a severity scale ranging from 1 (absence of psychopathology) to 7 (extremely severe). A possible range of scores on both Positive and Negative psychopathology subscale is 7–49 and on General psychopathology subscale is 16–112. Item G12 of the PANSS (higher scores indicate worse insight into the illness) was used to assess insight into the illness. Higher PANSS scores indicate greater symptoms.

The MARS [15] is patient completed scale. It contains 10 questions that require a Yes or No answer and indicates both problematic behaviors with the questions from the Medical Adherence Questionnaire (MAQ) [16], a 4-item questionnaire regarding ways in which patients may fail to take their prescribed medication (forgetting, carelessness, stopping the drug when they feel better, and stopping the drug because they believe in makes them feel worse), along with attitudes toward medication, from 6 items based on the Drug Attitude Inventory (DAI) [17] regarding taking medication only when being sick, being controlled by medication, clearer thoughts on medication, prevention of getting sick by medication, feeling weird, like a zombie on medication and feeling tired and sluggish on medication. The DAI provide rating of participants' attitude at the time of assessment; no time frame is specified in the MAQ, which is a potential limitation of the measure.

Higher MARS scores indicate behavior and attitudes that are more consistent with treatment adherence.

The Statistical Package for Social Science (SPSS) for Windows, Version 13.0 was used for the analysis. Comparison of categorical variables of the two study groups was performed using the Pearson's χ^2 test and comparison of continuous variables was performed using the Student's *t*-test. The Pearson's correlation was used to test the correlation significance. For all tests, a level of $p = 0.05$ (two-sided) was considered significant.

Results

The sociodemographic and clinical characteristics of the group D and the group O of patients are summarized in Table 1. The patients of the group D were significantly older and had significantly longer illness duration in comparison with the patients of the group O.

Table 1

Sociodemographic and clinical characteristics of schizophrenic outpatients

Variables	Depot administration (n = 19)		Oral administration (n = 37)		χ^2	*p*
Categorical variables	n (%)		n (%)			
Gender						
male	9 (47.3)		23 (62.2)		0.599	0.439
female	10 (52.7)		14 (37.8)			
Marital status						
married	2 (10.5)		3 (8.1)		1.077	0.584
single	15 (79.0)		26 (70.3)			
divorced / widow	2 (10.5)		8 (21.6)			
Live arrangement						
alone	2 (10.5)		3 (8.1)		0.000	1.000
Work situation						
working	6 (31.6)		8 (21.6)		0.239	0.625
Continuous variables	$\bar{x}$	SD	$\bar{x}$	SD	*t*	*p*
Age (yrs)	44.4	8.0	34.9	8.8	-3.892	0.000
Years of education	11.7	1.9	12.3	1.8	1.068	0.290
Duration of treatment (yrs)	20.2	7.5	10.9	7.5	-4.335	0.000

n – number of patients, % – percentage of patients, $\bar{x}$ – mean value, SD – standard deviation

Table 2 presents average doses of antipsychotic medications and mean chlorpromazine equivalent doses as well as percentages of patients using concomitant psychotropic medication in the groups D and O. Significantly lower doses of clozapine were prescribed to the patients from the group D and the patients from the same group were treated with significantly higher antipsychotic doses in chlorpromazine equivalents in relation to the patients from the group O. No patient in the group D was treated with risperidone and haloperidol and *t* could not be computed.

Table 2

Antipsychotic and concomitant medication of schizophrenic outpatients

Variables	Medication	Depot administration (n = 19)			Oral administration (n = 37)			*t*	*p*
		n	x̄	SD	n	x̄	SD		
Continous	Fluphenazine decanoate	19	25 mg /4w.	0	–	–	–	–	–
	Fluphenazine	5	2.7	1.3	8	5.4	3.4	1.693	0.069
	Haloperidol	–	–	–	6	6.8	4.4	–	–
	Chlorpromazine	5	82.4	37.1	4	100.0	35.3	0.722	0.494
	Levomepromazine	3	33.3	14.4	2	25.0	0.0	-0.775	0.495
	Clozapine	3	75.0	0	17	189.7	128.7	3.647	0.002
	Risperidone	–	–	–	8	3.3	1.3	–	–
	Chlorpromazine equivalents	19	588	194	37	342	216	-4.145	0.000
		n	(%)		n	(%)		χ^2	*p*
Categorical	Antidepressants	3	(15.7)		2	(5.4)		0.633	0.426
	Mood stabilizers	5	(26.3)		2	(5.4)		3.289	0.070
	Anticholinergics	7	(36.8)		4	(10.8)		3.866	0.049

n – number of patients, % – percentage of patients, x̄ – mean dose of the medication (mg/day), SD – standard deviation

The proportion of patients using anticholinergic drugs was significantly higher in the group D of patients in relation to the group O of patients.

The mean total PANSS, insight item G12 of the PANSS, MARS as well as MAQ and DAI subscales of MARS scores were shown in Table 3. Considerably lower mean total PANSS score, Positive, Negative and General psychopathology subscores in the group D of patients in comparison with the group O of patients were found. The average DAI subscale of MARS score was significantly higher in the group D of patients in relation to the group O of patients.

A significant negative correlation between item G12 of the PANSS subscore and MARS score (r = -0.326, p = 0.014) was found. A significant positive correlation between receiving depot therapy (the group D = 1, the group O = 0) and DAI subscore (r = 0.364, p = 0.006), as well as between illness duration and both DAI subscore (r = 0.483, p = 0.000) and MARS score (r = 0.313, p = 0.019) were also found using the Pearson's Correlation.

Table 3

Mean PANSS and MARS scores of schizophrenic outpatient

Psychometric scales	Depot administration (n = 19)		Oral administration (n = 37)		*t*	*p*
	x̄	SD	x̄	SD		
PANSS [a]	70.0	14.1	84.6	19.9	2.846	0.006
POS [b]	12.4	3.3	15.2	5.4	2.048	0.045
NEG [c]	22.5	5.3	27.1	6.9	2.476	0.016
GEN [d]	34.9	6.7	42.2	10.2	2.790	0.007
G12 item [e]	2.7	1.1	3.2	1.3	1.238	0.221
MARS [f]	8.5	1.4	7.7	2.4	-1.612	0.113
MAQ [g]	3.0	0.7	2.8	1.1	-0.611	0.544
DAI [h]	5.2	0.7	4.2	1.3	-3.403	0.001

[a]The Positive and Negative Syndrome Scale; [b]Subscale of positive symptoms from the PANSS (higher scores indicate greater symptoms); [c]Subscale of negative symptoms from the PANSS; [d]Subscale of general psychopatology from the PANSS; Item [e]G12 of the PANSS (insight into the illness)(higher scores indicate worse insight into the illness); [f]The Medical Adherence Rating Scale; [g]Medical Adherence Questionnaire; [h]Drug Attitude Inventory; x̄ – mean score, SD – standard deviation

A significant positive correlation between better insight and medication adherence, between receiving depot treatment and attitude toward medication and between illness duration and both attitude toward medication and medication adherence (medium strength of the relationships) were also found.

Fluphenazine decanoate, as maintenance treatment in the group D of patients and haloperidol decanoate were the most frequently used classical depot antipsychotics in the previous decades in our environment, in addition to atypical risperidone long-acting injection. Also, fluphenazine decanoate and haloperidol decanoate are still most available for the greatest number of patients. Second-generation antipsychotics prescription is most frequent in the last decade. For these reasons, significantly older age and longer illness duration of the group D of patients in comparison to the group O of patients, could be expected results.

The majority of patients included in the study were treated with more than one kind of antipsychotic drugs, including concurrent use of oral and depot antipsychotics.

Discussion

According to the results obtained in this study, the schizophrenic patients on typical depot antipsychotic maintenance treatment (the group D) had the following significant differences in relation to the schizophrenic patients on oral antipsychotics only (the group O): older age, longer illness duration, lower symptom severity, higher antipsychotic doses and more favorable attitude to treatment. A significant positive correlation between better insight and medication adher-

Prolonged polypharmacy with antipsychotic drugs is prevalent in clinical practice [18, 19] although, according to relevant guidelines, it may be considered only in some cases of treatment resistant patients [20]. However, it is believed that the use of two or more antipsychotic drugs concomitantly (coprescribing) optimises symptom control, enables the reduction of positive as well as of negative symptoms and avoids high doses of single drugs, thus reducing potential adverse effects [19].

The group D of patients had a significantly higher mean chlorpromazine equivalent dose (588 +/- 194) than the group O of patients (373 +/- 384) which is in accordance with the findings from similar study [21]. Prescription of oral antipsychotics (clozapine or low potency neuroleptics when necessary) in the group D of patients influenced the results relating to chlorpromazine equivalent doses in this study. One difficulty in determining the lowest effective maintenance dose for depot antipsychotics is the delay in relapse of symptoms after a dosage reduction because a significant level of drug remains in the tissues for weeks to months after drug discontinuation [22, 23].

Concomitant medication use in the patients included in our study ranges from 11% to 37% for anticholinergics, 5% to 16% for antidepressants and 5% to 26% for mood stabilizers. Higher percentages of the patients from the group D were treated with both antidepressants and mood stabilizers in relation to the patients from the group O, but the differences were not considerable. The frequency of anticholinergic use as proxy indicator of extrapyramidal side-effects was significantly higher in the group D of patients in comparison with the group O of patients, possibly accounting for a significantly higher dose (chlorpromazine equivalents) prescription in the D group in relation to the group O. The results of Larsen and Gerlach's study [24] regarding the attitude towards treatment, side-effects, mental state and quality of life of chronic schizophrenic out-patients on maintenance treatment with depot neuroleptics showed that hypokinesia and hyperkinesis were the adverse effects least noticed by the patients, but most noticed by the treating physician, while the opposite was the case with psychic side-effects (dullness/tiredness). However, 88% of the patients included in that study who reported no side-effects had at least one. The neglect of this dimension may lead to non-compliance. A consistent correlation between the presence or severity of side-effects and the degree of adherence could not be found in a systematic review [25]. Although intolerability is a major cause of antipsychotic drug discontinuation in schizophrenia, it often accounts for fewer discontinuations than the lack of efficacy [16]. In a cross-sectional study of Patel et al. [26] on adherence to depot *versus* oral antipsychotic medication, beliefs and attitudes have been more important than side effects in predicting self-reported adherence and influencing factors thereof.

The findings of our study relating to psychopathology (significantly lower symptom severity of total as well as positive, negative and general psychopathology in the group D of patients in regard to the group O of patients) suggested a more favorable course of the illness of the group D of patients compared with the group O of patients. Several other studies showed that antipsychotic drugs that are administered in a depot injection are associated with lower rates of relapse and hospital admission than medications that are administered orally, because of the greater likelihood that the patient will receive medication [27]. Meta-analytical study of David and Adams [28] showed that depot antipsychotic preparations appear useful in relapse prevention when utilized for patients with difficulties in medication compliance, despite limitations of the analysis. However, data is still limited in this area.

The two groups of patients included in our study did not differ in the level of insight into the illness that was described as a strong predictor of adherence to medication [4, 25], despite significant differences in symptoms severity. This result points out once again how much is difficult to attain full insight into the disorder in patients with schizophrenia irrespective illness duration, reduction of severity of other symptoms and phase of treatment. However, insight correlated significantly with medication adherence, according to the results of our study. The group D of patients had better insight, but not significantly in relation to the group O of patients and both patients groups had intermediate level of insight. In considering these findings, we should take into account the following: firstly, item G12 of the PANSS (used in this study for assessment of insight into the illness) addresses only to an improvement in understanding illness as well as medication consequences and secondly, the patients included in the study were continuously attending outpatient's service for depot administration and/or prescription of oral antipsychotic therapy which implies better insight into disorder in regard to those not attending scheduled outpatients visits. We can speculate that the majority of the participants on oral antipsychotics were started and maintained on oral antipsychotics because of their better insight and adherence. However, because of the cross-sectional nature of the study design, it is not possible to ascertain the insight of the participants when they were started on their medication. In addition, patient who uses his/her medication because it improves well-being does not necessarily need to have insight into the disorder. This might explain why Nageotte et al. [29] found that 38% of patients were compliant despite the fact that they did not believe themselves to be ill. Hogan et al.[17] demonstrated that patients' experience of and adherence to antipsychotic regimens depended on how they felt on medication, rather than what they knew or believed about it.

Medication adherence was taken as continuous variable in our study, having in mind that it is a dynamic phenomenon and could change during a long-term treatment of schizophrenia. The patients on depot antipsychotic therapy had significantly better experience toward medication in comparison with the patients on oral antipsychotic therapy in this study. There are few data examining patient satisfaction or attitudes regarding depot antipsychotics. The meta-analysis of Walburrn et al.[30] showed that in 10 out of 12 studies, a positive opinion towards depot antipsychotics was expressed. Five out of six studies that compared depot with oral antipsychot-

ics showed patient preference for depots, although, patients tended to state a preference for the formulation that they were taking at the time. In a study by Patel et al.[31], the attitudes regarding current formulation were influenced by illness duration, extrapyramidal symptoms and insight but not by formulation (depot *vs* oral).

Despite considerably better medication attitude of the group D of patients in relation to the group O of patients in this study, the patients on depot therapy had less than a significantly better medication-taking behavior and adherence to the therapy in comparison with the patients on oral maintenance therapy. The patients from both study groups had intermediate level of compliance with medication. The first two questions of the MAQ subscale (assessing medication-taking behavior) of MARS related to unintentional non-compliance, regarding forgetfulness and carelessness (often confusing for patients) might influence the results of the study referring to compliance behavior. However, there are findings showing the lack of correlation between medication attitudes and medication-taking behavior of the patients [32] as well as that patient's attitudes to medication may be completely different from their actual medication-taking behavior [33]. Having in mind the frequent need for concurrent prescribing of oral medication in patients with schizophrenia on depot antipsychotic therapy, findings regarding medication-taking behavior seem to be important not only for patients on oral therapy alone, but also for the patients receiving depot maintenance therapy.

The findings from this study relating to medication adherence in the patients with schizophrenia on maintenance treatment, obtained by examination of certain variables, show the complexity of this issue. Compliance behavior remains problematic in both the patients receiving classical depot antipsychotics and those using oral antipsychotics only. They are needed prospective longitudinal studies on medication adherence in patients with schizophrenia on depot antipsychotics, from the introduction of depot therapy and the course of the treatment process.

There are several limitations of the present study which included a heterogeneous sample of 56 participants. This number is relatively low (particularly in the group D as a reflection of the lower frequency of the use of classical depot antipsychotics) for analysis of between-group differences. However, between-group differences in some variables which were examined in this study were significant even with this low numbers per group.

The patients included in this study had to be clinically stable for at least six months and to regularly attend outpatient's service before inclusion. These inclusion criteria probably influenced our results because these patients maybe stressed the importance of factors that positively influenced medication adherence, but data of non-attendee's and non-compliers were hard to obtain.

Both patients groups were mixed regarding the type of antipsychotics which were prescribed (both atypical and typical antipsychotics were prescribed either as monotherapy or in combination in the group O of patients and clozapine or low-potency antipsychotics in one number of patients in the group D). That probably influenced the finding addressing medication attitude, having in mind different profile of adverse effect of typical *vs* atypical antipsychotics.

The group D included the patients with additional oral medication (antipsychotics or/and concomitant non-antipsychotic psychotropic drugs). For these reasons, a significantly better medication attitude of the group D compared to the group O could not address to depot therapy in particular. Further, the group O included the patients who had been either on depot in the past or at least offered them. The views of such patients on depot medication would complete the picture.

Future investigations designed as prospective clinical studies, with larger sample including patients covered by antipsychotic depot monotherapy and subject groups matched by sociodemographic and clinical characteristics could decrease limitations of our study.

Conclusion

In comparison with schizophrenic patients on oral maintenance therapy alone, patients on classical depot antipsychotic maintenance treatment were significantly older, had longer illness duration, were treated with higher antipsychotic chlorpromazine equivalents doses, had more often prescribed anticholinergics, had lower severity of psychopathology and more favorable attitude toward medication.

Insight into the disorder and medication adherence, treatment with typical depot antipsychotics and attitude to medication as well as illness duration and both medication adherence and attitude to treatment were significantly correlated.

This study was completed with the idea of applicability in everyday clinical practice, given that classical depot antipsychotics are still frequently used in a population of schizophrenic patients on maintenance therapy in Serbia.

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Autologous blood transfusion in total knee replacement surgery

Primena autologne transfuzije krvi kod ugradnje totalne proteze kolena

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Abstract

Background/Aim. Total knee replacement (TKR) surgery is one of the most frequent and the most extensive procedures in orthopedic surgery, accompanied with some serious complications. Perioperative blood loss is one of the most serious losses, so it is vital to recognize and treat such losses properly. Autologous blood transfusion is the only true alternative for the allogeneic blood. The aim of this study was to to examine if autologous blood transfusion reduces usage of allogenic blood in total knee replacement surgery, as well as to examine possible effect of autologous blood transfusion on postoperative complications, recovery and hospital stay of patients after total knee replacement surgery. **Methods.** During the controlled, prospective, randomised study we compared two groups of patients (n = 112) with total prosthesis implanted in their knee. The group I consisted of the patients who received the transfusion of other people's (allogeneic) blood (n = 57) and the group II of the patients whose blood was collected postoperatively and then given them [their own (autologous) blood] (n = 55). The transfusion trigger for both groups was hemoglobin level of 85 g/L. **Results.** In the group of patients whose blood was collected perioperatively only 9 (0.9%) of the patients received transfusion of allogeneic blood, as opposed to the control group in which 98.24% of the patients received the transfusion of allogeneic blood ($p \leq 0.01$). The patients whose blood was collected stayed in hospital for 6.18 days, while the patients of the control group stayed 7.67 days ($p < 0.01$). **Conclusion.** Autologous blood transfusion is a very effective method for reducing consumption of allogenic blood and thus, indirectly for reducing all complications related to allogenic blood transfusion. There is also a positive influence on postoperative recovery after total knee replacement surgery due to the reduction of hospital stay, and indirectly on the reduction of hospital costs.

Key words:
blood transfusion, autologous; blood transfusion; arthroplasty, replacement, knee; orthopedic procedures.

Apstrakt

Uvod/Cilj. Operacija ugradnje totalne proteze kolena spada u jednu od najčešćih i najekstenzivnijih intervencija u ortopedskoj hirurgiji i udružena je sa brojnim komplikacijama. Perioperativni gubitak krvi je jedna od najozbiljnijih komplikacija te ga je neophodno na vreme prepoznati i adekvatno tretirati. Jedina prava alternativa za transfuziju alogene krvi (tuđe krvi, krvi dobijene od dobrovoljnih davalaca) je transfuzija autologne (svoje) krvi. Studija je primarno imala za cilj da ispita da li i koliko primena autologne krvi utiče na redukciju primene alogene krvi kod operacija zamene totalne proteze kolena. Sekundarni ciljevi su bili uticaj autologne transfuzije na perioperativne komplikacije, postoperativni oporavak bolesnika i broj dana koji bolesnik provede u bolnici. **Matode.** Tokom kontrolisane, prospektivne, randomizovane studije upoređivali smo dve grupe bolesnika kod kojih je operativnim putem ugrađivana totalna proteza kolena, ukupno 112 bolesnika. Grupu I činili su bolesnici koji su dobijali transfuziju tuđe (alogene) krvi (n = 57), a grupu II bolesnici kod kojih je postoperativno prikupljana njihova (autologna) krv (n = 55). Transfuziji krvi smo u obe grupe pristupali pri vrednosti hemoglobina od 85 g/L. **Rezultati.** U grupi bolesnika kod kojih se perioperativno prikupljala krv (autologna transfuzija) samo 9,09% je dobilo transfuziju alogene krvi, za razliku od kontrolne grupe u kojoj je 98,24% dobilo transfuziju alogene krvi ($p \leq 0,01$). Broj dana provedenih u bolnici kod grupe bolesnika kod kojih je prikupljana sopstvena krv bio je 6,18, a kod kontrolne grupe 7,67 dana ($p < 0,01$). **Zaključak**. Autologna transfuzija je efikasan način smanjenja upotrebe alogene krvi. Njenom primenom se redukuje pojava potencijalnih komplikacija vezanih za primenu alogene krvi, ima pozitivan uticaj na postoperativni oporavak bolesnika, smanjuje broj dana koje bolesnik provede u bolnici i na, indirektan način, smanjuje ukupne troškove lečenja bolesnika koji se podvrgavaju operaciji ugradnje totalne proteze kolena.

Ključne reči:
autotransfuzija; transfuzija krvi; artroplastika kolena; ortopedske procedure.

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Introduction

Total knee replacement (TKR) surgery is one of the most frequent and the most extensive procedures in orthopedic surgery, accompanied with some serious complications. Perioperative blood loss is one of the most serious losses, so it is vital to recognize and treat it properly. Timely and precise treatment of perioperative blood losses has an impact on the outcome of the surgery and the quality of postoperative recovery. Transfusion of allogeneic blood carries certain risks, such as allergic reactions, anaphylaxis, hemolytic reactions, transmissive diseases, transfusion related lung injury (TRALI), graft-versus-host disease, etc. [1–5]. In the past few decades, a lot of effort has been made to find a solution to the problems connected with allogeneic transfusion. One of the alternatives is autologous blood transfusion, which is widely accepted as probably the only true alternative for allogeneic blood. The justification for the use of this alternative method could be found in a certain level of morbidity and mortality which accompanies allogeneic blood transfusions [6, 7].

The autologous blood transfusion is a collection and reinfusion (transfusion) of the patient's own blood or blood components before, during or after surgical procedure. So, the donor and recipient of blood is the same person. Although not completely risk-free, autologous blood is the safest blood donation.

According to the American Association of Blood Banks the most important strategies for blood donation are**:** preoperative autologous donation, acute normovolemic hemodilution, and perioperative blood salvation.

Perioperative blood salvage is intraoperative collection by aspiration from the operative fields and postoperative collection of blood from wound drains [8, 9].

Autologous transfusion is indicated in certain surgeries when major blood losses are expected. The prerequisite for this procedure is no wound or systematic infection and normal hemoglobin levels in patient's blood.

Total knee replacement surgery is one of the most serious operations in orthopedic surgery. Frequently accompanied with serious intraoperative and postoperative bleeding, it is usually performed with pneumatic tourniquet, so autologous blood salvation takes place from wound drains in the postoperative period.

The aim of the study was to improve our everyday clinical practice, to contribute to better understanding of perioperative blood loss and its treatment in TKR surgery, and thus to affect the outcome of the surgery in a positive way.

Methods

This single-center (Clinic for Orthopaedic Surgery and Traumatology, Clinical Centre of Vojvodina, Novi Sad), prospective, randomised, controlled study included 112 patients undergoing TKR surgery in a 3-months period during 2010. The patients were randomely divided in two treatment groups, the group I (n = 57) receiving allogeneic blood, and the group II (n = 55) receiving autologous blood.

The transfusion trigger for the group that received allogeneic blood was 85 g/L. We chose this value for the hemoglobin trigger because the majority of our patients were elderly people, usually with comorbidities. For the group that received autologous (their own) transfusion, blood was collected from wound drains postoperatively within 4 h. The minimal amount of drained blood was ≥ 200 mL for the process to be successful (according to the manufacturer's manual and our experience). We used Cell Saver (Haemonetics 5+, USA) apparatus; blood was collected, processed and reinfused to the patients or by the trained anesthesiology technician. One unit of autologous blood was 250 mL.

Hemoglobin levels were measured preoperatively, and postoperatively after 6, 24 and 48 h for all the patients. Preoperatively, as well as 24 h after the surgery, we measured activated partial thromboplastin time (APTT) and partial thromboplastin time (PT).

TKR surgery was performed as a routine, with the use of pneumatic tourniquet inflated to the level 100 mmHg more than systolic pressure. The patients underwent general (balanced) anesthesia or spinal anesthesia, standardized in terms of drugs and procedures.

Postoperative blood losses were measured as losses in wound drains during the period of the first 48 h after the surgery for all the patients, accompanied with clinical examination of the patients.

The time when patients sat, stood, walked and had their meal for the first time after the surgery recorded, to indirectly measure the quality of postoperative recovery. The length of staying in hospital was also recorded.

The exclusion criteria for this study were: patients with septic complications, multiple fractures, malignancy, American Society of Anaesthesiologists (ASA) physical status classification IV or more, hemiarthroplasty and all patients with incomplete data.

All the data were analyzed in SPSS 16.0 software package. All frequencies, percentages, and median standard deviation were calculated. Binary variables were comparated by the χ^2 test, continuous variable were compared by the Fisher's Exact test and the *t*-test. A statistically significant difference was defined as p value < 0.05. All data (text, tables, and charts) were arranged by Microsoft Word 2003 and Microsoft Excel 2003.

Results

Out of 112 patients, 86 were women and 26 men. For the purpose of this study we compared age, gender, ASA status, comorbidities, chronic non-steriodal anti-inflamatory drugs (NSAID) and aspirin use, anesthesia method, the type of prosthetic material, perioperative levels of hemoglobin, hematocrit, thrombocyte count, the mechanism of hemostasis, blood losses, the number of blood units of allogeneic and autologous blood per each patient, the time when patients sat, stood, walked and had their meals for the first time after the surgery, as well as the length of staying in hospital to evaluate their impact on the outcome of the surgery.

In both groups the majority of patients were women, 86 (76.78%).

The American Society of Anesthesiology (ASA) status III (ASA III) patients were most frequent in both groups – 83 patients in total (74.10%). There were no ASA I patients.

The majority of patients received spinal anesthesia – 83 (74.10%) patients, and 29 (25.90%) patients received general anesthesia. All the patients had a cemented knee prosthesis (Table 1).

Comparing hemoglobin and hematocrit levels measured postoperatively, there was a significant difference after 48 h in favour of the allogeneic group (Table 2). The values of APTT and PT preoperatively and 24 h postoperatively were higher and showed a significant difference in the autologous group (Table 2). That can be explained by blood processing in the autologous transfusion method. In this process only "washed" erythrocytes are reinfused back to the patient, and the rest of plasma and coagulation factors, with cell detritus,

Table 1

General characteristics of the patients

Characteristics	Autologous group	Allogeneic group	*p*-value
Mean age (min–max)	65.24 (50–81)	67.72 (53–82)	0.05
Gender, n (%)			
male	14 (25.5)	12 (21.1)	
female	41 (74.5)	45 (78.9)	
Methods of anesthesia, n (%)			
general	16 (29.1)	13 (22.8)	0.05
spinal	39 (70.9)	44 (77.2)	0.05
Type of knee prosthesis, n (%)			
cemented	55 (49.1%)	57 (50.88%)	0.05
cementless	0	0	

Table 2

Preoperative and postoperative mean values of hemoglobin, hematocrit, thrombocytes, activated partial thrombaplastin time (APTT), partial thromboplastin time (PT) and blood losses

Parameters	Autologous group	Allogenic group	*p* value
Hemoglobin (g/L)			
preoperatively	134.85	133.94	0.05
postoperatively:			
6 hrs	121.62	119.12	0.05
24 hrs	110.15	110.54	0.05
48 hrs	97.62	107.40	0.01
Hematocrit (g/L)			
preoperatively	39.83	38.99	0.05
postoperatively:			
6 hrs	35.25	34.86	0.05
24 hrs	32.07	32.18	0.05
48 hrs	27.65	31.14	0.01
Thrombocytes ($\times 10^9$/L)			
preoperatively	252.55	268.93	0.05
postoperatively:			
6 hrs	187.95	202.53	0.05
24 hrs	177.62	188.49	0.05
48 hrs	161.22	190.35	0.01
APTT (sec.)			
preoperatively	0.934 (0.78–1.14)	0.932 (0.74–1.13)	0.05
after 24 hrs	0.974 (0.79–1.25)	0.941 (0.80–1.11)	0.01
PT (sec.)			
preoperatively	0.944 (0.82–1.17)	0.991 (0.86–1.20)	0.01
after 24 hrs	1.199 (0.94–1.72)	0.986 (0.10–1.21)	0.01
Blood losses (mL)			
postoperatively:			
immediatelly postoperatively	1229.06 (300–3000)	1328.0 (800–2800)	0.05
after 24 hrs	252.88 (50–900)	401.75 (100–1450)	0.01
after 48 hrs	206.67 (50–900)	240.60 (100–1100)	0.05

Comorbidities were very frequent; almost all the patients had some comorbidities – 99 of them (88.39%) in both groups; only 13 (11.6%) patients had none.

Almost all the patients in both groups used some aspirin or NSAIDs, only one patient did not use any of these drugs.

anticouagulants, normal saline and bone micro fragments are disposed and wasted.

In both groups, most promminent postoperative blood lossess were in the imediate postoperative period. In the autologous group blood losses were less in general. There

were statistically significant difference in the blood losses in the first 24 hours postoperatively, blood losses were significantly less in the autologous group (Table 2).

Out of 55 patients in the autologous group, only 5 (9.09%) patients received an additional transfusion of allogeneic blood (n = 8 units of allogeneic blood), while 50 (90.99%) patients received only their own (autologous) blood.

In the allogeneic (control) group 56 patients received allogeneic blood, 32 (57.1%) patients, received 2 units of allogeneic blood, 7 (12.5%) patients received 1 unit of allogeneic blood, 17 (30.4%) patients received more than three units of allogeneic blood. Only one patient did not receive allogeneic blood (Table 3).

Table 3

The number of blood units in autologous and allogeneic group of the patients

Blood units	Autologous group n (%)	Allogeneic group n (%)
Allogeneic		
1	2 (40)	7 (12.5)
2	3 (60)	32 (57.1)
> 3	0 (0)	17 (30.41)
Autologous		
1	22 (40)	0
2	22 (40)	0
3	4 (7.3)	0
4	6 (10.9)	0
5	1 (1.8)	0

In the autologous group the majority of patients received one or two units of autologous blood (n = 22 patients), four patients got 3, six patients got 4, only one patient got 5 units of autologous transfusion (Table 3).

The time when patients sat, stood, walked and had their meal for the first time after the surgery served as the indirect indicator of postoperative recovery quality. In the autologous group, the patients sat ($p < 0.001$) able to eat (their first meal) 18 h earlier than in the allogeneic (control) group ($p < 0.001$).

There was a significant difference ($p < 0.001$) in the length of staying in hospital. An average hospital stay in the autologous group was 6.18 days, and in the allogeneic (control group) 7.67 days. The final decision about when to discharg the patient from hospital was made by the attending surgeon (Table 4).

logeneic (control) group. One was the wound infection and other was chest pain with no major morbidity. In the autologous group there were no complications.

Discussion

The average patient in our study was female, 66.5 years old, ASA III status with comorbidities and chronic usage of NSAID's or aspirin. These data are consistent with the fact that indications for TKR surgery are degenerative diseases of the knee, which are painful and, more frequent in elderly females [10].

The patients in the autologous group lost significantly less blood, in general. There is also a significant difference in the postoperative blood loss between two groups 24 h after the surgery. The patients in the autologous group lost less blood, too. Our study showed blood loss mostly in immediate postoperative period which is in accordance with some other studies [11].

We think that the most important result of our study is the result showing that autologous transfusion is a very effective measure in reducing consumption of allogeneic blood. In the allogeneic (control) group 98.24% of the patients postoperatively received allogeneic blood transfusion. In the autologous group of patients only 9.09% received allogeneic blood transfusion, which is almost ten times reduction in the consumption of this type of blood.

This is in accordance with the research performed by Thomas et all. [11] which showed the reduction of allogenic blood consumption (only 7% in the research group received additional allogenic blood transfusion). Some other studies, however, did not show that autologous transfusion reduced consumption of allogenic blood transfusion [12, 13].

Recovery following TKR surgery is multifactorial, but there is a statistically significant difference in the speed and quality of postoperative recovery in the autologous group, accompanied with fewer complications. Unfortunately, we were not able to follow the patients and complication rate after hospital dismissal, and we know that such data (collected for the first six months postoperatively at least) could be very important for the introspection of this method itself. Hospital stay is reduced in this group of patients [14].

Table 4

Postoperative recovery in autologous and allogenic group of the patietns

	Autologous group mean (min–max)	Allogenicgroup mean (min–max)	*p* value
Postoperative recovery (h)			
sitting	9.35 (8–12)	24.21 (12–48)	<0.01
stending	23.78 (12–24)	24.21 (12–48)	>0.05
walking	24.65 (24–48)	27.15 (24–72)	>0.05
eating	9.67 (4–36)	27.37 (24–48)	<0.01
Hospital stay (days)	6.18 (2–11)	7.67 (3–14)	<0.01

We analyzed deep venous thrombosis (DVT), pulmonary thromboembolic complications, sepsis, wound infection and major cardiovascular complications. Perioperative complications were rare and there were only two cases in the al-

There is a shortage of blood everywhere in the world, the same situation is in Serbia, so every method that reduces consumption of allogeneic blood is of vital importance. In our country blood donation is voluntary, which leads to a

wrong conclusion that blood itself is free of charge. The process of making blood and blood components safe is an expensive part of blood production. The analysis of cost-effectiveness of autologous transfusion was not the aim of this study, and it is very hard to analyze it because there is no official data about the cost of blood in our country. Today, blood and blood products are safer than ever, but still there are some known morbidities and mortalities connected to allogeneic transfusion, so by reducing its consumption we reduce those risks. Autologous transfusion has its own costs, but an additional justification for its usage can be found in the improved safety of this method [15, 16].

This study, however, has some limitations. In spite of the local study recommendations for the transfusion trigger of 85 g/L, sometimes this strict protocol was not followed and some surgeons are still reluctant to apply these recommendations since they consider them too low. This fact maybe explains higher hemoglobin levels in the allogeneic group, because there is a strict protocol appliance in the autologous group controlled by the anesthesia technician and the anesthesiologist.

The length of staying in hospital is reduced in the autologous group of patients. There is no consensus in our clinic about how long patients should be hospitalized after TKR surgery, so this decision was made by consulting the surgeon, as well.

Conclusion

Autologous blood transfusion is a very effective method for reducing consumption of allogenic blood and that reduction, indirectly reduces all complication related to allogenic blood transfusion. There is also a positive influence on postoperative recovery after total knee replacement surgery due to the reduction of hospital stay, and indirectly on the reduction of hospital costs.

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Migration of fluoride ions from the permanent teeth into saliva in children with glass ionomer cement restorations: an *in vitro* study

In vitro migracija jona fluora u pljuvačku iz stalnih zuba dece sa restauracijom od glas-jonomer cementa

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Abstract

Bacground/Aim. Glass ionomer cements (GIC) belong to the group of polycarboxyl cements, and one of the principal characteristics of these materials is their anticariogenic potential of fluorine release into saliva and enamel-dentin substance. The aim of this study was to examine the content of released fluorine from GIC restorations (Fuji IX, GC, Japan) of young permanent teeth in the medium of artificial saliva and similar releases in the same medium by the restorations of these teeth treated with a low concentration fluoride solution. **Methods.** We examined 12 premolars exctracted from orthodontic reasons. The GIC restored teeth were divided into the group treated daily with low concentration fluoride solution (334 ppm) and the control, not treated group. The samples of artificial saliva were analyzed for fluorine ion content using an ion selective electrode. **Results.** Our comparative analysis of the mean values using the Student's *t*-test demonstrated a statistically significant difference in fluorine ion concentration in artificial saliva of fluoridated and non-fluoridated teeth with GIC fillings after 14 and 21 days ($p < 0.05$), while the difference detected after 7 days was with no statistical significance. **Conclusion.** The results of this *in vitro* study indicated that low-concentration fluoride solutions could serve to refluoridate GIC fillings and contribute to an increased fluorine content in saliva. The process of refluoridation of GIC fillings should be advised 2–3 weeks after the restoration, since the release of fluorine from GIC fillings diminishes in time.

Key words:
dental cements; saliva, artificial; fluorides; child.

Apstrakt

Uvod/Cilj. Jedna od najznačajnih karakteristika glas-jonomer cementa (GJC) je antikariogeni potencijal oslobađanja fluorida u pljuvačku i gleđnodentinsku supstancu. Cilj ove studije bio je praćenje sadržaja oslobođenih jona fluora iz restauracija od GJC (Fuji IX, GC, Japan) na mladim stalnim zubima u medijumu veštačke pljuvačke, kao i praćenje ovog oslobađanja u istom medijumu, iz restauracija kod pomenutih zuba tretiranih niskokoncentrovanim rastvorom fluorida. **Metode.** U istraživanju je korišćeno 12 premolara ekstrahovanih iz ortodontskih razloga. Zubi restaurisani glas-jonomer cementom bili su podeljeni u grupu koja je svakodnevno tretirana rastvorom niskokoncetrovanog fluorida (334 ppm) i kontrolnu grupu koja nije tretirana fluoridima. Uzorci veštačke pljuvačke su analizirani na sadržaj jona fluora primenom jon selektivne elektrode. **Rezultati.** Komparativnom analizom srednjih vrednosti Studentovim *t*-testom utvrđena je statistički značajna razlika između koncentracije jona fluora u veštačkoj pljuvački, fluorisanih i nefluorisanih zuba sa GJC ispunom posle 14. i 21. dana ($p < 0,05$), dok je analiza posle 7 dana pokazala da razlika postoji, ali bez statističke značajnosti. **Zaključak.** Rezultati istraživanja ove *in vitro* studije pokazuju da niskokoncetrovani fluoridni rastvori mogu poslužiti za refluorizaciju GJC ispuna i time doprineti povećanju fluoridnog sadržaja u pljuvački. Proces refluorizacije GJC ispuna predlaže se posle 2–3 nedelje od restauracije, pošto se oslobađanje fluora iz GJC ispuna vremenom smanjuje.

Ključne reči:
zub, cement; pljuvačka, veštačka; fluoridi; deca.

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Introduction

Glass ionomer cements (GIC) belong to the group of polycarboxyls, introduced in dentistry by Smith [1] in the late 1960s in order to improve the adhesiveness of restoration materials to hard dental tissues.

The development of GIC in the last decade has witnessed some significant changes in the composition of the glass component of powder and in polycarboxyl acids of the fluid component. Original GICs were based on SiO_2-Al_2O_3-CaF_2-$AlPO_4$-Na_3AlF_6 composition. According to Wilson and McLean [2], the Al_2O_3/SiO_2 ratio should be 1 : 2 or more, with fluoride component content reaching even 23%. The typical chemical composition of a GIC powder is shown in Table 1. More recently, GICs supplemented with Sr, Ba, and Zn have become commercially available [2].

Table 1
Composition of glass ionomer cement powder according to Wilson and McLean [2]

Substances	Quantity (ppm)	Mass percentage
SiO_2	41.9	35.2
Al_2O_3	28.6	20.1
AlF_3	1.6	2.4
CaF_2	15.7	20.1
NaF	9.3	3.6
$AlPO_4$	3.8	12.0

In spite of the fact that mechanical properties of these materials limit their usefulness as the materials for final cavity closure in all fillings, its anticariogenic property made GIC one of the most attractive materials in pedodontics. These materials release fluorine ions, chemically attach to hard dental tissues, possess thermical compatibility with the enamel, biocompatibility, and low cytotoxicity, and can be used with milk teeth [3].

Fluorine ions released from the restoration materials contribute to the reduction of caries *via* the physical-chemical and biologic pathways, with anticariogenic potential of the materials largely depending on the amount of released fluorine, as well as on the duration of that release [4–6].

Studies have shown that GICs are the most effective fluorine-releasing materials, but also that in the situation of continued presence of fluorides in the mouth cavity, these materials show the ability to uptake them [7].

The aim of this study was to establish the presence of released fluorine ions from GIC restorations in young permanent teeth in the medium of artificial saliva, and similar release in the same medium from restorations of these teeth treated with low-concentration fluoride solutions.

Methods

The study was performed in the Department of Preventive and Pediatric Dentistry, Dentistry Clinic the Department of Pharmacy - Analytical Chemistry, the Institute of Histology and Embryology, and the Public Health Institute of the Faculty of Medicine in the town of Niš.

In this *in vitro* study, we used 12 young, permanent, healthy premolars exctracted from orthodontic reasons, kept after extraction in physiologic solution for one month. The study was perform in three phases: teeth extraction and preparation; teeth incubation and fluoridation, and determination of fluorine ion concentration.

Phase I: *Teeth extraction and preparation*

After extraction, the surfaces of all the teeth were cleaned, roots were cut off with a metal cutter at the level of enamel-cement borderline, and the remaining pulp tissue was removed. The average mass of the studied tooth samples was 0.627 ± 0.105 g.

From the vestibular aspect, class V cavities were prepared, $3 \times 2 \times 2$ mm in size, using a diamond drill, and all the teeth were restored with GIC (Fuji IX, GC, Japan) following the manufacturer's guidelines. After GIC binding, the excess material was removed and the teeth were washed under the current of distilled water and placed in 100 mL of artificial saliva. Chemical composition of the artificial saliva solution is shown in Table 2.

Table 2
Chemical composition of an artificial saliva solution

Substance	Concentration (moL/dm^3)
$NaHCO_3$	1.5×10^{-2}
KCl	2.0×10^{-2}
$KHCO_3$	1.5×10^{-2}
Lactic acid	10.0×10^{-2}

The pH value of artificial saliva was around 6.7, as the closest approximation to physiologic values for saliva in the mouth cavity. Fluorine ion concentration in the artificial saliva was 0.071 ppm.

All glass-ionomer cement restored teeth (GICrT) were divided into two groups with six teeth each. The first group was treated daily with low concentration fluoride, while in the second group there was no fluoridation. Both groups were further divided into three subgroups with two teeth each, according to the experiment duration (7, 14, and 21 days).

Phase II: *Teeth incubation and fluoridation*

The prepared teeth samples were treated with the solution of artificial saliva incubated at 37 °C during the aforementioned periods of time.

The first group of GICrT (six samples) was fluoridated with the fluoride solution (concentration of 334 ppm), composed of 10 mL of low concentration fluoride solution and 5 mL of artificial saliva solution. The teeth in this group were fluoridated daily, being submersed in this solution for 1 minute, and then washed for 5 seconds with distilled water, being returned after drying into the artificial saliva. After the planned treatment periods, the samples of artificial saliva were analyzed for fluorine content.

Phase III: *Determination of fluoride ion concentration*

The content of fluorine ions was determined by way of automated potentiometric titration using a ion selective fluorine electrode (Ma-5705, Iskra, Slovenia). The obtained fluo-

rine concentrations in artificial saliva solution were expressed in ppm.

The obtained values were compared using the Student's *t*-test for independent small samples, with the test statistical significance cut-off value of $p < 0.05$. Statistical analysis was done using the SPSS software (version 15).

Resuls

The concentrations of fluorine ions released into the artificial medium for non-fluoridated and daily fluoridated GICrT after 7, 14, and 21 days are shown in Table 3.

all the studied teeth, a statistically significant difference was established between the total fluorine concentration released by all fluoridated and nonfluoridated GICrT ($p = 0.0193$).

Comparing the concentration of released fluorine ions in the medium within the groups in Figure 2, we can see that the highest ion concentrations were released in the artificial saliva medium in the first week, in both fluoridated and non-fluoridated teeth (0.883 and 0.664 ppm, respectively). During the second week the observed release trend continued, although with a lower concentration of newly released fluorine ions compared to the first week in both studied groups (0.220 and 0.204 ppm, respectively). In the third week, compared to the second week, the trend of reduction of concentration of newly released ions of fluorine continued (0.156 and 0.033 ppm, respectively). These data demonstrated that the release was still present, with the lowest concentration of newly released fluorine ions in the third week, and with a lower reduction rate in fluoridated teeth (Figure 2).

Table 3

Comparative analysis of released ions of fluorine in the artificial saliva medium, from non-fluoridated glass-ionomer cement restored teeth (GICrT) and GICrT treated with the solution of low-concentrated fluorides (334 ppm)

	Concentration		$\bar{x}_f - \bar{x}_{nf}$	*t*-test
	fluoridated GICrT $\bar{x}_f$ ** (ppm) ± SD	non-fluoridated GICrT $\bar{x}$ *** (ppm) ± SD		
7 days	0.833 ± 0.069	0.644 ± 0.036	0.188	0.0762
14 days	1.053 ± 0.030	0.848 ± 0.047	0.204	**0.0354**
21 days	1.209 ± 0.067	0.881 ± 0.001	0.328	**0.0203**
$\bar{x}$ *	1.032 ± 0.175	0.791 ± 0.118	0.241	0.0193

***The mean value of released fluoride ions of all the teeth in the group; **The mean value of relased fluoride ions in fluoridated teeth; ***The mean value of relesed fluoride ions in non-fluoridated teeth; f – fluoridated; nf – non-fluoridated**

The release of fluorine from GICrT in the medium of artificial saliva was highest in the first week in both fluoridated (0.833 ppm) and non-fluoridated teeth (0.644 ppm). Cummulative values of released fluorine ions were highest after the day 21 for GICrT treated daily with fluoride solution (1.209 ± 0.067 ppm). The median values demonstrated the highest difference (0.328 ppm) for GICrT kept in the artificial medium for 21 days. By way of comparative analysis of $\bar{x}$, a statistically significant difference was found between fluoridated and non-fluoridated GICrT after 14 and 21 days ($p < 0.05$). Statistical analysis for non-fluoridated and fluoridated GICrT after 7 days demonstrated a difference, although not a statistically significant one ($p = 0.076$) (Figure 1).

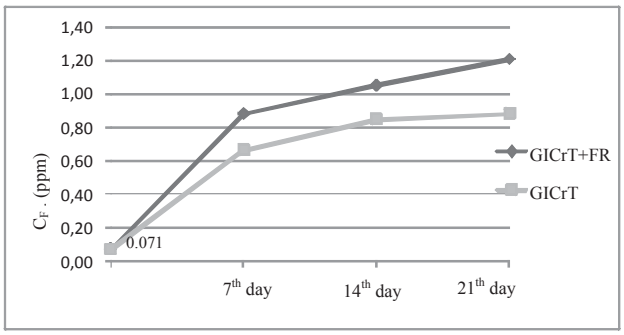

Fig. 1 – Concentration of released fluoride ions (ppm) in the medium of artificial saliva after 7, 14, and 21 days in the fluoridated [glass ionomer cement restored teeth (GICrT) + fluoride] and non-fluoridated teeth (GICrT)

All non-fluoridated GICrT released 0.791 ± 0.118 ppm of fluorine, while fluoridated GICrT released 1.032 ± 0.175 mg/dm^3 of fluorine. By way of comparative analysis of $\bar{x}$ of

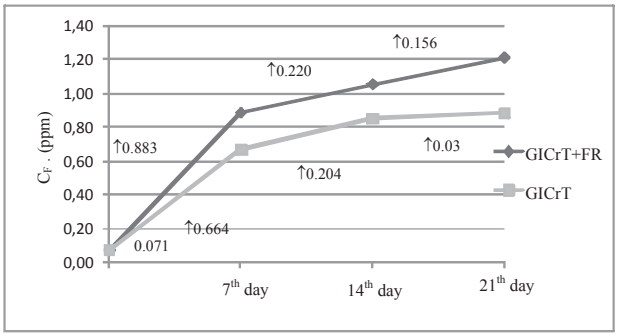

Fig. 2 – Level of release of fluoride ions (ppm) in the medium of artificial saliva after 7, 14, and 21 days in the fluoridated [ionomer cement restored teeth (GICrT) + fluoride] and non-fluoridated teeth (GICrT)

Non-fluoridated group of teeth released on the average 0.29 mg/dm^3 of fluorine a week in the medium of artificial saliva, while fluoridated teeth released 0.40 mg/dm^3 of fluoride a week during this three week study.

Discussion

The use of restoration materials based on glass ionomers and the use of oral low concentration fluorides are among the best solutions to treat and prevent caries in chil-

dren [8]. This combination, in particular, has shown a synergistic anticaries effect as the result of GIC refluoridation ability [9–11].

Our results in the first week demonstrated that the concentrations of fluorine ions released into the artificial saliva medium in fluoridated GICrT were insignificantly higher compared to non-fluoridated teeth (0.188 ppm), which could be explained by an initial release of fluorine from non-fluoridated GICrT, and the statistical significance could not be confirmed ($p = 0.076$). If we compare the differences between the groups of teeth after 14 and 21 days, we may say that the fluorine concentration in the medium rose after 14 days to 0.204 ml/dm^3 and after 21 days to 0.328 mg/dm^3 (the advantage on the part of fluoridated teeth).

In non-fluoridated and fluoridated GICrT, there was a statistically significant difference in the concentrations of released fluorine after 14 and 21 days ($p = 0.035$ and 0.020, respectively), demonstrating that with diminished fluoride concentration in GIC there was an increased affinity towards fluorine from the fluoride solution. GICs were able to uptake and release fluorine due to their high reactivity. It was established that the materials with higher initial release of fluorine were characterized by a higher reuptake ability; moreover, old, refluorinated GICs could never reach the initial level of fluorine release [12].

In our study, we used low concentration fluoride solution of 334 ppm, intended for everyday use. The studies showed that the degree of refluoridation was higher if more concentrated solutions were used, as well as with more frequent applications and lower pH of the environment (e.g., the conditions favoring the development of caries) [13,14]. However, most researchers thought that everyday use of low concentration solutions was more effective compared to highly concentrated weekly or biweekly solutions; it was not because of their stronger action or effectiveness, but because they additionally motivated users to maintain their oral hygiene [15].

The results of this study are compatible to other studies demonstrating the mode of fluorine release by GICs, characterized at first by an initial rapid release, and by rapid reduction of fluorine release afterwards [16–18]. Wiegand et al. [12] reported two mechanisms of fluorine release from GICs, the first being an abrupt reaction of dissolution of the external GIC layer, and the second being a slower one, involving a continued migration of ions from the deeper GIC layers.

In our study we used pure premolars, submersed in the solution of artificial saliva, representing just an experimental model, the characteristics of which could be markedly different from the real saliva. In the mouth cavity environment, higher viscosity of the saliva or accumulation of the dental plaque can both have an impact on the ion diffusion into or from GICs [19]. Moreover, ionic composition of saliva can have an impact on the migration of fluorine ions [20].

Conclusion

In this *in vitro* study both groups of teeth restored with GIC released initially the highest concentration of fluorine ions in the medium of artificial saliva during the first week, with fluoridated GICrT releasing more. Comparing the values of released fluorine ions during the second and third week in the medium of artificial saliva, a higher value was established in fluoridated GICrT compared to non-fluoridated ones, the difference reaching a statistical significance.

From the obtained results, a conclusion may be drawn that oral, low concentration fluoride solutions can serve to refluoridate GIC fillings and thus increase the content of fluorine in saliva, plaque, and hard dental tissues adjacent to fillings, and on the other enamel surfaces *via* saliva. The process of refluoridation of GIC fillings should be advised 2–3 weeks after the restoration, since fluorine release from GIC fillings diminishes in time.

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Relationship of adipokine to insulin sensitivity and glycemic regulation in obese women – the effect of body weight reduction by caloric restriction

Veza između adipokina, insulinske osetljivosti i glikoregulacije kod gojaznih žena – uticaj sniženja telesna mase ograničavanjem kalorija

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Abstract

Bacground/Aim. Visceral fat is highly active metabolic and endocrine tissue which secretes many adipokines that act both on local and systemic level. It is believed that adipokines and "low-grade inflammatory state" represent a potential link between obesity, metabolic syndrome, insulin resistance and cardiovascular disease. Leptin and adiponectin are considered to be the most important adipokines with the potential metabolic and cardiovascular effects. Body weight loss improves insulin sensitivity and decreases risk for most complications associated with obesity. The aim of this study was to determine the effects of moderate loss of body weight on the level of leptin and adiponectin, insulin sensitivity and abnormalities of glycoregulation in obese women, to determine whether and to what extent the secretory products of adipose tissue, leptin and adiponectin contribute to insulin sensitivity, as well as to assess their relationship and influence on glycemia and insulinemia during the period of losing body weight using a calorie restricted diet. **Methods**. The study involved 90 obese female subjects (BMI $\geq$ 30 kg/m^2) of different age with weight loss no less than 5% during a six-month period by application of restricted dietary regime. The calorie range was between 1,100–1,350 kcal. Serum levels of leptin and adiponectin, fasting glucose, fasting insulinemia, and Homeostasis Model Assessment of Insulin Resistance (HOMA-R) index were determined in all the subjects initially and after weight reduction. The presence of glycemic disorders was assessed on the basis of oral glucose tolerance test – OGTT. **Results.** Applying a 6-month restrictive dietary regime the subjects achieved an average weight loss of 8.73 $\pm$ 1.98 kg and 8.64 $\pm$ 1.96%, which led to the reduction of fasting glycemia, fasting insulinemia and HOMA-R index at the maximum level of statistical significance ($p < 0.001$). The achieved reduction led to a statistically significant decrease of leptin level and increase of adiponectin level ($p < 0.001$). The correction of the established pre-diabetic disorders of glycoregulation was not statistically significant. There was a statistically significant correlation between the anthropometric parameters, leptin, adiponectin, fasting glycemia, fasting insulinemia and HOMA-R index. There was a positive correlation between leptin, fasting insulinemia and HOMA-R, as well as a statistically significant negative correlation between adiponectin, fasting insulinemia and HOMA-R index ($p < 0.01$). **Conclusion.** Body weight increase and central fat accumulation lead to changes in serum levels of leptin and adiponectin, reduction of insulin sensitivity and development of glycemic dysregulation. Secretory products of adipose tissue, leptin and adiponectin contribute to the genesis of these disorders. The obtained results show that the effect of adiponectin on insulin sensitivity is more significant. The analysis of the effects of weight loss on the investigated parameters shows that moderate weight reduction by restrictive dietary regime lead to changes of investigated parameters at the maximum level of statistical significance. Such results emphasize the importance of weight reduction in obese persons, as well as the need for consistent implementation of restricted dietary regime in the process of treatment of obesity.

Key words:
obesity; leptin; adiponectin; body mass index; women; diet, reducing; insulin resistance.

Apstrakt

Uvod/Cilj. Visceralna mast, visokoaktivno metaboličko i endokrino tkivo, sekretuje mnoge adipokine koji deluju na lokalnom i sistemskom nivou. Smatra se da su adipokini i „stanje niskog stepena inflamacije" potencijalna veza između gojaznosti, metaboličkog sindroma, insulinske rezistencije i kardiovaskularnih oboljenja. Kao najvažniji adipokini navode se leptin i adiponektin. Gubitak telesne mase poboljšava insulinsku senzitivnost i smanjuje rizik od većine komplikacija povezanih sa gojaznošću. Cilj ove studije bio je da se utvrde efekti umerenog sniženja telesne mase na nivo leptina i adiponektina, insulinsku senzitivnost i poremećaje glikoregulacije kod gojaznih žena, da se utvrdi da li i u kojoj meri se-

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kretorni produkti masnog tkiva, leptin i adiponektin, doprinose insulinskoj senzitivnosti, kao i da se proceni njihov međusobni odnos i uticaj na glikemiju i insulinemiju u toku snižavanja telesne mase primenom kalorijski ograničavajućeg načina ishrane. **Metode.** Ispitivanjem je obuhvaćeno 90 gojaznih žena (BMI ≥ 30 kg/m^2), kod kojih je u periodu od šest meseci primene ograničavajućeg dijetetskog režima došlo do gubitka telesne mase ne manjeg od 5%. Kalorijski raspon kretao se od 1 100–1 350 kcal. Kod svih ispitanica pre i posle sniženja telesne mase određivan je serumski nivo leptina i adiponektina, glikemija našte, insulinemija našte i *Homeostasis Model Assessment of Insulin Resistance* (HOMA-R) indeks. Na osnovu testa oralne tolerancije glikoze (OGTT) vršena je procena postojanja glikemijskih poremećaja. **Rezultati.** Primenom šestomesečnog restriktivnog režima ishrane kod ispitanica postignut je prosečni gubitak težine od 8,73 ± 1,98 kg ili 8,64 ± 1,96% što je uslovilo snižavanja nivoa glikemije našte, insulinemije našte i HOMA-R indeksa na maksimalni nivo statističke značajnosti, ($p < 0,001$). Postignuta redukcija dovela je i do statistički značajnog sniženja nivoa leptina i porasta nivoa adiponektina ($p < 0,001$). Korekcija ustanovljenih predijabetesnih poremećaja glikoregulacije nije bila statistički značajna. Ustanovljena je statistički značajna korelacija između antropometrijskih parametara, leptina, adiponektina, glikemije našte, insulinemije našte i HOMA-R indeksa. Ustanovljena je pozitivna korelacija između leptina, insulinemije našte i HOMA-R indeksa, kao i statistički značajna negativna korelacija između adiponektina, insulinemije našte i HOMA-R indeksa ($p < 0,01$). **Zaključak.** Gojaznost i centralna akumulacija masti dovode do izmene u serumskim nivoima leptina i adiponektina, sniženja insulinske senzitivnosti i nastanka glikemijske disregulacije. Sekretorni produkti masnog tkiva, leptin i adiponektin, doprinose nastanku ovih poremećaja, pri čemu je uticaj adiponektina na insulinsku senzitivnost, na osnovu dobijenih rezultata, značajniji. Analizom efekata gubitka telesne mase na ispitivane parametre, pokazano je da je umereno sniženje težine kod većine ispitanica uslovilo značajne promene praćenih parametara. Ovako postignuti rezultati snažno naglašavaju značaj sniženje telesne mase kod gojaznih osoba, kao i neophodnost doslednog sprovođenja ograničavajućeg načina ishrane u procesu lečenja gojaznosti.

Ključne reči:
gojaznost; leptin; adiponektin; telesna masa, indeks; žene; dijeta, redukciona; insulin, rezistencija.

Introduction

Obesity belongs to a group of most common metabolic diseases getting epidemic proportions despite public health education and initiatives to reduce it. It is one of leading causes of morbidity and mortality in contemporary society. Numerous studies, including the Framingham one as the first, clearly identify obesity as an independent cardiovascular risk factor, pointing out that its association with other known risk factors, primarily glucose dysregulation and hypertension, leads to enormous increase in the incidence of cardiovascular diseases [1].

Obesity induces insulin resistance, or "the state of reduced insulin action" in insulin-sensitive tissues with the consequent hyperinsulinemia, which is the underlying mechanism in the development of metabolic syndrome and diabetes mellitus. The prevalence of diabetes type 2 is 5 fold higher in obese men and 8.3 fold higher in obese women. The link between insulin resistance and obesity is complex, and numerous evidence suggests that adipose tissue, as hormone-active system, has effect on insulin action and glucose and lipid metabolism [2–4].

Adipose tissue produces a large number of bioactive molecules, known as "adipokines" (adipocytokine) including leptin, adiponectin, resistin, visfatin, apelin, TNF-α, IL-6, etc, that contribute significantly to the development of metabolic abnormalities associated with obesity. They participate in the regulation of appetite and energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism and hemostasis. The effects of adipokines on vascular function, immune regulation and fat metabolism, make them key players in the pathogenesis of the metabolic syndrome, and thus responsible for development of diabetes and atherovascular disorders. This refers primarily to leptin and adiponectin [5–7].

Leptin is one of the first identified adipokines with numerous effects, including effects on energy homeostasis, neuroendocrine and immune function. Leptin suppresses food intake, increases energy consumption and regulates body weight. In humans, leptin levels correlate positively with body mass index and fat distribution [8]. Clinical conditions with reduced fat mass (lipodystrophy) are characterized by reduced concentrations of leptin, significant ectopic triglyceride deposition in muscle, liver and β cells and insulin resistance, whereby administration of leptin significantly improves glycemic control, reduces level of triglycerides and improves insulin sensitivity. Consequently, inadequate action of leptin due to leptin resistence, which characterizes obesity, may contribute to the development of insulin resistance and glycemic dysregulation [9, 10].

Along with the increase of fat mass there occurs an increase in the production and secretion of numerous proinflammatory/prothrombic adipokines, including TNF-α, IL-6, CRP, PAI-1, angiotensinogen. It is recognized that obesity is a condition characterized by chronic, systemic low-grade inflammation, which is significantly supported by decline of adiponectin [11–14]. The physiological role of adiponectin has been unclear yet, although it seems that it has significant anti-inflammatory, vasculoprotective and antidiabetic properties [15]. Application of recombinant adiponectin in pharmacological studies reduces serum glucose in healthy and diabetic rodents without stimulation of insulin secretion, suggesting that it functions primarily as an insulin sensitizer and then as a regulator of glucose homeostasis. Moreover, prospective studies have shown that low level of adiponectin is associated with the increased risk of onset of diabetes which implies its potential role in the pathogenesis of insulin resistance and diabetes [16]. However, some further studies are required to support this finding [17]. Body weight (BW) loss im-

proves insulin sensitivity and decreases large number of complications associated with obesity. However, the physiological factors that play a role in improving insulin sensitivity induced by body weight loss have not been fully identified yet.

The aim of this study was to: determine the effects of moderate loss of body weight on leptin and adiponectin levels, insulin sensitivity and glycoregulation in obese women to determine relationships and influence of leptin and adiponectin on glycemia, insulinemia and insulin sensitivity.

Methods

The study included 90 obese female subjects (BMI ≥ 30 kg/m^2) of different age, who had undergone restrictive hygienic-diet regime for six months and lost no less than 5% of their body weight. The body weight of the subjects had been stable for at least three months before they were included in the study.

The weight-reduction diets were prescribed by a medical specialist and a dietitian (at the Department of Dietetic Counseling, the Institute of Public Health in Niš). The diet was administered individually based on health condition, energy needs, anamnestic data on nutrition (nutritional surveys) and established nutritional status. The calorie range was between 1,100–1,350 kcal. The study did not include individuals with established endocrine cause of obesity, diagnosed diabetes, clinically significant active cardiovascular disease, including myocardial infarction within the past six months and/or heart failure, individuals with chronic renal failure, liver failure, malignant disease or those with acute or chronic disease where therapeutic regimen might have affected research results.

For each subject anthropometric measurements and biochemical analyses were done at the beginning of the stady and after six months.

Anthropometric measurements – height, weight, waist (WC) and hip (HC) circumference were measured with the subject standing. Weight was measured while they were minimally clothed without shoes, using digital scales and recorded to the nearest 100 g. Height was measured in a standing position without shoes, using a standard anthropometer to the nearest 0.1 cm. The body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared (kg/m^2). With the participant standing and breathing normally, waist circumference was measured midway between the superior iliac crest and the costal margin (at the level of the umbilicus), using a tape measure. Hip circumference was measured at the point of maximum circumference over the buttocks. Waist to hip ratio (WHR) was calculated.

Biochemical analyses – blood samples after overnight fasting were collected for determination of fasting plasma leptin, adiponectin, glucose (FPG) and insulin. Fasting plasma leptin was measured using the ELISA method (DRG leptin enzyme immunoassay kit), expressed in ng/ml. Fasting plasma adiponectin was measured using the ELISA method (DRG human adiponectin enzyme immunoassay kit), expressed in mg/mL. Fasting plasma glucose was measured using enzymatic UV test with hexokinase, expressed in mmol/L (reference range 4.1 to 6.1 mmol/L). Plasma insulinemia was measured by ELISA method (Biosource), using a test for the quantitative measurement, expressed in mU/L (reference value to 25.0 mU/L). Insulin resistance was estimated according to homeostasis model assessment (HOMA-IR) formula [fasting glucose (mmol/L) x fasting insulinemia (mU/L) / 22.5], where it is assumed that normal weight, healthy individuals under 35 years of age have an insulin resistance of 1, which correlates well with the values obtained by means of euglycemic clamp technique [18]).

The oral glucose tolerance test (OGTT) with 75 g glucose dissolved in 300 mL of water was done in all subjects in order to screen existing disorders of glycemic control according to the current World Health Organization (WHO) classification:

- Normal glucose regulation (NGR) – fasting glycemia < 6.1 mmol/L and in the second hour OGTT < 7.8 mmol/L;
- Impaired fasting glucose (IFG) – fasting glycemia ≥ 6.1 < 7.0 mmol/L and in the second hour OGTT < 7.8 mmol/L;
- Impaired glucose tolerance (IGT) – fasting glycemia < 7.0 mmol/L and in the second hour OGTT ≥ 7.8 < 11.1 mmol /L.

Diabetes mellitus (DM) - fasting glycemia ≥ 7,0 or in the second hour OGTT ≥ 11,1 mmol/L.

Examination was conducted in the Clinic for Endocrinology, Diabetes and Metabolic Diseases, Institute of Nuclear Medicine, Clinical Center Niš, Institute of Public Health in Niš and Biochemical Laboratory "NeoLab" in Niš.

Statistical analysis was performed using SPSS (version 15.0) software. The results were presented in tables. Data are presented as frequencies, mean ($\bar{x}$), standard deviations (SD) and 95% confidence interval (95% CI). The Student's *t*-test for dependent (paired) samples (with normal distributions) and Wilcoxon Signed Ranks Test (with distributions deviating from normal) were done to test the statistical significance of differences between the parameters at the beginning and the end of the study. The χ^2-test or Fisher's exact probability test were used as non-parametric tests to compare the frequency of some attributive numerical parameters. Using Spearman's correlation coefficient – ρ or the Pearson's correlation coefficient, – *r*, respectively, the correlation and the extent of its significance between the studied parameters were determined. The strength of correlation defined by Cohen was asumed as low level – 0.10 to 0.29, mid-level – 0.30 to 0.49 and high level – 0.50 to 1.00 [19].

Results

The examined group consisted of 90 female subjects, of the average age of 41.77 ± 10.51 years (the youngest being 19, and the oldest 63 years). The coefficient of age variation was 25.16, indicating group homogeneity.

Obeying a sixth-month restrictive dietary regime the subjects lost 8.3 ± 1.98 kg or 8.64 ± 1.96% of weight on av-

erage. Of the total number of subjects, 21 (23.33%) achieved body weight loss ≥ 10%.

The basic anthropometric data, values of FPG, insulin, HOMA-R indeks, leptin and adiponectin are presented in Table 1. After 6 months of restrictive diatary regime we find a statisticaly significant reduction of BMI, waist circumference, waist/hip ratio, fasting glucose and insulinemia, as well as HOMA-R index, to the maximal level of statistical significance ($p < 0.001$). The achieved average fasting glycemia decrease was 0.47 mmol/L. Achieved body weight reduction caused a change in levels of adipokines, so that after a 6-month period there was a statistically significant decrease in leptin levels and a statistically significant increase in adiponectin levels ($p < 0.01$) (Table 1).

with the level of fasting insulinemia and HOMA-R index. All these correlations were at medium level ($\rho = 0.30–0.49$), except for a high correlation between the BMI and the HOMA-R index. Before body weight reduction a significant positive correlation was determined only between FPG and WC ($p < 0.05$). After body weight reduction this correlation persisted ($p < 0.05$) and it also became significant between FPG and BMI ($p < 0.01$) (Table 3).

A statistically significant positive correlation between leptin and all anthropometric parameters ($p < 0.001$) was determined before BW reduction. A correlation with body weight and WHR was at medium level, and with WC and BMI at high level. There were no significant correlations after body weight reduction. Correlations of adiponectin with

Table 1

Anthropometric data, FPG, insulin, HOMA-R index, leptin and adiponectin before and after body weight reduction

Parameters	Before body weight reduction	After body weight reduction
Body weight (kg)	102.37 ± 17.1*** (97.7–105.96)	93.63 ± 16.58 (90.16–97.11)
BMI (kg/m^2)	36.43 ± 5.42*** (35.3–35.57)	33.34 ± 5.26 (32.24–34.44)
Waist circumference (cm)	103.12 ± 14.3*** (100.1–106.1)	93.79 ± 12.71 (91.13–96.45)
Waist/hip ratio	0.89 ± 0.08*** (0.88–0.83)	0.82 ± 0.06 (0.81–0.83)
FPG (mmol/L)	5.72 ± 0.66*** (5.58–5.85)	5.25 ± 0.69 (5.11–5.40)
Insulin (mU/L)	27.28 ± 7.36*** (25.74–28.82)	21.36 ± 5.80 (20.14–22.57)
HOMA-R	6.96 ± 2.10*** (6.52–7.40)	5.05 ± 1.74 (4.96–5.42)
Leptin (ng/mL)	54.22 ± 25.61*** (48.85–59.58)	27.09 ± 13.56 (24.25–29.93)
Adiponektin (μg/mL)	7.11 ± 3.30 (6.42–7.80)	10.79 ± 4.60*** (9.83–11.76)

Data are presented as mean ± SD (95% confidence intervals); FPG – fasting plasma glucose; BMI – body mass index; HOMA-R – homeostasis model assessment of insulin resistence; *** $p < 0.001$

The results of OGTT show that the reduction in body weight increases the number of normoglycemic subjects from 62.22% to 71.11% and reduces the number of subjects with increased fasting glycemia and impaired glucose tolerance (Table 2). These changes are not statistically significant.

the tested parameters were negative and low, both before and after body weight reduction but one should notice a that statistically significant correlation exists only between adiponectin and BMI as well as adiponectin and WC ($p < 0.05$) before weight reduction (Table 4).

Table 2

The oral glucose tolerancie test (OGTT) results before and after body weight reduction

OGTT	Before body weight reduction	After body weight reduction
NGR	56 (62.22)	64 (71.11)
IFG	9 (10.00)	7 (7.78)
IGT	25 (27.78)	19 (21.11)
Total	90 (100.00)	90 (100.00)

Data are presented as n (%)
NGR – normal glucose regulation; IFG – impaired fasting glucose; IGT – impaired glucose tolerance

Table 3

Correlation between anthropometric parameters and fasting plasma glucose (FPG), insulin and homeostasis model assessment of insulin resistance – HOMA-R index

Parameters	Before body weight reduction			After body weight reduction		
	FPG (mmol/L)	Insulin (mU/L)	HOMA-R index	FPG (mmol/L)	Insulin (mU/L)	HOMA-R index
Body weight (kg)	0.03	0.29**	0.27**	0.15	0.39***	0.35***
BMI (kg/m^2)	0.20	0.49***	0.51***	0.34**	0.60***	0.58***
Waist (cm)	0.22*	0.38***	0.42***	0.23*	0.45***	0.40***
Waist/hip	0.04	0.37***	0.33**	0.19	0.38***	0.34***

The results are expressed as the Spearman's correlation coefficient – ρ; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Before and after the body weight reduction we determined positive statistically significant correlations between anthropometric parameters (BW and BMI, WC and WHR)

Positive low correlations of leptin and a negative correlation of adiponectin with FPG, fasting insulinemia and HOMA-R index had been established. There was a statistically significant

Table 4

Correlations between anthropometric parameters and leptin and adiponectin

Parameters	Before body weight reduction				After body weight reduction			
	BW (kg)	BMI (kg/m^2)	Waist (cm)	Waist / Hip	BW (kg)	BMI (kg/m^2)	Waist (cm)	Waist / Hip
Leptin (ng/mL)	0.38***	0.61***	0.59***	0.41***	0.03	0.03	0.06	0.10
Adiponectin (μg/mL)	-0.13	-0.23*	-0.27**	-0.01	-0.06	-0.06	-0.15	-0.05

The results are expressed as the Spearman's correlation coefficient – ρ; BW – body weight; BMI – body mass index; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

negative correlation of adiponectin with fasting insulinemia and HOMA-R index before body weight reduction ($p < 0.01$). After completion of the hygienic-dietetic regimen there was no significant correlation (Table 5).

Since there is a close link between fasting glycemia and beta cell function, it is considered that the increase of FPG within the normal range has already been associated with a decrease of beta cell function in adults. The state of increased FPG threefold increases the risk of developing type 2 diabetes and may be considered a good marker of acute insulin response [28, 29]. Several previous studies identified high normal FPG as an independent risk factor for the reduction of insulin secretion and type 2 diabetes [30]. Reports from the Bogalusa Heart study showed that adults who developed IGT or type 2 diabetes had higher values of FPG in childhood and adolescence, compared with normoglycemic persons [31]. Nichols et al. [32] observed a 6% increased risk of developing type 2 diabetes with each 0.06 mmol/L increase in FPG. People with FPG levels between 5 to 5.56 mmol /L, were at a significantly higher risk of developing beta cells disfunction and diabetes, compared to those whose values were below 4.72 mmol/L [33].

Table 5

Correlation of leptin and adiponectin with fasting plasma glucose (FPG), insulin and homeostasis model assessment of insulin resistance (HOMA-R) index

Parameters	Before			After		
	FPG (mmol/L)	Insulin. (mU/L)	HOMA-R index	FPG (mmol/L)	Insulin. (mU/L)	HOMA-R indeks
Leptin (ng/mL)	0.07	0.16	0.20	0.05	0.01	0.04
Adiponectin (μg/mL)	-0.06	-0.30**	-0.29**	-0.02	-0.08	-0.05

The results are expressed as the Spearman's correlation coefficient – ρ; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Discussion

Obesity induces increase in insulin levels and insulin resistance which further aggravates by the increase in BMI and especially with the increase in visceral fat mass. The mechanisms that influence this relationship have not yet been fully explained. There are some possible mediators like high free fatty acid levels generated by overactive lipolysis in fat, and changes in adipokines levels produces by adipose tissue, such as adiponectin and leptin [20–22].

High levels of free fatty acids interfere with glucose utilization in muscles and liver and cause various functional abnormalities (lipotoxicity), including steatohepatitis, reduction in insulin secretion, and perhaps heart failure [23–25].

Obesity predisposes to type 2 diabetes primarily by causing insulin resistance, although some other associated metabolic abnormalities may contribute to β-cell dysfunction and increased glycemic values [26]. Nowadays it is considered that the β-cell function decreases significantly in the phase of normoglycemia, that is, significantly before the development of IGT and severe degree of insulin resistance. Impaired first phase of insulin release and reduced insulin sensitivity both predict the development of type 2 diabetes. In fact, insulin resistance and β-cell dysfunction are considered to be essential defects in type 2 diabetes, but undoubtedly operate to different degrees among individuals, whereby obesity contributes to the development of both disorders [27].

Since weight gain and central obesity significantly increase the risk of developing disorders of glucose metabolism, OGTT was performed in all subjects in addition to fasting glycemia. OGTT results show that a total of 37.8% subjects had prediabetes (10% IFG and 27.78% IGT) and the largest number of obese people examined had normal glucose regulation. The average value of FPG can be categorized as "high normal fasting glucose".

The achieved body weight reduction caused statistically insignificant correlation in the frequency of prediabetic disorders, and a statistically significant reduction in fasting glycemia of 0.47 mmol/L in our patients (Table 1).

Other authors also found positive effect of body weight reduction on glucose control and prevention of diabetes. In people with prediabetes, who changed their lifestyle and lost their weight moderately (~ 5%) a reduction in the risk of developing type 2 diabetes was registered by The Da Qing diabetes study over 60%. For example, a great followed 600 people with prediabetes. After six years of follow-up, the incidence of diabetes was 68% in the group of people who received no therapy, while the risk of developing diabetes was reduced to 32%–40% in the intervention group [34]. Finnish diabetes prevention programme also showed a statistically significant risk reduction of developing diabetes (by about 60%) in a group of people with prediabetes who had adequate diet and physical activity compared to non-intervention group. This study also showed the greatest impact of body weight reduction (4.2 kg), in the very first year of follow-up [35]. Similar results were obtained by U.S. diabetes prevention program, which showed advantage of body weight loss over

the use of metformin in reducing the incidence of diabetes in people with prediabetes [36]. Data obtained in Framingham study suggested that weight loss of more than 6.8 kg reduced the risk of developing type 2 diabetes by 50% [37].

Analysing the obtained results it may be observed that the value of FPG has the strongest correlation with waist circumference, thus emphasizing the importance of abdominal obesity in development of glucose control disorders. After weight reduction, there was a statistically significant medium correlation between BMI and FPG ($p < 0.01$) and WC and FPG ($p < 0.05$), which also confirms the importance of reduction of both total and visceral fat in improving of glucose control. The correlation of the average values of BMI, waist circumference and waist/hip ratio with insulinemia and HOMA-R index before and after body weight reduction was positive and statistically significant (Table 3).

The obtained results clearly indicate that body weight gain and obesity contribute to fasting glycemia increase and insulin resistance and that weight reduction significantly leads to their reduction and improvement of cardiometabolic profile. Although the available literature data highlight stronger effects of greater weight loss on insulin sensitivity and glucose control, it is clear that even a slight weight correction (5%–10%) may lead to a statistically significant improvement in insulin sensitivity and risk reduction of developing diabetes, which was actually shown by the results of our study.

It is considered that adipokines and "low-grade inflammatory state" represent a potential link between metabolic syndrome, insulin resistance and cardiovascular disease. Leptin and adiponectin as hormones with potent metabolic and cardiovascular effects are considered to be the most important adipokines. Both hormones achieve their effect by stimulation of AMP-activated protein kinase, a key enzyme in maintaining cellular energy homeostasis. After its activation, leptin and adiponectin lead to an increase of fatty-acid oxidation, thus preventing accumulation of triglycerides and lipotoxicity, as well as to an increase of glucose transport with a reduction of triglyceride synthesis, lipolysis and glyconeogenesis, thereby synergistically causing reduction in the levels of free fatty acids and improved insulin sensitivity. These hormones also reduce the secretion of important cytokines such as TNF-α and IL-6, which contribute significantly to the development of insulin resistance [38, 39].

Obesity and the increase of fat mass cause alterations of adiponectin and leptin levels, thus provoking pathogenic mechanisms that lead to the development of comorbidity and higher mortality of these people. Although leptin level rises parallel with BMI and the increase of body fat mass its effect is attenuated due to the increase of tissue insensitivity to it, the phenomenon known as "leptin resistance". On the other hand, the circulatory levels of adiponectin inversely correlates with BMI and total fat mass, which consequently leads to its significant reduction in obese persons [40, 41].

The correlation of adiponectin with anthropometric parameters before body weight reduction is negative and statistically significant in relation to BMI and WC ($p < 0.001$). On the other hand, the correlation between leptin and these parameters is statistically significant and positive (Table 4). Fat mass and its central distribution are important for leptin and adiponectin levels. Reduction of body weight resulted in a statistically significant changes in the level of leptin and adiponectin. The values of leptin was significantly reduced, while the values of adiponectin in this period was significantly increased (Table 1). Similar results were confirmed by studies of other authors [42–45].

Previous studies also indicate that changes in the relationship between leptin and adiponectin in obese subjects result in modification of insulin sensitivity and contribute to the development of insulin resistance [46–49]. For example, Matsubara et al. [50] in a study including 486 non-diabetic females find that adiponectin and leptin are significant predictors of HOMA-R and insulin levels, regardless systolic pressure, BMI and triglycerides. Zoico et al. [51] also find that leptin and adiponectin are strongly related to total fat mass and insulin resistance in both sexes with values of these hormones significantly higher in women than in men. Ebinç, et al. [22] find that the level of serum adiponectin may represent a useful marker for identifying individuals at risk of developing obesity-related diseases, primarily cardiovascular atherosclerotic disease, regarding the determined difference of its level and the degree of insulin resistance between metabolically normal obese persons/overweight persons and obese/overweight persons with associated complications. These authors suggest that the decline of serum adiponectin is followed by an increase of HOMA-R index in all groups of subjects, whereby the largest decrease in adiponectin and insulin sensitivity was established in the group of obese patients with dyslipidemia and/or type 2 diabetes. Yamauchi et al. [52] suggest that normalization of adiponectin and leptin levels in obese and diabetic lipoatrophic mice completely eliminates insulin resistance and improves insulin sensitivity.

The analysis of our results prior to weight loss shows a positive correlation of leptin and negative correlation of adiponectin with fasting glucose, fasting insulinemia and HOMA-R index. A statistically significant correlation was found only between adiponectin with fasting insulinemia and HOMA-R index ($p < 0.01$). This indicates that decreased level of adiponectin and increased level of leptin in obese persons have effect on insulin sensitivity, but the effect of adiponectin was more significant. These results lead to a conclusion that some other pathogenetic mechanisms, apart from leptin and adiponectin, may also play a role in improving metabolic disorders induced by body weight loss. This issue, however, requires some further investigations.

Conclusion

The analysis of the effects of weight loss on the investigated parameters shows that moderate weight reduction, by the restricted diet only, caused changes of these parameters at the maximum level of significance. Leptin and adiponectin levels in obese persons have effect on insulin sensitivity and effect of adiponectin is more significant. Such results emphasize the importance of weight reduction in obese persons, as well as the need for consistent implementation of restricted dietary regime in the process of treatment of obesity.

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Comparative study of surgical treatment of acromioclavicular luxation

Komparativna studija hirurškog liječenja akromioklavikularne luksacije

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Abstract

Background/Aim. Acromioclavicular (AC) luxations most often affect athletes. The published results regarding the treatment of AC joint luxations vary. Each method has its advantages and disadvantages, so there is still no consensus on the best method of treatment. The aim of this study was to review the results of a number of surgical approaches to stabilization of AC joint recorded over the span of five years. **Methods.** This study was based on the data acquired from the analysis of 28 patients with AC luxation surgically treated in the Clinical Center of Montenegro. One group of 16 patients underwent the traditional AO method (with transfixation of AC joint with Kirschner wire and Zuggurtung tension bands) or the Bosworth method (using the coracoclaviculartransfixation screw – Zugg-Bosw group). The second group of 12 patients underwent a newer techinque with the Hook plate (Hook plate group). **Results.** All the patients had AC luxation of higher degree, stage IV–VI acording to the Rockwood scale. The average age of the two groups was very similar, with 28 being the average age of the Zugg-Bosw group, and 25 of the Hook plate group. Most patients were males (82%), injured mostly during athletic activity (75%–83%). Complications were more common and more complex in the Zugg-Bosw group, with 2 early and 8 late comlications. There are only 3 late complications in the Hook plate group, but with no significant statistical difference (p = 0.19; t = -1.34; df = 27). With respect to the subjective patient satisfaction following the treatment, the Hook plate group gave significantly better evaluations (4.4 ± 0.19)(p = 0.007; t = 2.95; df = 27). Constant score showed no significant statistical difference (p = 0.078; t = 1.8; df = 27). The Hook plate group had a better median score (90 ± 0.18) with respect to the Zugg-Bosw group (85 ± 0.40). **Conclusion.** The Hook plate method achieved somewhat better results, which indicate that this method is one of the ways to ensure a strong, stable fixation of the AC joint without transfixation. At the same time, this method does not inhibit the ligament healing and allows an early mobilisation.

Key words:
acromioclavicular joint; wounds and injuries; traumatology; surgical procedures, operative; postoperative complications; montenegro.

Apstrakt

Uvod/Cilj. Akromioklavikularne (AC) luksacije najčešće se događaju kod sportista. Objavljeni rezultati liječenja luksacije AC zgloba variraju, svaki metod ima svoje slabosti i nedostake, pa još uvijek ne postoji konsenzus o najboljem načinu liječenja. Cilj rada bio je prikaz petogodišnjeg praćenja rezultata operativnog liječenja različitim operativnim tehnikam astabilizacije AC zgloba. **Metode.** Studija je urađena na osnovu podataka koji su dobijeni analiziranjem svih 28 operativno lečenih bolesnika sa AC luksacijom tokom petogodišnjeg perioda u Klinici za ortopediju i traumatologiju Kliničkog centra Crne Gore. Prva grupa (16 osoba) operisana je ustaljenom AO metodom (transfiksacija AC zgloba sa Kirschnerovim iglama i žičanom svezom "*Zuggurtung*") i korakoklavikularnom transfiksacijom šrafom, Bosworth-ovim metodom (*Zugg-Bosw* grupa). Drugu grupu (12 osoba) činili su bolesnici, koji su operativno lečeni novijom tehnikom sa pločom Hook (*Hook plate* grupa). **Rezultati.** Svi bolesnici imali su AC luksaciju težeg stepena, stadijum IV–VI prema Rockwood-u. Prosječna starost bila je ujednačena, u prvoj grupi 28 godina, u drugoj 25 godina. Zastupljeniji su bili muškarci (82%), a najčešće su se povređivali prilikom sportskih aktivnosti (75–83%). Komplikacije su bile brojnije i ozbiljnije u prvoj grupi (*Zugg-Bosw*) – 2 rane i 8 kasnih, a u grupi *Hook plate* samo 3 kasne, ali bez statistički značajne razlike (p = 0,19; t = -1,34; df = 27). Kad je u pitanju bila subjektivna satisfakcija bolesnika nakon završenog liječenja, grupa *Hook plate* imala je znatno povoljnije i statistički značajno različite ocjene (4,4 ± 0,19) (p = 0,007; t = 2,95; df = 27).

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Constant skor pokazao je da nije bilo statistički značajne razlike (p = 0,078; t = 1,8; df = 27). Grupa *Hook plate* imala je bolji srednji skor (90 ± 0,18) u odnosu na pacijente iz grupe Zugg-Bosw (85 ± 0,40). **Zaključak.** Nešto povoljniji rezultati dobijeni su kod bolesnika operisanih *Hook plate* metodom, te se ovaj metod preporučuje kao jedan od načina koji obezbjeđuje stabilanu i čvrstu fiksaciju AC zgloba bez transfiksacije. Istovremeno, ne spriječava se zarastanje ligamenata, a omogućava se rana mobilizacija.

Ključne reči:
akromioklavikularni zglob; iščašenje; traumatologija; hirurgija, operativne procedure; postoperativne komplikacije; crna gora.

Introduction

The first studies on acromioclavicular (AC) luxation repair were by Hippocrates, Galen, and Paul of Aegina. They recommended conservative management with compressive bandages to keep the clavicle in a normal position. The first surgical repair of an acute AC dislocation is credited to sir Samuel Cooper who, back in 1861, used a loop of silver wire to approximate the clavicle and acromion process [1]. Subsequently, numerous other techniques were reported, including suture repair of the AC ligaments and coracoclavicular (CC) ligament, tendon graft for reconstruction, and fixation with nails, screws or wires. Even today, however, there is no consensus on the best resolution of this problem [2, 3].

More often than not, the injury occurs when a direct force is applied to the upper part of the acromion, when, during the fall, the arm is in adduction. Less comonly, the injury occures when a force is applied indirectly like, for instance, when a person falls on a streched-out arm [4, 5].

AC luxations mostly affect athletes, especially those who engage in contact sports (football, rugby, judo, hokey) [6]. Young athletes (in their teens or twenities) are particularily prone to this type of injury. Also, men are five to ten times more likely to be affected than women. These injuries are very common, and cause up to 40% of all shoulder injuries and up to 3% of all sports injuries [7].

AC joint luxations can be classified in several ways. Cadenat [8] differentiated incomplete injuries, in which only the capsular AC ligaments were torn, from injuries that involved disruption of both the AC and CC ligamentous structures. Allman [9] and Tossy et al. [10] later recognized 3 different types of AC separation based on the similar criteria.

Rockwood [11] has expanded this classification by including 3 additional variants. Type IV injuries are defined by posterior displacement of the clavicle relative to the acromion with buttonholing through the trapezius muscle. In type V injuries, the clavicle is widely displaced superiorly relative to the acromion as a result of disruption of muscle attachments. The rare type VI injuries are characterized by inferior displacement of the distal clavicle below the acromial process or the coracoid process. This classification is dominant today [11, 12].

In general, it is commonly accepted that lower degree AC luxations (I–III degree) are treated conservativelly, while higher degree AC luxations (IV–VI degree) are treated surgically. There is, however, lack of concensuse on the treatment of III and IV degree of AC luxation. Minority of authors [13, 14] argue for a conservative approach, while the majority contends that surgery is the more approprate approch.

There is a number of different surgical approaches to affixiate the AC joint, such as the use of Kirschner wires, cerclage wires, transfixation screws, different types of plates, together with the use of sutures, ligament transpositions, or various ransplants (fascia lata, hamstring tendons, etc.) [15, 16]. The newest technques include artroscopic fixations, the use of which requires endobutton, special types of hard seams, anchor with or without tendom grafts. Also, the authors often favorize the modified Weaver-Dunn method [17, 18]. The published results of all these approaches vary, every method has its strengths and weaknesses, so consensus on the best approach remains unclear [19].

The goal of this study was to compare both early and later results of the surgical approaches to luxation of the AC joint, as they are used at the Traumatology Clinic at the Clinical Center of Montenegro (CCM). The focus will be on the approach using Kirschner wire – the "Zuggurtung" and Bosworth method, and on the approach using the Hook plates. The later approach has been utilized at the CCM since 2005.

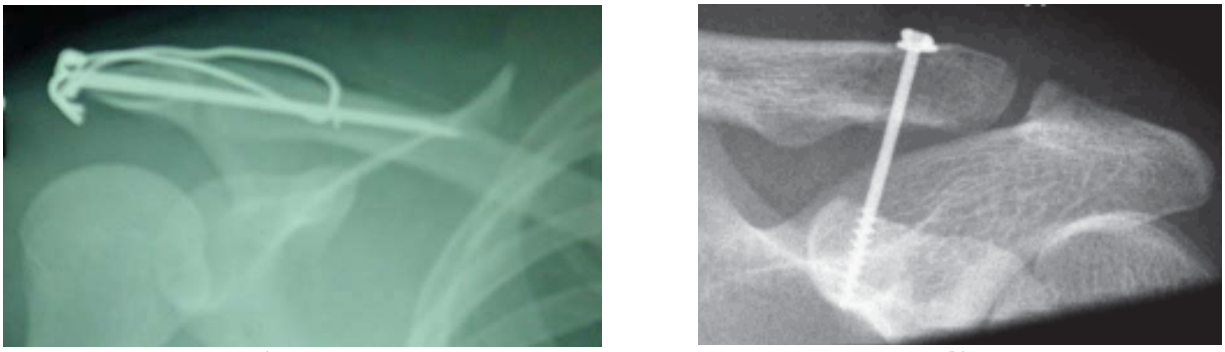
Methods

This study analysed the results of surgical treatment of 28 patients treated from January 2005 to June 2010 in the CCM Traumatology Department. These patients were divided in two groups based on the method of the surgical approach to AC joint luxation. The first group was made of 16 patients treated with, up to that point, widely accepted surgical methods: the AO method [20], which encompasses the use of two Kirschner wires and the Zuggurtung tension band, and the Bosworth method, which requires the use of coracoclavicular transfixation screw [21, 22]. This group we marked as the Zugg-Bosw group (Figures 1a, b).

The second group was made of 12 patients who were treated with the newer method which utlizes the Hook plate, and the group was named accordingly [23] (Figure 2).

Presurgical procedure was standard for all patients and included detailed anamnesis, clinical examination of the AC joint (with all patients suffering a loss of normal shoulder contours, with a sticking-out clavicle, pain and an inability to function normaly) and radiographic diagnostics (axillary, radiographic, radiographic in AP position without pressure and radiographic with a 5 kg pressure).

Indication for surgical treatment was based on the degree of the joint instability, which in turn was based on Rockwood's classification of different degrees of the AC joint luxation. The patients with IV–VI degree underwent surgery.



a) **b)**

Fig. 1 – a) Two Kirschner wires and a Zuggurtung tension band; b) Coracoclavicular transfixation screw, Bosworth method

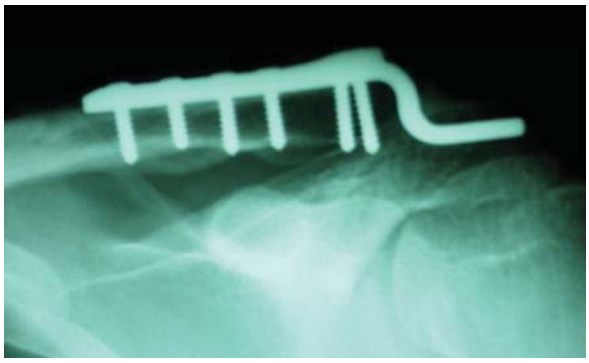


Fig. 2 – Clavicle Hook plate

The average duration of the postsurgical follow-up review was 11 months (a span of 6–36 months). To achieve the most objective analysis of the clincal results of these patinets we used the following parameters: pain, activities, range of motion, power (PARP) – where we used the Constant Score Scale (CSS) [24, 25].

Naturally, we also understood that a final result would be incomplete without a subjective evaluation by patients. We asked our patients about their opinion on the achieved results like, for instance, whether they are able to work in the same manner as before the injury, whether any pain was left in the shoulder, whether they felt an equal mobility and strenght in the shoulder as before the injury, and whether they experinced any other complications connected to their treatment at the CCM. The subjective evaluation was done according to the Likert scale [26].

The comparisons between the groups were carried out using one way ANOVA, with Bonferroni *post-hoc* testing for multiple comparisons. A repeated measure ANOVA model was fit for each response using SAS Proc Mixed software (SAS Institute, Inc, Cary, NC), and the Bonferroni test was again employed to control for multiple comparisons. The *t* values and degrees of freedom were reported for all linear regression ANOVAs. Differences were considered significant at values of $p \leq 0.05$. All results were presented as mean $\bar{x} \pm SD$.

Results

The results are based on the five years of a follow-up examination of the two groups of pateints treated in the CCM, the Zugg-Bosw group (n = 16) and Hook plate group (n = 12). The average age in the first group was 28 (18–52 years), and in the second 25 (17–50 years). Statistically, no significance existed between the two groups with respect to age. In addition, with respect to gender, there were much more male than female patients (82% *vs* 12%, respectively). The Zugg-Bosw group had 13 male and 3 female patients (81% and 19%, respectively), and the Hook plate group had 10 male and 2 female patients (83% and 17%, respectively).

With respect to the manner of the injury of the AC joint, athletic activity proved to be the main cause in both groups. The Zugg-Bosw group numbered 12 (75%) and the Hook plate group numbered 10 (83%) such patients. Statistically, there was no significant difference between the two groups with respect to the manner of injury (p = 0,61; t = 0,52; df = 27). A small number of patients were injured due to traffic accidents (Zugg-Bosw, n = 2; Hook plate, n = 1). Accidental falls also had a minor presence (Zugg-Bosw, n = 2; Hook plate, n = 1). The analysis showed no significant difference in the presence of either of these two causes in either of the two groups (p = 0.74; n = -0.34; df = 27). The causes of the AC joint injuries are presented in Table 1.

Table 1

Demographic evaluation and classification of injuries in the studied population

Patients' characteristics	Zugg-Bosw group	Hook plate group	*p*
Mean age (years)	28 (17–50)	25 (18–52)	n.s
Male [n (%)]	13 (81)	10 (83)	n.s
Female [n (%)]	3 (19)	2 (17)	n.s
Injuries/sports [n (%)]	12 (75)	10 (83)	0.61
Injuries/traffic [n (%)]	2 (12.5)	1 (8.5)	0.74
Injuries/falls [n (%)]	2 (12.5)	1 (8.5)	0.74

Most patients did not wear any imobilizators after the surgery. In the Zugg-Bosw group, 2 patients wore Desault's bandage for 3 and 4 weeks, respectively, and 2 patients wore arm slings for 2 weeks each. In the Hook plate group, only 3 patients wore imobiliztors, that is, arm slings, and again for 2 weeks each. The results show that patients in the Zugg-Bosw group spent on average more time in immobilization when compared to patients from the Hook plate group (0.75 + 0.34 *vs* 0.41 + 0.29, respectively). However, there was no statisticaly significant difference between these two groups (Figure 3).

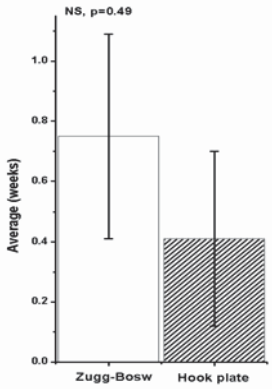


Fig. 3 – Postoperative immobilization; Bar graph showing the average time (in weeks) that the patients spent in postoperative immobilization after Zugg-Bosw (white column, left) and Hook plate (dashed column, right) types of surgery. Note that patients in the Zugg-Bosw group spent a slightly longer time in immobilization than in the Hook plate groups, but the difference was non-significant. The results were presented as averages with standard error bars (SE)

During surgeries, we used the appropriate osteosynthetic material. The next surgical manuever involved the removal of that material. Our results showed that the average period from surgery to removal of osteosynthetic material was 4.6 months in the Zugg-Bosw group, and 4.5 months in the Hook plate group. There was no statisticaly significant difference in the lenght of time from surgery to the removal of osteosynthetic material between these two groups (p = 0.82; t = -0.22; df = 27) (Figure 4).

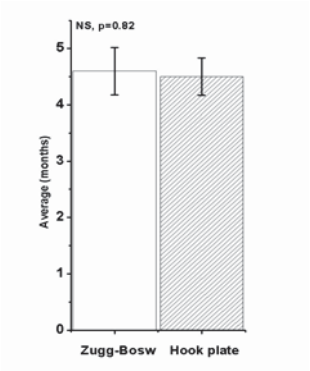


Fig. 4 – Removal of osteosynthetic material; Bar graph showing the average time (in months) for the removal of osteosynthetic material after Zugg-Bosw (white column, left) and Hook plate (dashed column, right) types of surgery. Note that there was no statistical difference in length of removal of osteosynthetic material between these two groups of patients. The results were presented as averages with standard error bars (SE)

Postsurgical complications were different in kind, time of apperance and degree. The patients from the Zugg-Bosw group had a higher number of later complications (8 *vs* 16) than was the case with the Hook plate group patients (2 *vs* 12; p = 0.19; t = -1.34; df = 27). There were also more deformities in the first group (2 *vs* 1; (p = 0.74; t = -0.34; df = 27). In addition, there were more calcifications found in the Zugg-Bosw group (2/16) than in the Hook plate group (1/12; p = 0.74; t = -0.34; df = 27). However, statistical analysis revealed no significant difference in the occurence of these complications. Notably, the Zugg-Bosw group had 2 post-surgical infections and 3 looseing of alenthesis (p = 0.12; t = -1.6, df = 27). Such complications were absent the Hook plate group (Table 2).

Evaluation of patient's subjective satisfation showed a very significant difference between two goups. Using the Likert scale from 1 (bad) to 5 (excellent) to grade their postsurgical states, the patients from the Zugg-Bosw group evaluated their state as good (3.0 ± 0.39), while patients from the Hook plate group gave a much better grade (4.4 ± 0.19; p = 0.007, t = 2.95, df = 27) (Table 3).

Table 2

Postoperative complications after Zugg-Bosw and Hook plate treatments

Complications	Zugg-Bosw group	Hook plate group	p
Early [n (%)]	2 (12.5)	0 (0)	0.22
Late [n (%)]	8 (50)	3 (25)	0.19
Infection [n (%)]	2 (12.5)	0 (0)	0.22
Loosening of alenthesis [n (%)]	3 (19)	0 (0)	0.12
Deformity-limited movement [n (%)]	2 (12.5)	1 (8)	0.74
Calcification [n (%)]	2 (12.5)	1 (8)	0.74
Impingement [n (%)]	1 (6)	1 (8)	0.84

Table 3

Evaluation of patient satisfaction and pain, activity, range of motion and power (PARMP)

Scale	Zugg-Bosw group	Hook plate group	p
Patient satisfaction (Likert)	3.0 ± 0.39	4.4 ± 0.19	0.007
PARMP (constant score scale)	85 ± 1.9	90 ± 1.1	0.078

Values are expressed as $\bar{x}$ ± SD

An important objective indicator of the postsurgical state – Pain, Activity, Range of Motion, Power – was graded by using the CSS. The maximum number of points for Pain was 15, for Activity 20, for Range of Motion 40 and for Power 25 (Table 3). There was statistically no significant difference between the two groups ($p = 0.078$, $t = 1.8$, $df = 27$). Patients from the Hook plate group had a better median score (90 ± 0.18) with respect to the patients from the Zugg-Bosw group (85 ± 0.40).

The latter two parameteres show that the Hook plate method gave somewhat better results for our patients who suffered from the AC joint luxation than did the classical Zugg-Bosw method which was almost an exclusive approach in the preceding years.

Discussion

In the last five years (2005–2010), there were 28 patients treated in the CCM Traumatology Clinic for luxation of the AC joint. Indications for surgical treatment were clinical examination and radiography of the shoulder which revealed IV–VI degree of injury based on the Rockwood's scale.

Many methods of fixating the AC joint have been described, but there are certain dilemmas as to which implants are to be used. The AO technique with two Kirschner wiresand a wire binder of the Zuggurtung type often causes migration of the Kirschner wire, while transclavicular screw may break the clavicle, which warrants their early removal, which in turn brings more dislocation and instability to the AC joint, ultimatelly ending in pain and disfunctionality.

The Hook plates have been on the market for a relativelly short time. Its design, where the plate is above the clavicle and the hook below the acromion, provides a very good stability of the AC joint. However, it also provides a danger of a subacromial impingement.

As there is no unanimous view about the best approach to AC joint luxation, in our clinic we used both the traditional methods: Zugg-Bosw method and the newer Hook plate method.

With respect to gender, male patients were much more numerous than female patients (82% *vs* 12%, respectively). In the Zugg-Bosw group, gender distribution was 13 male and 3 female patients (81% and 19%, respectively). In the Hook plate group, there were 10 male and 2 female patients (83% and 17%, respectively). This is in accordance with the statistical data presented by other authors. Rockwood contends that AC joint injuries are seen especially in competitive athletes, and occur most frequently in the second decade of life. Males are more commonly affected than females, with a male-to-female ratio of approximately 5:1 [27].

Most of our patients injured themselves during athletic activities (22 out of 28, 78%), some received injury due to traffic accidents (3 out of 28, or 11%) and some received injury due to accidental falling (3 out of 28, 11%). The analysis revealed no statistically significant difference in the occurrence of these causes of injury ($p = 0.74$; $n = -0.34$; $df = 27$).

Most of our patients did not wore any imobilizators during the post-surgical tretment. The subjective opinion of the surgeon about the stability of the osteosynthesis was the key factor with regards to placement of the imobilizators (Desault or arm slings). Cirstoiu et al. [28] and Zarzycki et al. [29] contend that post-surgical imobilizators should be in lace for up to 4 weeks, especially in the case of percutaneous fixations.

The average period from surgery to removal of osteosynthetic material was 4.6 months in the Zugg-Bosw group, and 4.5 months in the second Hook plate group. There was no statisticaly significant difference in the lenght of time from surgery to the removal of osteosynthetic material between these two groups. Koukakis et al. [30] recommend extraction of the osteosynthetic material within 3 months because of the possibility of subacromial impingement.

With respect to postsurgical complications, the patinets from the Zugg-Bosw group had a larger number of complications than did the patients from the Hook plate group. Zugg-Bosw group had 2 exterior infections which were treated with regular dressings and oral antibiotics. The osteosynthetic material became loose (2 screws used in the Bosworth method and 1 Kirschner wire), so one patient experinced deformity in the AC joint, limited movement and pain. Two patients in this group had a deformity-limited movement. Calcification between clavicle and processue coracoideus was identical, but there were no functional or esthetic irregularities. There was one case of subacromial impingment. In the Hook plate group, there was one case of deformity-limited movement, and one case of calcification and subacromial impingment, without functional irregularities. Still, the difference was not statistically significant. This is in accordance with Winstein et al [31].

The evaluation of the patients' subjective satisfation showed very significant difference between the two goups. Using the Likert scale from 1 (bad) to 5 (excellent) to grade their post-surgical states, the patients from the Zugg-Bosw group graded their state as good while patients from the Hook plate group gave a much better grade. In the available literature, we did not find that other authors graded the subjective satisfaction in this way.

Using the CSS, we received an objective indicator of the post-surgical state of our patients from the both groups. The PARMP results show that there was no statistically significant difference, but the patients from the Hook plate group received a better median score than the patients from the Zugg-Bosw group. These results are in accordance with those published by Ladermann et al. [32].

The newest data reveals that posttraumatic artritis occurs more frequently when transarticular fixations of the AC joint are used [33]. Therefore, the majority of authors argues for a temporary fixation between the coracoideus and the clavicle, and not via the acromioclavicular joint. Otherwise, migration of the wires is likely to happen and will probably cause certain complications, as described by Lindsey et al. [34].

Conclusion

Because of the small number of patients examined, the results of this study must be taken with some reserve. Still,

we can conclude that Hook plate allows stabile and strong fixation of AC luxation, and at the same time does not inhibit healing of the ligaments and allows for early mobility. This method provides good short term results with a small number of complications. This study shows that further research on both short and long term results are needed to bring a clearer understanding of the more advanced techniques.

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Changes in motor cortex excitability associated with muscle fatigue in patients with Parkinson's disease

Promene ekscitabilnosti motorne kore udružene sa zamorom mišića kod obolelih od Parkinsonove bolesti

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Abstract

Background/Aim. Transcranial magnetic stimulation (TMS) is a standard technique for noninvasive assessment of changes in central nervous system excitability. The aim of this study was to examine changes in responses to TMS in patients suffering from Parkinson's disease (PD) during sustained submaximal isometric voluntary contraction [60% of maximal voluntary contraction (MVC)] of the *adductor pollicis* muscle, as well as during a subsequent recovery period. **Methods.** Cortical excitability was tested by single TMS pulses of twice of the motor threshold intensity applied over the vertex. Testing was carried out during the sustained contraction phase every 10 s before and every 5 s after the endurance point, as well as at rest and during brief 60% MVC contractions before (control), immediately after the sustained contraction, and at 5 min intervals during the recovery period. **Results.** Although the PD patients could sustain the contraction at the required level for as long period of time as the healthy subjects (though contraction level subsided more rapidly after the endurance point), effects of muscle fatigue on the responses to TMS were different. In contrast to the findings observed in the healthy people where motor evoked potentials (MEP) and EMG silent period (SP) in fatigued muscle gradually diminished during contraction up to the endurance point, and increased thereafter, in the majority of patients no changes occurred in MEP size (peak and area) of the *adductor pollicis* muscle, either before or after the endurance point. On the other hand, changes in the SP of this muscle differed among the subjects, showing a gradual increase, a decrease or no changes in duration. The trends of changes in both MEP size and SP duration in the *musculus brachioradialis* varied among the tested PD patients, without any consistent pattern, which was in contrast with the findings in the healthy people where both measures showed a gradual increase from the beginning of the sustained contraction. A complete dissociation between changes in MEP and SP during fatigue was also of note, which differed sharply from the findings in the healthy people in who fatigue induced changes in these measures followed identical patterns. **Conclusion.** These results in the PD patients suggest the presence of impairment and/or compensatory changes in mechanisms responsible for adaptation of voluntary drive as well as for matching between cortical excitation and inhibition which become manifest in demanding motor tasks such as those imposed by muscle fatigue.

Key words:
muscle fatigue; parkinson disease; motor cortex; transcranial magnetic stimulation.

Apstrakt

Uvod/Cilj. Transkranijalna magnetna stimulacija (TMS) je standardna tehnika za neinvazivnu procenu promena ekscitabilnosti centralnog nervnog sistema. Cilj rada je bio da se prikažu promene odgovora na TMS kod obolelih od Parkinsonove bolesti (PB) za vreme trajanja submaksimalne voljne izometrijske kontrakcije [60% maksimalne voljne kontrakcije (MVK)] mišića *adductor pollicis*, kao i tokom perioda oporavka. **Metode.** Kortikalna ekscitabilnost testirana je TMS pulsevima dvostruko većeg intenziteta od motornog praga. Testiranje je vršeno za vreme održavanja kontrakcije na svakih 10 s do tačke izdržljivosti i na svakih 5 s posle toga, a, takođe, u miru kao i za vreme kratkotrajnih 60% MVK u periodu pre (kontrola), neposredno posle održavanja kontrakcije, i u intervalima od pet minuta za vreme perioda oporavka. **Rezultati.** Iako su bolesnici sa PB mogli da održavaju zahtevani nivo kontrakcije jednako dugo kao i zdravi ispitanici (mada je nivo opadao brže nakon tačke izdržljivosti), efekti mišićnog zamora na odgovor izazvan TMS-om

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bili su različiti. Za razliku od zdravih ispitanika kod kojih se motorni evocirani potencijali (MEP) i trajanje perioda EMG tišine (PT) u zamaranom mišiću postepeno smanjuju tokom kontrakcije do tačke izdržljivosti, a zatim rastu, kod većine bolesnika nije došlo do promena veličine (maksimalna amplituda i površina) MEP mišića *adductor pollicis*, bilo pre ili posle tačke izdržljivosti. S druge strane, promene PT ovog mišića su se razlikovale među ispitanicima, pokazujući bilo postepeno povećanje, smanjenje ili odsustvo promena. Promene kako amplitude MEP tako i trajanje PT u EMG mišića brahioradialisa varirale su među bolesnicima sa PB, bez nekog dominantnog obrasca, po čemu su se, takođe, razlikovale od promena nađenih kod zdravih ispitanika, kod kojih su se oba parametra postepeno povećavala od početka održavanja tonične kontrakcije. Upadljiva je, takođe, i potpuna disocijacija između promena MEP i PT tokom zamora, što je u oštroj suprotnosti sa nalazom kod zdravih ispitanika gde su promene ovih parametara pratile identičan obrazac. **Zaključak.** Rezultati kod bolesnika sa PB ukazuju na postojanje oštećenja i/ili kompenzatornih promena mehanizmima odgovornih za adaptaciju voljne pobude i usklađivanja kortikalne eksitacije i inhibicije, koji se manifestuju tokom mišićnog zamora i u drugim zahtevnim motornim zadacima.

Ključne reči:
mišići, zamor; parkinsonova bolest; motorna kora; stimulacija, magnetna, transkranijalna.

Introduction

A possibility that the central motor drive might also be affected in fatigue has received the least experimental attention as a possible factor in the development of muscular fatigue. In fact even though few would argue that the changes in voluntary effort to adequately maintain desired contraction level, is the most likely explanation of fatigue in the majority of normal activities, it was only until recently that this phenomenon was examined in a more direct way. Using transcranial magnetic stimulation (TMS), standard technique for noninvasive assessment of changes in central nervous system excitability [1], several studies have reported on changes in central motoneurone drive during muscle fatigue [2–5]. In our previous study [6], it was shown in healthy subjects that both the motor evoked potential (MEP) magnitude (peak and area) and duration of the silent period (SP) in electromyoneurography (EMG) of the *adductor pollicis* muscle change in parallel during a sustained 60% maximal voluntary contraction (MVC): they gradually decrease up to the endurance point and increase thereafter. MEPs elicited at rest immediately after the fatiguing contraction were larger while those elicited later on during the recovery period did not differ significantly from the controls. MEPs and SPs of the *musculus brachioradialis*, which was not activated voluntarily, increased gradually throughout the sustained 60% MVC of the *adductor pollicis* muscle, while those during the recovery period did not differ from the controls. The changes in both MEP magnitude and SP duration have been supposed to be due mainly to changes in central excitatory and inhibitory processes, foregoing to motor cortex output neurons, in an attempt to sustain muscle activity in spite of its fatigue.

Cerebral motor cortex areas receive most of the basal ganglia output, therefore deficits in movement control that occur in basal ganglia diseases should inevitably be reflected on the activity of cortical cells. In monkeys, it was shown that lesion of the substantia nigra can produce substantial changes in the activity of neurons in the motor areas of the cortex [7]. Also, involvement of basal ganglia in the regulation of motor activity in healthy humans was presented in the study by Dettmers et al. [8], by showing that basal ganglia take part in sustaining submaximal isometric contraction. On the other hand, fatigue has long been recognized as a common and frequently disabling symptom in Parkinson's (PD) disease [9–11]. Patients with PD report that fatigue prevents sustained physical activity [11]. A pathophysiological correlate of fatigue associated with PD is unknown, with the emphasize on the mental aspects [12]. However, impaired adaptation of cortical motor activity to muscle fatigue in PD disease could also be expected.

Therefore, the aim of this study was to examine changes in the excitatory and inhibitory motor processes in PD patients, during fatiguing submaximal (60% MVC) voluntary contraction of the *adductor pollicis* muscle using TMS. Responses of a remote muscle (*brachioradialis*), not voluntarily activated, were also recorded.

Methods

The study involved 11 right-handed PD patients (4 women), aged 39–67 years (mean 56.2 ± 9.7 years). All the patients were on optimal dopaminomimetic therapy for at least three months, had no medication related complications and/or side effects, and showed neither marked motor deficits nor signs of dementia (in all the patients the Mini Mental State Examination score was above 24; 8 patients were in stages I or II according to Hoehn and Yahr, and 3 patients in stage III). The patients with marked tremor were excluded from the study. The procedures were approved by the local Ethics committee and all the subjects gave their informed consent.

For comparison, we used data from our previous study obtained in a group of healthy people using the same experimental design [6]. The group consisted of 13 right-handed people (5 women) aged 25–45 years. This historical control group was younger than the group of PD patients in this study. However, in view of a recent report of lack of aging effect on the MEP/SP ratio in healthy people by Oliviero et al. [13], and given that the study was designed to study the pattern of changes in MEP and SP during development of fatigue, rather than their absolute values, and that one of the main findings of our previous study was the same pattern of changes of MEP and SP, this control group might be considered as good enough for the purpose of the study.

Muscle contraction and EMG recording

Experiments were performed on the *adductor pollicis* muscle as described previously for healthy subjects [6]. The forearm and fingers were firmly fixed and held in pronated position. The thumb was attached to the force transducer (Grass FT-10). Its output was fed to the computer (see later) and displayed on the oscilloscope screen to provide a visual feedback signal for the sustained muscle tension. Surface EMG was recorded from the *adductor pollicis* muscle as well as *musculus brachioradialis* (in 10 PD patients) by Arbo silver/silver chloride electrodes positioned, for the thenar, as described by Bigland-Ritchie et al. [14]. EMG signals were amplified (2.000x) using QT-5B Leaf Electronics amplifiers and filtered (1 Hz–3 kHz). Both the force and EMG (actual and full wave rectified) signals were digitized (sampling rate 3,000 Hz) by CED 1401 plus. SIGAVG computer program was used for further analysis. MEP latency, amplitude (base to peak in the rectified signal), area and duration were measured. To minimize the errors that might be induced due to basic EMG and/or mechanical artifacts MEP start and end were estimated by observing both unrectified and rectified records. Also, some records were analyzed independently by two experimenters. In the activated muscls, duration of the SP, from the end of MEP to the reappearance of EMG, was also measured.

Transcranial magnetic stimulation

Motor cortex was stimulated by a Magstim 200 stimulator with 90 mm diameter round coil. The coil was centered at the vertex and held tangentially with respect to the skull. Threshold at rest was estimated by applying magnetic pulses of increasing strength until MEPs ≥ 100 μV occurred in 6/10 trials [15]. To elicit MEPs during the experiment, TMS of twice of the threshold strength was applied. Particular care was taken to preserve the initial position of the coil throughout the experiment.

Electrical nerve stimulation

Electrical nerve stimulation of the ulnar nerve was applied to the wrist to obtain maximal M waves in order to check the appearance of peripheral muscle fatigue. In total 6 single 500 μs stimuli were delivered at 5 s intervals, before and immediately after fatiguing contraction was performed. When changes in H-reflex were observed (see later) the same stimuli were applied of the strength eliciting 50% of the maximal H-reflex amplitude.

The experimental protocol

The experimental protocol was as described before [6]. Briefly, first the MEP threshold and 60% MVC had been determined. Given that the patients with PD have bradykinesia, MVC was measured during the 3 consecutive attempts at 1 min intervals, each time allowing sufficient time to the patients to reach maximum force. It should also be noted that there were no significant differences in the absolute level of the exerted forces between the PD patients and normal subjects [6]. After MVC had been determined 20 min rest was allowed to the muscle. Thereafter 6–10 TMSs of twice as the threshold intensity were applied at rest and during 6–10 short-lasting (3–4 s) 60% MVC contractions at 10 s intervals. Electrical ulnar nerve stimulation was then applied. After 10 min rest sustained 60% MVC contraction was performed. It was maintained up to the endurance point (60–140 s in 8 subjects and around 3 min in the remaining 3) and as long as possible thereafter (up to 30 s in 6 subjects, 50 s in the additional 4 and 160 s in 1 subject). Since this period was rather short, in the most of the subjects, TMS was carried out at 10 s intervals up to the endurance point but at 5 sec thereafter. Electrical nerve stimulation was then applied to check for the peripheral fatigue. Immediately after that, 6–10 TMSs at 10 s intervals were applied at rest. During the period of recovery, 5 and 10 min after the end of the fatiguing contraction, 6–10 TMSs both at rest and during short-lasting (2 s) contractions of 60% MVC intensity were applied.

H-reflex was tested, on separate days, in 6 subjects. It was obtained in 4 of them and its changes were observed following the same protocol.

Data analysis

Statistical significance of the differences between the measured characteristics of MEPs (latency, peak, area) and SPs (duration) elicited after the sustained 60% MVC contraction and those elicited before (control) was estimated using the Student's *t*-test. Changes in M-wave and H-reflex amplitude were estimated in the same way. A significance of trends of changes in MEP magnitude (peak and area), SP duration and H-reflex amplitude during the sustained contraction was estimated by linear regression analysis.

Results

Both MEPs and SPs of normal characteristics occurred in EMG records of both *adductor pollicis* and *brachioradialis* muscle in response to TMS.

Fatigue-associated changes in TMS cortical excitability in the adductor pollicis muscle

In contrast to the responses we had previously described in healthy subjects MEP magnitude (both peak and area) showed no consistent changes, either before or after the endurance point, in all but one of the PD patients examined, in which it gradually decreased from the start up to the end of the sustained 60% MVC contraction. A significant gradual decrease in the peak but not in the area was found in an additional subject. Actual EMG records of one subject and the mean MEP areas for the group, normalized for every subject with respect to the mean of control MEPs elicited during the short-lasting contractions before the fatiguing one, and centered at the endurance point are presented in Figures 1A and B, respectively. The trend of changes in the MEP area for the group was not significant either up to the endurance point ($p = 0.747$) nor thereafter ($p = 0.683$), as well as for the whole period ($p = 0.573$). No significant differences were found in the areas and/or peaks of MEPs neither at rest nor during the short-lasting contractions, during the recovery period in

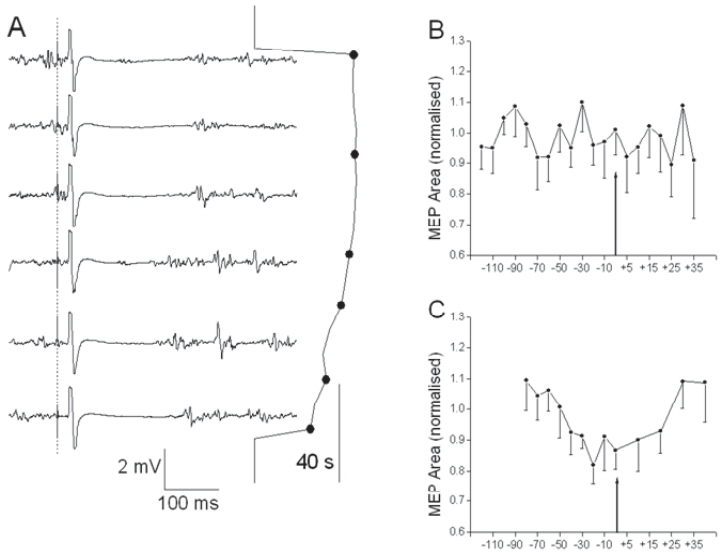

Fig. 1 – Changes in the *adductor pollicis* motor evoked potential (MEP) magnitude and cortical silent period during and after sustained 60% maximal voluntary contraction (MVC)

A – electromyoneurographic records (left) taken at the moments indicated on the 60% MVC force trace (right). Vertical broken line in MEP records indicates transcranial magnetic stsimulation (TMS) pulse. B – Parkinson diseases (PD) patients; MEP area, mean and standard deviation (SD) for 11 subjects, normalized for each subject with respect to the control MEP during short-lasting 60% MVC contractions before the sustained contraction, and centered at the endurance point (arrow). Abscissa – time of TMS, starting from the endurance point (0). C – healthy subjects (data taken from [6])

comparison to those obtained before the sustained contraction (control). Neither MEP latency nor duration showed consistent changes either before or after the endurance point during the sustained 60% MVC contraction or during the recovery thereafter.

In the healthy subjects SP duration in EMG activity changed in parallel with the MEP magnitude during sustained 60% MVC contraction. In 6 PD patients SP duration behaved in the same way as MEP magnitude, showing no changes during the sustained contraction. In the remaining subjects it showed changes that differed in trend both from changes in MEP magnitude and among the subjects (Figure 2A). SP duration in response to TMS during the recovery period did not differ significantly from the responses recorded before the sustained 60% MVC.

Fatigue-associated changes in TMS cortical excitability in the brachioradialis muscle during sustained contraction of the adductor pollicis muscle

As we previously showed in the healthy subjects both MEP magnitude and SP duration of the *brachioradialis* muscle increased gradually throughout sustained 60% MVC of the *adductor pollicis* muscle. In contrast, in the PD patients their changes showed different trends both within and between the subjects (Figure 2B). The magnitudes of the MEPs and duration of SPs in response to TMS, applied both at rest

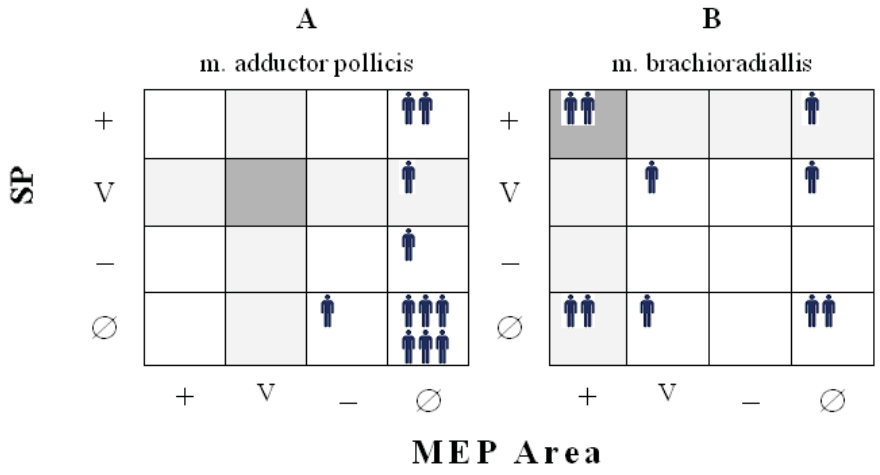

Fig. 2 – Distribution of patterns of changes in motor evoked potential (MEP) magnitude and silent period (SP) duration in electromyography (EMG) of the *adductor pollicis* muscle (A) and *musculus brachioradialis* (B) during sustained 60% maximal voluntary contraction (MVC) of the *adductor pollicis* muscle

+ indicates increase, - decrease, 0 no changes, "V" profile – decrease up to endurance point and increase thereafter. Shaded areas indicate patterns found in the healthy subjects [6]

and during short-lasting *adductor pollicis* contractions during the recovery period did not differ significantly from those elicited before the sustained contraction. Neither MEP latency nor duration showed consistent changes either before or after the endurance point in the sustained contraction or in the recovery thereafter.

H-reflex and M-wave amplitude

The amplitude of the M-wave in the *adductor pollicis* muscle, elicited by ulnar nerve electrical stimulation after the sustained, fatiguing 60% MVC contraction, in 6 of the subjects did not differ significantly from the responses to the same stimulation applied before this contraction, while in the other 5 it showed a decrease with simultaneous increase in duration.

H-reflex was tested in 6 subjects and it was possible to obtain it in 4 of them. In 3 subjects its amplitude showed no changes during the sustained fatiguing 60% MVC contraction, while in the remaining one it was decreased after the endurance point. In this subject it was smaller also at rest immediately after this contraction, while later on during the recovery its amplitude did not differ from the control.

Discussion

Transcranial magnetic stimulation (TMS) has been shown to activate motor cortical output neurons both directly and transsynaptically [1]. Therefore, changes in the responses to TMS, both in MEPs as well as in the SP should reflect changes in excitability of corticospinal neurons and/or their inputs, of both cortical and subcortical origin. While SP duration depends primarily on central nervous activity [16, 17] indicating the level of inhibition in the cortex at the time of the stimulus [18, 19], MEP magnitude might be influenced by changes in spinal cord neurons and muscle excitability. Contribution of changes at the levels below the motor cortex should therefore also be taken into account. Changes in the M-wave amplitude and duration in the 5 examined subjects indicate that peripheral fatigue [20, 21] might contribute to the decrease in MEP magnitude. At the spinal level, however, fatigue-induced changes in either skeletomotor neuron activity or reflex mechanisms have, to our knowledge, not been investigated in PD patients. It could be expected that in PD patients, as in normal subjects, the firing rate of skeletomotor neurons would tend to decline during the prolonged contraction due to their intrinsic properties [22, 23] as well as due to the development of inhibitory reflexes [24] with muscle fatigue. These effects, however, might be less expressed in PD patients in which skeletomotor neurons are under different central drive causing difficulties not only in their activation, but also in their deactivation [25, 26]. However, the absence of any consistent changes in H-wave amplitude related to fatiguing contraction, found in three subjects, would not be in accordance with the presence of changes in excitability at spinal level. It seems, therefore, that the observed changes in both MEP amplitude and SP duration mainly reflect changes in the cortical activity.

In this study we were able to record MEPs and SPs in EMG records of both *adductor pollicis* and *brachioradialis* muscle in response to TMS. The MEP sizes and SP durations were comparable in magnitude to those recorded in healthy people in our previous experiments performed under simular conditions [6]. This was in accordance to the existing data [18, 27–32].

The main finding of this study was that the effects of submaximal voluntary fatiguing contraction on TMS responses in PD patients differed markedly from those in normal subjects. In a few patients only, the pattern of either MEP or SP changes was similar to those found in normal subjects, i.e. in the *adductor pollicis* a decrease in their magnitude up to the endurance point an increase thereafter, and, in *brachioradialis* an increase either from the start or soon after the start of the sustained contraction. On the contrary, in the majority of the patients examined MEP magnitude, not only in the voluntarily activated *adductor pollicis*, but also in the remote *brachioradialis* muscle, remained at the control level both up to the endurance point and beyond. This could be interpreted as if the central excitatory drive, both in terms of the magnitude of input to motor cortex output cells, as well as to its spreading, did not change in muscle fatigue. On the other hand, changes in SP duration would indicate that the inhibitory input to both the agonist *adductor pollicis* and *brachioradialis* muscle is modified differently in different patients. It is of particular note that responses to TMS in the PD patients differed sharply from those in the healthy subjects in almost complete dissociation of patterns of changes in MEP magnitude and SP duration during sustained 60% MVC contraction in both observed muscles, *adductor pollicis* and *brachioradialis*. This would suggest differential effect of the disease process on inhibitory and facilitatory cortical motor systems during development of motor fatigue in PD.

The PD patients studied were on therapy and their parkinsonian symptoms were mild to moderate. Also, their responses to TMS at rest and during short lasting 60% MVC contractions were not different from those found in healthy subjects [6]. Therefore, the differences in pattern of responses to TMS during sustained 60% MVC contraction could indicate that in PD patients the central mechanisms responsible for adaptation of motor drive to prolonged contraction failed under more demanding conditions of fatigue. On the other hand, the patients could sustain the required 60% MVC level for at least as long period of time as healthy subjects [6]. Thus, it could also be supposed that they used mechanisms of central motor control in sustaining muscle contraction that differed from those acting in healthy subjects. Dissociation of patterns of MEP and SP changes in PD patients, in contrast to matching patterns found in healthy subjects [6], further supports the proposal that the differences are due to central changes at a level preceding the cortical motor output cells, the input to cortex from subcortical nuclei included, rather than to changes in excitability of these cells. Nevertheless, the rapid fall in tension after the endurance point could also speak for the failure of compensation in central motor drive.

Conclusion

These results in the PD patients suggest the presence of impairment and/or compensatory changes in mechanisms responsible for adaptation of voluntary drive as well as for matching between cortical excitation and inhibition which become manifested in demanding motor tasks such as those imposed by muscle fatigue.

Acknowledgments

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The role of confocal scanning laser ophthalmoscopy in stereometric differentiation of eye papilla in ocular hypertension, normal tension glaucoma and primary open-angle glaucoma

Uloga konfokalne skening laser oftalmoskopije u stereometrijskoj diferencijaciji očne papile kod okularne hipertenzije, normotenzivnog glaukoma i primarnog glaukoma otvorenog ugla

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Abstract

Background/Aim. Primary open angle glaucoma (POAG) and normal tension glaucoma (NTG) demonstrate the same structural changes in the optic disc along with visual field defects but only POAG includes an abnormal elevation of intraocular pressure. Heidelberg retina tomograph based on confocal scanning laser ophthalmoscopy (HRT) and Moorfields regression analysis (MRA) have been employed to quantitatively assess the topography of eye papilla. We measured stereographic parameters of eye papilla in patients with POAG, NTG, and ocular hypertension (OH) using an HRT in order to determine whether HRT topographic parameters can be used to differentiate those conditions. **Methods.** The results of 145 eyes of 145 patients with OH, NTG and POAG were analyzed by age, refractive error, quality of HRT images, stereometric and MRA parameters. **Results.** Significant differences were found between NTG and other two groups for a majority of the HRT parameters, and also no differences between OH and POAG patients for a majority of the investigated parameters, except thickness of retinal nerve fiber layer. By reading the MRA no differences were found in the distribution of mostly damaged and mostly preserved neuroretinal rim sectors between NTG and POAG patients, and also all sectors of the neuroretinal rim in OH patients were preserved. **Conclusion.** HRT stereometric parameters are useful to differentiate patients with OH and NTG, and also for differentiation between NTG and POAG patients, but most of parameters showed no difference between OH and POAG patients. MRA may serve to confirm the diagnosis of OH, but not for precise distinction between NTG and POAG.

Key words:
glaucoma; glaucoma, open-angle; ocular hypertension; diagnosis, differential; diagnostic techniques, ophthalmological.

Apstrakt

Uvod/Cilj. Primarni glaukom otvorenog ugla (POAG) i normotenzivni glaukom (NTG) pokazuju jednake strukturalne promene u optičkom disku zajedno sa defektom vidnog polja, ali samo POAG podrazumeva abnormalno povišen intraokularni pritisak. Heidelbergova retinalna tomografija (HRT) bazirana na konfokalnoj skening laser oftalmoskopiji i Moorfields regresiona analiza (MRA) korišćeni su u našoj studiji za kvantitavnu procenu topografije očne papile. Primenom HRT mereni su stereometrijski parametri optičkih diskova bolesnika sa okularnom hipertenzijom (OH), NTG i POAG. Cilj rada bio je da se odredi primenjivost HRT parametara u OH, NTG i POAG. **Metode.** Rezultati nalaza 145 očiju od 145 bolesnika sa OH, NTG i POAG analizirani su po starosti, refrakcionoj grešci, kvalitetu HRT fotografija i stereometrijskim parametrima. **Rezultati.** Utvrđena je statistički značajna razlika između bolesnika sa NTG i druge dve grupe bolesnika za većinu parametara, kao i odsustvo razlike između OH i POAG grupe za većinu parametara, izuzev za debljinu retinalnog sloja nervnih vlakana. Nalazi MRA pokazali su da nije bilo

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razlike u distribuciji oštećenih i očuvanih sektora neuroretinalnog oboda između bolesnika sa NTG i POAG, kao i da su svih šest sektora neuroretinalnog oboda kod bolesnika sa OH bili očuvani. **Zaključak.** Stereometrijski parametri HRT korisni su u diferencijaciji bolesnika sa OH i NTG, kao i bolesnika sa NTG i POAG, ali većina parametara ne pokazuje razliku između OH i POAG. Takođe, MRA može poslužiti za potvrdu dijagnoze OH, ali ne i za preciznu diferencijaciju NTG i POAG.

Ključne reči:
glaukom; glaukom, otvorenog ugla; hipertenzija, okularna; dijagnoza, diferencijalna; dijagnostičke tehnike, oftalmološke.

Introduction

Primary open-angle glaucoma (POAG) is a disorder that demonstrates typical structural changes in the optic disc along with visual field defects related to an abnormal elevation of intraocular pressure (IOP), while normal-tension glaucoma (NTG) is a type of glaucoma that shares clinical features and mechanisms with POAG, except for the abnormal elevation of IOP. Ocular hypertension (OH) is intraocular pressure higher than normal in the absence of optic nerve damage or visual field loss. Assessment of the optic disc is included in the standard examination of patients with OH or suspected or manifest glaucoma. Such evaluation is performed not only by glaucoma experts, but also by general ophthalmologists, ophthalmology residents, and ophthalmologists with special skills in areas other than glaucoma. Glaucomatous optic nerve damage may manifest itself not only as a morphological change in the optic disc but also as a decrease in the thickness of the retinal nerve fiber layer (RNFL) [1]. Loss of axonal fibers results in the decreased thickness of the RNFL, and this structural change has been found to precede both any morphological changes of the optic disc and functional changes in the visual field [2–13]. Thus, measuring the RNFL thickness, along with morphological analysis of the optic disc lies at the cornerstone of early glaucoma detection. Various computerized quantitative imaging techniques have been developed to help doctors identify structural glaucomatous damage. Confocal scanning laser tomography using the Heidelberg retina tomograph II (HRT II); (Heidelberg Engineering, GmbH, Heidelberg, Germany) was introduced in the beginning of the 1990s and has been further developed since then. HRT II uses confocal scanning laser ophthalmoscopy to evaluate quantitatively the three-dimensional surface topography of the optic nerve head and the surrounding nerve fiber layer [14–21]. There fore, HRT II is considered to be a promising tool for the early detection of glaucoma.

The aim of this study was to investigate whether the HRT instrument can make distinguish between stereometrical characteristics of papilla in groups of patients with OH, NTG and POAG. We wanted to know whether the three examined identity may vary based on size of neuroretinal rim damage, as well as the distribution of damaged and preserved neuroretinal rim sectors. All that in order that the results obtained in our study help ophthalmologists in routine examinations of the HRT findings, to help them to avoid errors in diagnosis of the glaucomatous or OH damage to the optic disk and its surroundings.

Methods

This retrospective study included 145 eyes of 145 patients from the Institute of Ophtalmological of Medical of Medicine Faculty of the Belgrade University. The research followed the tenets of the Declaration of Helsinki and was approved by the Regional Ethical Review Board. Stereographic parameters of 61 eyes in 61 patients with POAG, and 45 eyes in 45 patients with NTG, and 39 eyes in 39 patients with were investigated OH (Table 1). The restriction of the study considering the one eye of each patient for each group was made in order to facilitate statistical analysis. Those eyes with excessive refractive error (of more than +6 diopters or less than –6 diopters), cataracts, diabetic retinopathy or with any history of surgical treatment or eye trauma were excluded. The NTG eyes included in this study were defined as those showing both glaucomatous optic disc changes and IOP never exceeded 21 mmHg on repeated measurements. Subsequently, the eyes enrolled as POAG group included those whose IOP exceeded 21 mmHg prior to or after initiation of therapy. The OH eyes included in this study were defined as those showing no glaucomatous optic disc changes and IOP exceeded 21 mmHg on repeated measurements. We used HRT II in our study for the collection of all necesary data.

Table 1
Basic data of patients with ocular hypertension (OH), normal tension glaucoma (NTG), and primary open angle glaucoma (POAG)

Variables	OH	NTG	POAG
Number of eyes	39*,†	45	61
Male/female (n)	15/24	17/28	24/37
Age (year), mean value ± SD	51.7 ± 15.8	61.9 ± 10.7	57.3 ± 9.2
Refractive error, mean value ± SD	-0.5 ± 1.5	-0.8 ± 2.5	-1.3 ± 3.3
Topographic standard deviation	26.3 ± 6.9	28.2 ± 5.6	21.5 ± 8.5

*$p < 0.05$ *vs* POAG group; †$p < 0.01$ *vs* NTG group (*t*-test)

By using HRT II we can get a series of photographies of the cross section of the optical nerve head of different deepness and after 3D reconstruction it produces topographical photographies of the papilla and peripapillar retina [22]. To quantify morphometric rim and cup parameters in optic disc topography, a reference plane is defined. The reference plane is parallel to the retinal surface. It needs to be stable so that the parameters change only when true structural changes in the optic disc occur. Within the disc margin, the retinal surface located above the reference plane is defined as rim and below the reference level as cup.

In order to verify the quality of topographic images we used images with standard deviation less than 40 μm. Eight stereometric parametres were taken into consideration in this study: disc area (mm^2), cup area (mm^2), rim area (mm^2), cup-to-disc area ratio (C/D ratio), cup volume (mm^3), rim volume (mm^3), cup shape measure (mm) and mean retinal nerve fiber layer (mRNFL) thickness (mm). Moorfields regression analysis (MRA), a program contained in the basic package of HRT device was used for comparison of the examined six sectors of neuroretinal rim (1. temporal, 2. supero-temporal, 3. infero-temporal, 4. nasal, 5. supero-nasal, and 6. infero-nasal) with a normative. It defines these sectors as damaged, borderline and normal based on the 95% and 99.9% confidence intervals.

The aim of this study was to find which group has larger damage (in percent) of the of the neuroretinal rim and which segment of the neuroretinal rim is the most frequently and the least frequently often represented as the damaged for each group separately. Also, the aim of this study was to find if we can confirm by reading the MRA findings that the neuroretinal rim of OH patients is preserved.

By using SPSS version 20 we analysed the basic demographic characteristics (age, gender), also a refractive error and standard deviation of HRT images and examined eight morphometrical parametres of the optical disc in all three groups, with the aim to establish the existance of statisticaly significant difference between the same parametres in the groups (statisticaly significant difference is when $p < 0.05$). We used methods of descriptive statistics, and an analytical statistical methods (*t*-test).

Results

Basic statistics relating to sex, age, size of refractive error in patients eyes and standard deviation of topographic HRT images were shown in table 1. Between all patients who met the entry criteria there were no significant differences in refractive error and standard deviation of topographic HRT images among the three groups. There was statistically significant differences in age between patients wih OH and NTG, and patients with OH and POAG. Patients with OH were significantly younger than patients with NTG and POAG. A basic statistical summary of the results of the HRT parameter measurements was shown in Table 2. Examining the significance of differences among parameters between groups we found different values. The mean values of disc area (mm^2) were significantly larger in NTG than in the other two groups. The NTG group also showed significantly the largest cup area (mm^2), followed in order by POAG and OH group. On the other hand, the mean values of rim area (mm^2) were significantly higher in OH than in NTG group. Rim area were not significantly different between OH and POAG patients, and also between NTG and POAG patients. Cup volume (mm^3) were significantly higher in HTG than in other groups, and the same parameter were not significantly different between OH and POAG group. The mean values of rim volume (mm^3) were significantly larger in OH than in NTG group, but there was no statistically significant differences between other groups in relation to this parameter. Further, the mean values of cup to disc area ratio were significantly larger in NTG eyes than in OH and POAG eyes, though at was not significantly different between OH and POAG group. The NTG patients showed the significantly larger values for cup shape measure (mm) compare to OH and POAG patients, and the same parameter were not significantly different between OH and POAG group. Last investigated parameter of optic disc was mean RNFL thickness (mm), and it was significantly larger in OH than in other two groups of patients. Mean RNFL thickness were not significantly different between NTG and POAG group (Table 2).

Table 2

Heidelberg retina tomograph (HRT) parameters in ocular hypertension (OH), primary open angle glaucoma (POAG) and normal tension glaucoma (NTG)

Variables	OH (n = 39)		NTG (n = 45)		POAG (n = 61)	
	(min–max)	mean	(min–max)	mean	(min–max)	mean
Disc area (mm^2)	(1.638–3.226)	2.398[a2]	(1.410–3.922)	2.814[b2]	(1.532–3.928)	2.484
Cup area (mm^2)	(0.019–1.652)	0.587[a2]	(0.099–3.354)	1.201[b2]	(0.048–3.168)	0.785
Rim area (mm^2)	(0.891–2.572)	1.810[a2]	(0.149–2.515)	1.571	(0.759–2.691)	1.699
Cup/disc area ratio	(0.053–0.650)	0.230[a2]	(0.071–0.958)	0.426[b2]	(0.023–0.807)	0.293
Cup volume (mm^3)	(0.004–0.691)	0.161[a2]	(0.005–1.104)	0.393[b2]	(0.002–1.747)	0.209
Rim volume (mm^3)	(0.118–0.967)	0.458[a2]	(0.006–1.194)	0.365	(0.101–0.769)	0.408
Cup shape measure (mm)	(-0.079– -0.305)	-0.195[a2]	(-0.284–0.129)	-0.130[b2]	(-0.414–0.013)	-0.183
Mean RNFL thickness (mm)	(0.080–0.396)	0.235[a1,b1]	(0.019–0.527)	0.184	(0.043–0.379)	0.203

RNFL – retinal nerve tiber layer; [a1] – $p < 0.05$ *vs* NTG; [a2] – $p < 0.01$ *vs* NTG; [b1] – $p < 0.05$ *vs* POAG; [b2] – $p < 0.01$ *vs* POAG

By the reading of MRA findings of all three groups, we found that the size of the damage of neuroretinal rim is higher in the NTG group (12.4 %), than in the group of the patients with POAG (6.5 %). We found that in group of the patients with POAG the segment which is most often classified as damaged was nasal, and the least often temporal, also in the group of the patients with NTG the segment the most often classified as damaged was nasal, and the least often temporal (Table 3). All six sectors of neroretinal rim of each eye in the OH group were classified as normal.

Table 3

Distribution of damaged sectors of neuroretinal rim in patients with normal tension flaucoma (NTG) and primary open angle glaucoma (POAG) based on Moorfield's regression analysis (MRA) findings

Groups	Demaged sectors of neuroretinal rim (n)					
	temporal	supero-temporal	infero-temporal	nasal	supero-nasal	infero-nasal
NTG (n = 45 eyes)	2	5	6	8	6	6
POAG (n = 61 eyes)	0	3	2	8	5	6

Discussion

Since the development of the HRT, many reports have demonstrated its advantages for quantitative assessments of optic disc topography during diagnosis and follow-up of glaucoma patients [23–34]. Several authors have made comparisons between the topographic parameters of optic discs among patients with glaucoma, individuals with OH, and normal controls [26, 28, 32, 34, 35]. However, there are few reports of studies that have compared those parameters among OH, NTG, and POAG patients [26, 27]. In our study we did not find any HRT parameter witch is significantly different among all three groups. In previous reports [26, 35, 36], disc area showed no significant difference among these disorders; however in our study the NTG patients have significantly largest disc area. In our study the NTG group also showed significantly the largest cup area, cup volume and cup to disc area ratio, followed in order by POAG and OH group. Same results can be found in study of Kiriyama et al. [36]. The mean values of rim area and volume were significantly higher in OH than in NTG group, and the same results we can find in the study of Kiriyama et al. [36]. Our study demonstrated no difference in the some parameters between NTG and POAG had shown group, as in a study of Iester et al. [37]. Further on, our study showed that the NTG patients had larger values of cup shape measure compared to OH and POAG patients, and the same parameter was not significantly different between OH and POAG group. Kiriyama et al. [36] reported that when comparing the same parameters cup shape was significantly different between POAG and OH, and NTG and OH eyes, but not between POAG and NTG eyes. Previous mentioned study [36] also showed that mRNFL thickness was significantly different between POAG and NTG eyes, and NTG and OH eyes, however, did not between POAG and OH eyes. Our study showed that mRNFL thickness was significantly larger in OH than in other two groups of patients. In sum, we found significant differences between NTG and other two groups for a majority of the parameters, and also no differences bettwen OH and POAG patients for a majority of the investigated parameters, except mRNFL. By reading the MRA findings we found no differences in the distribution of mostly damaged and mostly preserved neuroretinal rim sector between NTG and POAG patients. MRA findings also showed that all sectors of the neuroretinal rim in OH patients were preserved. Another study showed that by using HRT and following throw time parameters of the neuroretinal rim may prove the diagnosis of ocular hypertension [38].

Conclusion

Patients with NTG tend to have larger disc, larger cupping, smaller rims, and thinner RNFL as compared to POAG and OH patients. Patients with NTG also had a larger area of damage of the neuroretinal rim, compared to POAG. On the other hand, patients with OH were younger, and had largest rim area and largest cup shape measure. Looking at the size of the all tested parameters, the patients with POAG were positioned in the middle, with respect to all three groups. Thus, HRT topographic parameters are useful to differentiate patients with OH and NTG, and also for differentiation between NTG and POAG patients, but in most of them showed no difference between OH and POAG patients. Also, we can conclude that MRA may serve to confirm the diagnosis of OH, but not for precise distinction between NTG and POAG.

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CURRENT TOPICS

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The role of neurophysiological methods in the confirmation of brain death

Uloga neurofizioloških metoda u potvrdi moždane smrti

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Ključne reči:
mozak, smrt; dijagnoza; elektroencefalografija; evocirani potencijali, auditorni; evocirani potencijali, somatosenzorni; evocirani potencijali, vizuelni.

Introduction

For several decades the medical science society has been in dilemma and debating about when a person is actually considered dead. That a person is dead when his/her brain dies is the attitude of not only medical science, but culture as a whole [1, 2]. The notion that took years to establish of heart being not only the "*primum movens*" but also the "*ultimum morines*", that is that life begins with a heart beat and ends with its arrest, has been abandoned in the last 30 years. From a biological standpoint dying does not recognize the border between the death of the heart and the death of the brain. At the moment of termination of brain function breathing stops as well, and a few minutes or days after, heart failure occurs.

The concept of brain death as the death of an individual, has brought forward many philosophical, ethical, medical, legal and economic issues, and created a dilemma as to when a person is considered dead, from the first report of Mollaret and Goulon in 1959, as a "coma *depasse*" [1]. Soon after that the Harvard Medical School (Harvard criteria of 1968) [1] was the first one to define brain death as an "irreversible coma" which includes the lack of consciousness, spontaneous movement and all reflexes. Since then, the definition and diagnostic criteria have been subjected to significant changes and most of the problems, dilemmas and debates which had before been caused by the concept of brain death due to terminological confusion and great responsibility to declare someone dead with the preserved cardiac function, have been overcome. However, although brain death is now accepted worldwide, diagnosis and diagnostic criteria are far from perfect, therefore further adjustments are needed.

The diagnosis of brain death

Clinical testing is the golden standard and the first step in the diagnosis of brain death. However, the development of medical technology has enabled a more reliable diagnosis and confirmation of brain death using different diagnostic methods, which complement the clinical criteria. Then, when you need to diagnose and confirm brain death quickly and accurately, especially in adverse conditions, diagnostic methods, especially evoked potentials, are very important even though they are not 100% specific and sensitive [1–5]. In patients who meet clinical criteria for brain death, neurophysiological studies have shown that there are "active cerebral hemispheres over the dead brain stem", and *vice versa*. In this regard, it was shown that a female patient was bleeding profusely after cancer surgery in the cerebellopontine angle which led to brain stem death that was proven by clinical tests. Thanks to medical technology, the patient lived another 14 days having the electroencephalographic (EEG) findings similar to those taken during sleep, and normal visual evoked potentials caused by light flashes, which all point to the preserved function of cerebral hemispheres [1].

However, there are significant differences in the guidelines for using diagnostic tests to confirm clinical symptoms. The differences range from the outright rejection of all tests [6] to the acceptance of different neurophysiologic methods and cerebral flow methods, separately or in combination. In addition, differences arise in interpreting the findings and in the time required from the onset of the first symptoms to the procuring of secure evidence that a person is really dead, and that taking cadaveric organs can promptly be carried out.

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Today, in almost all European countries, the diagnosis of brain death is based on clinical, neurophysiologic and cerebral flow methods, except in Britain where only clinical criteria are used for the diagnosis and confirmation of brain death [1]. Additional diagnostic methods for confirmation of the diagnosis of brain death have been proposed by certain national associations in the cause of shortening the waiting period of several days to 6 to 12 h when the removal of cadaver organs can be performed.

Most European countries published recommendations and national guidelines for diagnosis and confirmation of brain death as a prerequisite for removing cadaveric organs. In addition to clinical criteria, in 52 countries of the world diagnostic tests are optional, and in 28 world countries, one of them being Serbia, they are mandatory [1, 7]. Most of them use EEG as a mandatory test that shows the isoelectric line in brain death. According to the recommendations of the American Academy of Neurology (AAN) (2010) for confirmation of brain death, clinical trials are essential and EEG as one of the methods [8].

However, some studies suggest the advantages of multimodal evoked potentials (MEPs) in the diagnosis of brain death compared to EEG [1–3, 9–16]. It is not an invasive method, less sensitive to the effects of sedatives, barbiturates, anesthetics, metabolic disorders, hypothermia, it evaluates the function of the brain stem that cannot be easily clinically examined and the function of the cerebral cortex and in comatose patients. So, it can provide useful information about clinical findings of the function of the brain stem and cerebral cortex and in adverse conditions without changing its parameters (latency, amplitude and morphology of the wave), which is not the case with the EEG [17, 18]. These tests are safe, accurate and they significantly improve and accelerate the procedure of taking the cadaver [11, 12, 19–23]. The significance of evoked potentials in the diagnosis of brain death is presented in the research done by Facco et al. [24] 2002. On a group of 130 patients diagnosed with brain death, the authors show the absence of auditory evoked potentials (AEPs) and in 92 patients, the presence of only I or I and II AEPs waves in 32 patients. However, in 6 patients III and V waves were still present, which excludes the death of the brainstem. The same authors [24] showed the presence of N9 and N13 waves (responses of the brahialisa plexus and cervical spinal cord segments) in 122 patients and the absence of N20 waves (cortical response). However, in 4 patients P14 or N18 waves were registered, which are generated in the brainstem therefore excluding brain death. Thus, the combined use of AEPs and somatosensory evoked potentials (SEPs) confirmed brain death in 93% of patients and have demonstrated a residual activity of the brain stem in 6 patients of which 3 met all EEG and clinical criteria for the entire brain death. The authors conclude that the combined use of EEG's, AEPs and SEPs significantly improves the diagnosis of brain death.

In 2009, Djuric et al. [14] published similar results in a group of 84 patients with clinical criteria of brain death. In 10 (11.90%) patients EEG showed certain cortical activity in the form of alpha, tetha and delta waves, AEP showed I, II and V waves in 3 (3.57%) patients, and median SEPs in 5 (95%) patients, which all exclude brain death. The authors conclude that EEG as the only method in confirming brain death is not sufficient.

Electroencephalography

The first applied neurophysiological method of brain death confirmation was EEG. It found its place in one of the few, widely-used and cited regulations for confirmation of brain death (Harvard, 1968) as a "mandatory" criterion [5]. At that time, it was the only available diagnostic method which could investigate the function of the brain and confirm brain death. However, ten years later the American Association of Neurology degraded this method from "mandatory criteria" to "useful indicator" for several reasons and this was proven by a number of research [3, 14, 25–27]. Heckmann et al. [26] showed that a 53-year-old patient with ischemic encephalopathy after cardiopulmonary arrest with spontaneous superficial respirations and the preserved cerebral perfusion on his EEG had an isoelectric line. He lived for another 7 weeks.

Regarding the application of EEG methods in confirming brain death, there are arguments "against" and arguments "for" its application.

Arguments against the application of EEG are:

1. EEG records the spontaneous bioelectric activity of the cortex to the depth of about 5 mm, so it is not an informative method for the detection of the brain stem function.

2. EEG does not show the function of neurons of the basal bark, interhemispheric fissures and deep sulci.

3. EEG can be a useful method when we do not accept the concept that the "brain stem death is the death of the individual", because studies have shown that patients with a dead brain stem have some electrical activity in the EEG within 48 hours [4, 28].

4. Technical problems arise in the intensive care units in which most often the brain death is confirmed due to an abundance of artifacts caused by the work of respirators, monitors, and the like, which make it difficult to identify electrocortical activity.

5. EEG can give false positive and false negative findings. Studies have shown that the isoelectric line on EEG heads to the erroneous diagnosis of brain death (with the comatose or vegetative patients after prolonged cardiac arrest, in sedation, hypothermia and metabolic disorders), and conversely, the preserved electrocortical activity in EEG gave false hope that the person is alive, according to clinical criteria of the dead brain stem [10, 13, 14, 29, 30] (Figures 1 and 2 [15]).

For these reasons, further investigations are directed towards the implementation of other more recent neurophysiological methods with different modalities of evoked potentials. Numerous studies proved that the isoelectric line on EEG is not a reliable evidence of brain stem death, because the acoustic evoked potentials in these patients were almost normal [3, 27, 29–32].

Despite these limitations, EEG is recommended in all countries that have adopted the definition of "the entire brain death", even so in the regulations applied in Serbia, as one of the auxiliary methods.

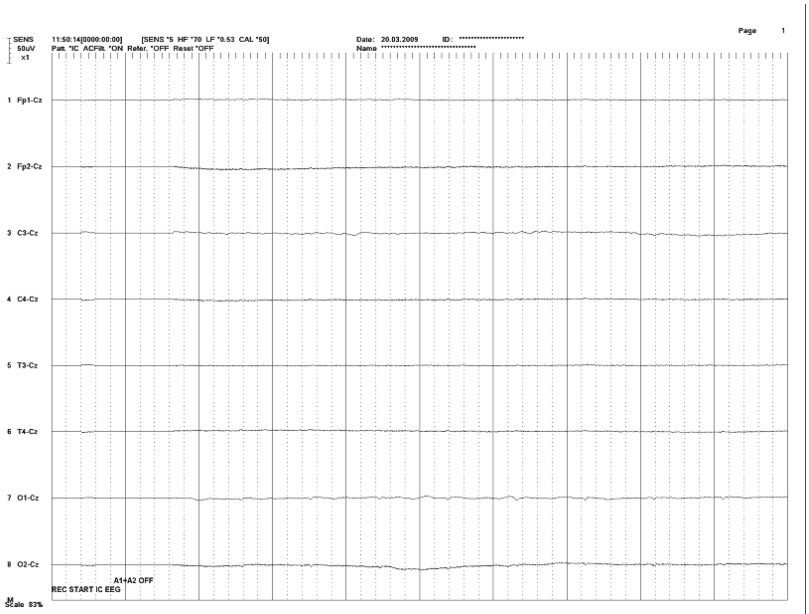

Fig. 1 – Electroencephalography (EEG) shows the isoelectric line in brain death [15]

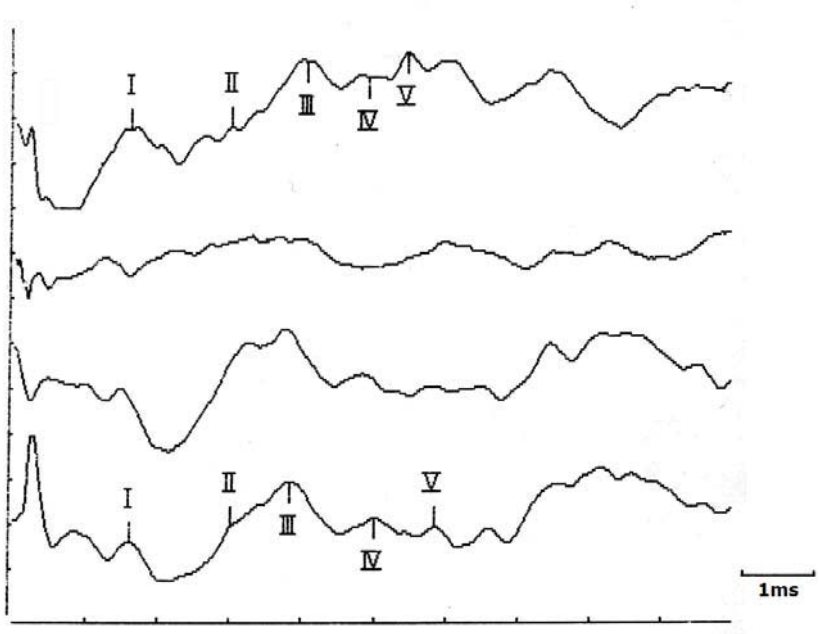

Fig. 2 – Auditory evoked potentials (AEPs) show almost normal findings [15] in the same patient whose EEG is described in Figure 1

When should we be careful in interpreting the EEG findings? The answers are as follows:

1. With medication intoxication in which case the isoelectric line can be maintained up to 50 h after poisoning with complete recovery.
2. After cardiac arrest and global cerebral ischemia, where the isoelectric line on EEG can be maintained for hours.
3. In adverse conditions such as hypothermia, metabolic disorders and apallic syndrome. In these states the electrocortical activity in the cortex is lost much earlier in relation to evoked potentials
4. In vegetative state

Auditory evoked potentials of the brain stem

Clinical application of this test is based on the evaluation possibilities of the acoustic system functions from the inner ear to the midbrain. In recent years, among other indications, these tests have been intensively applied in comatose patients as well, because of the resistance to the effects of barbiturates and anesthetics, and they hold a special place in the protocols for confirmation of brain death [31].

Numerous studies have determined AEPs findings indicating brain death. A typical finding of this test is the bilateral presence of only I and/or I and II waves, or rather, the absence of all waves (Figure 3) [10, 11, 31, 33]. We should bear in

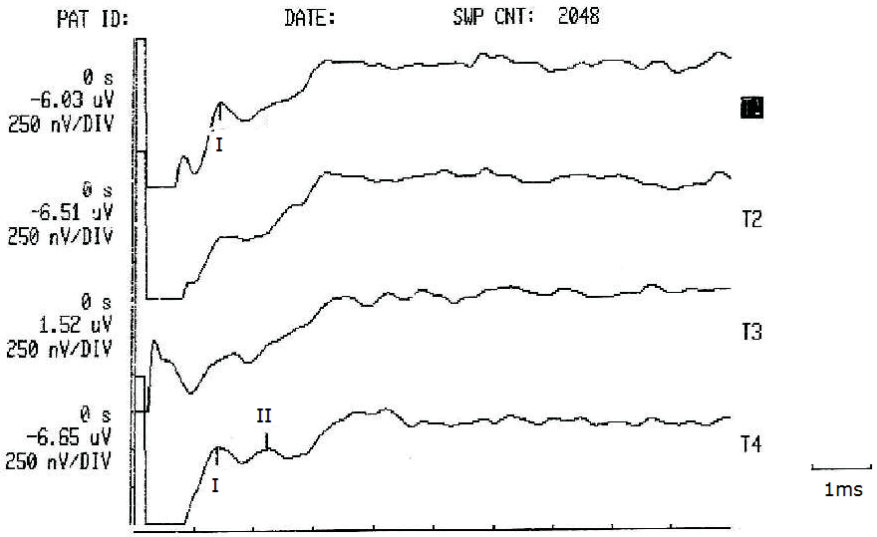

Fig. 3 – Auditory evoked potentials (AEPs) findings indicate brain death in the patient (I and II waves are present) [11]

mind that an I wave can be absent with hemorrhage in the inner ear, temporal bone fractures that can cause damage to the bone labyrinth and deafness which existed prior to the brain death.

Research done by Facco et al. [24] shows that 70% of brain dead patients had a straight line on AEPs as a proof of circulatory disturbance and in the cochlea which occurs after the cerebral flow cessationh. When AEPs findings are sequentially registered during the dying process, disappearance of the waves shows that the final image, i.e. the flat AEPs is the result of patient's death, thus confirming their diagnostic value. In contrast, AEPs play a key role in excluding false positive findings in comatose patients when the brain seems dead. In this regard, the absent brainstem reflexes and a flat EEG with intact AEPs were found in 4.5% of patients even in the absence of sedation or other reversible effects of coma, which confirms their advantage over the EEG and clinical criteria in excluding brain death. By using a combined application of AEPs and SEPs, the authors [24] have confirmed brain death in 93% of patients.

Somatosensory evoked potentials

Microcomputer technology and modern multichannel appliances for evoked potentials, allowed the intensive clinical use of this modality in the last 30 years. As a result, the method has taken its important role, not only in diagnostic process of neurological diseases, but also in protocols for determination of brain death. A typical finding in the brain stem death or brain hemispheres death is a normal potential over the brachial plexus (N9), the normal potential of the 7th vertebra [3] and the lack of response of thalamo-cortical projections and the somatosensory cortex (N20-P25 complex) [15, 22, 23].

Past research, as well as a 15-year experience of the author [25], have shown that this electrophysiological test is very reliable in confirming brain death, because it is the least sensitive to technical problems in the intensive care unit. This test allows the evaluation of the conductivity at the cervico-medullary level. Therefore, an analysis of the waves that are generated in the brainstem is needed. In brain death SEPs should be registered by using the non-cephalic reference electrode in order to register the "far field" potentials (P14 and N18) which are generated in the brainstem at the level of cervico-medullary circuit, medial lemniscus and nucleus cuneatus. The routine use of frontal reference electrode – Fz shuts down all the "far field" waves and allows only the assessment of cerebral cortical function, as is the case with the EEG, so it is there possible to verify the presence or absence of the activity of the somatosensory cortex, which is insufficient for the confirmation of brain death.

Therefore, SEPs with a non-cephalic reference electrode provide important information about the function of the medulla oblongata and the cervical-medullary circuit, which could lead to the improvement of criteria for the diagnosis of brain death. Therefore, a combined use of AEPs and SEPs provides testing of ponto-mesencephalic and bulbar levels until the death of the entire brain stem. With dying patients the disappearance of P14 and N18 waves is closely time-associated with the disappearance of the reflex to bronchial stimulation and the appearance of apnea. In fact, the apnea test would be an unthinkable harmful procedure in comatose patients, because it can lead to a serious increase in intracranial hypertension. For these reasons the apnea test should be the last test in the process of confermation of brain death after the disappearance of the evoked responses generated in the brain stam[14, 24].

Visual evoked potentials

Visual evoked potentials (VEPs) represent the neurophysiological method for examining the function of the visual pathway from the retina to the occipital cortex.

This method is often superior to ophthalmic and neurological examination because it shows not only clinical but also subclinical lesions of the optical path. That is why it has been applied in the last several decades in the diagnostic processes of ocular and neurological diseases. It is also useful for the confirmation of brain death, where a special stimulator with a flashing light in the form of spectacles is used. A response is recorded over the visual cortex and beneath the lower eyelid for recording the responses of the retina. VEPs with the simultaneous registration of electroretinogram may be a sensitive indicator of an early impairment of cerebral function. It shows the function and the subcortical structures which make it more sensitive than EEG.

The test is easily performed and is highly resistant to technical artifacts in the intensive care units. It provides useful information about the function and the integrity of the visual pathways. It is important in the differentiation of cortical and brain stem lesions [32]. With brain death a response of the retina is always present (Figure 4) [10, 15].

Conclusion

Neurophysiological methods are important in confirming brain death. In the recommendations and the national guidelines in most countries of the world, these tests are optional, and a smaller number of countries consider them obligatory, Serbia being one of them. EEG, applied as the first and most commonly used neurophysiological method, is not sufficiently reiable in confirming brain death, because it does not show the function of the deeper structure of brain hemispheres and brainstem, but rather of the cortex only. The application of evoked potentials, however, provides more information about the function of multiple afferent pathways of the brainstem and hemispheres. On the other hand, evoked potential tests are less sensitive to the so-called adverse conditions such as metabolic disorders, intoxication, coma, hypothermia, anesthesia, and similar, compared to EEG. The complemenary application of these methods is more reliable in confirming brain death.

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Trunk muscle activation patterns in subjects with low back pain

Obrasci aktivacije mišića trupa kod osoba sa lumbalnim sindromom

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Key words:
low back pain; muscle tonus; motor activity; postural balance; physcal exertion.

Ključne reči:
leđa, bol; mišići, tonus; motorna aktivnost; ravnoteža; vežbanje.

Introduction

Low back pain (LBP) is nowadays one of the most widely experienced health-related problems. First symptoms usually appear between the age of thirty and fifty, although it has been recorded in athletes in early twenties [1–3]. Etiology of LBP is multifactorial and it is thought that non-specific LBP is associated with lumbar spine instability [4, 5]. It is generally believed that spinal instability (such as in circumstances with no neurological deficit, deformity, or the presence of pain) is associated with reduced capabilities of neuromuscular system to respond to physiological loadings [4].

The spine is a mechanically complex structure which is inherently unstable. Due to the redundancy in the neuromuscular and spinal system, there is a large set of possible muscle activation patterns to meet the stability constraints [6]. However, different muscle activation patterns can significantly affect the magnitude and direction of the intervertebral loadings and, therefore, the spinal and core stability.

Muscle activation patterns when either retaining different postures or performing various movements and their relationship with LBP is of much interest for researchers and the clinical practice. Theoretically, the unbalanced activation and coactivation may lead to a mechanical imbalance of the whole body system [4, 6]. However, there is a disagreement among the researchers to what extent the changes in trunk muscles activation level and recruitment patterns contribute to the presence of pain (and later on to its reduction) and the altered core stability [7]. However, research in the area of motor control has made a significant contribution to understanding of the neuromuscular reorganization due to LBP.

Core stability and the role of deep trunk muscles

Core (or trunk) stability has been frequently emphasized in the literature. It is usually operationally defined as the body's ability to control the spine (e.g. to maintain or regain the balance) in response to internal and external perturbations. Panjabi [4] presented a conceptualization of core stability based on 3 systems of control: active (muscles), passive (passive stabilizers) and neural control unit. Conversely, Borghuis et al. [7] see the core stability as a product of motor control and the muscular capacity of the lumbar-pelvic-hip complex.

The importance of the two deep (local) trunk muscles, *m. transversus abdominis* (TrA) i *m. mulitfidus* (MF), has been particularly emphasized in the concept of core stability [2, 8, 9]. In particular, TrA has received a lot of attention as the main factor which provides anterior core stability, while MF provides dynamic control of segmental inter-vertebral motions inside the neutral zone. Cocontraction of these muscles increases the intra-abdominal pressure and presumably provides the stability and stiffness of the lumbar spine [8, 10] and which could possibly be either a cause or consequence of the nonspecific LBP.

Trunk muscles' activity

Differences in motor control and trunk muscle function of LBP in healthy individuals have been frequently reported in the literature [1, 5, 10–19]. These differences may either constitute a predisposing factor for low back injuries or a compensation mechanism aimed to stabilize the lumbar spine [5, 11–13]. Different hypothesis and models have been pro-

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posed in the attempt to explain the effects and mechanisms of LBP related changes in motor control, but the majority of them could be grouped into the following two main theories: changes in muscle activity cause spinal pain ("pain-spasm-pain model"), and changes in muscle activity serve to restrict spinal motion ("pain adaptation model") [11].

Under the assumption that the muscle activation pattern is altered in patients with LBP (e.g. an altered recruitment, delayed activity, asymmetrical activity of contralateral muscles and others), the researchers have recorded their elektromiographic (EMG) activity under various conditions (different contraction types, difficulty and movement complexity [1, 3, 6, 11, 12, 16, 18, 20–30]). The results have indicated that TrA and MF are primarily affected by LBP [10], as well as that the individuals with LBP (as compared with the healthy ones) have a decreased ability of activation of deep muscles during the trunk flexion motion [12, 13], suggesting that the presence of differences in activity between deep and superficial trunk muscle is consistent [12, 16, 24]. Even though changes in their function relates to LBP etiology, some researchers emphasize that the muscle weakness could be a consequence of pain and the associated inactivity [9, 24, 25]. Earlier findings of Hodges [8], Hodges et al. [12] and Hodges and Moseleyet [16] revealed an association of the rapid limb movements and delayed latency in TrA activity of LBP subjects. Changes were also observed within MF [12, 16, 29] in the form of both a hypoactivity and delayed activation during the expected and unexpected perturbations. In more complex bimanual aiming tasks, an additional load applied upon the subjects' hands caused a delayed onset of MF and errector spinae (ES) as compared to deltoid muscle, associated with both a lack of activity of abdominal muscles and longer overall movement time than in their healthy peers [15]. During the period of induced pain, the response of TrA, *obliquus extermus abdominis* (OE), and ES to arm flexion was both delayed and reduced, but with earlier onset of MF [12, 18, 19], while changes in other muscles were more variable and also dependable on the movement phase. The muscle activation pattern remained altered even after the pain disappeared, which implies the possibility that even the smallest exposure to pain stimuli may have long lasting consequences on motor control. It also remains possible that the pain represents a delayed adaptation which develops and progresses over time, in an attempt to provide the necessary trunk stifness and stability through enhanced muscle activation, and thus fights with the symptoms [1, 4, 7, 8, 18].

In contrast to healthy individuals, the patients with LBP also demonstrate significantly different muscle response pattern in response to a sudden load release. As found by Silfies et al. [14], adding an external load during the task performance induces increased activity of ES, MF and *rectus abdominis* (RA), but not in *internus obliquus abdominis* (IO) and *externus obliquus abdomimis* (EO). Abdominal (IO/RA) and extensor (MF/ES) synergist ratios become decreased, and since activity of ES is likely to be significanlty more increased than in RA, the flexor/extensor ratio could also decrease. Individuals with chronic LBP also demonstrate a decreased variability in anticipatory postural adjustments [19, 21], which suggests a reduction in the repertoire of motor control strategies utilized to reestablish the posture. It has been also observed that the gait of LBP patients is accompanied by poorly coordinated activity of the lumbar ES [17, 22]. Since the pain intensity, fear and disability were unrelated to the observed changes, it suggests that the discussed impaired coordination could be a direct consequence of LBP *per se* [16, 17, 22].

Measuring muscle activation patterns during various perturbations as a way to evaluate the efferent response to proprioception may be important in rehabilitation. If these patterns can be normalized, than proprioception may be improved through the well-planned exercise program. As it was found by Newcomer et al. [13] in both toes-up position and medium amplitude forward movement, RA shows decreased activation, while asymmetry was observed between muscle pairs both in RA and ES. Similar findings regarding the RA muscle were obtained by Hodges et al. [12, 16]. Recordings of muscle activity during different arm movement velocities showed absence of abdominal muscles activity when arms were moved slowly. The results suggested that LBP was associated with the increase in the velocity threshold required to induce abdominal muscle response. In addition, delayed activation of the abdominal (including IO and EO) and lumbar paraspinal muscles was observed prior to expected and following the unpredicted perturbations [5, 12, 19, 26].

LBP patients also demonstrate the inability to turn off the agonist and turn on the antagonist muscles during unanticipated extension moments around the trunk [24], accompanied with slower reaction times and less forceful corrections of ES activity. Jacobs et al. [21] believe that the history of LBP is associated with higher baseline of ES and RA activation, as well as that the EMG responses are modulated from this activated state rather than exhibiting sudden burst activity from a quiescent state. Consequently, if the ability to independently modulate, relax, or decouple muscle activity is compromised (as found in chronic LBP conditions; [12, 16, 19, 21, 24], the ability to safely reestablish posture and balance following an unexpected event could also be compromised.

Trunk muscle response to exercise interventions

Intents to remodulate the acitvation paterns of trunk musles with active therapy (general and stabilizing exercises) have revealed confounding results. Some researchers emphasized the importance of TrA specific exercises (e.g. bracing and hollowing) in prevention and treatment of LBP [8, 12, 16, 20, 27–30], wile others suggest that the importance of deep muscles has been overestimated and, therefore, specialized exercises unjustified [9, 10, 25]. Although causal relationships between the alterations in TrA activation and appearance of LBP cannot be implied, the research results [17–20] suggest that TrA specific exercises might contribute to the long-term symptom improvement through assistance in dynamic spine stabilization during functional tasks. Regaining neuromuscular control of the TrA and MF has been shown to reduce pain and improve function in chronic LBP patients, particularly in young athletes [3, 7, 28].

Contribution of exercise to changes in activity of other muscles, such as ES, has only partial effect on its activation. Active therapy contributes to an increase in ES activation, but has no effect on the loss of the ES's incomplete relaxation phenomenon which has been consistently observed in individuals with LBP [8, 9]. The sustained activity of ES at the end of the range of trunk flexion has been shown to limit the intervertebral motion. In addition, a high of impairment could be associated with an increase in hip flexion when moving to and from the full flexion, which could be associated with decreased alterations of movement patterns. Since the discussed changes were observed in the third quartile, the hip contribution to flexion might be a strategy put forth by the patients to limit both the motion and loading of the painful lumbar segments.

Conclusions

The results of a recent research on muscle activation in LBP do not reveal a consistent support for either the pain-spasm or the pain-adaptation model. Neither of the two models adequately predicts the effects of pain on trunk muscle activation, nor can fully explain the causality of LBP. Nevertheless, based on the presented research results, some recommendations for active therapy could be made. Specifically, the therapy based on the improvement of proprioception and motor re-education should be focused not only on pain reduction, but also on the long-term changes in trunk muscles' function.

The prescription of exercise as a conservative treatment for lumbar pain is a frequent approach that seems effective for the chronic cases of the nonspecific low back pain. However, there is no evidence for favoring one type of exercise over another. In general, TrA specific exercies should be included, as well as the gait training, to improve intersegmental and muscle coordination, stability and mobility.

Some important recommendations should be considered when designing an exercise program. First, a program should be systematic, progressive, and functional. More importantly, the program should also be individually designed. Second, since the musle response to perturbations is altered, the exercises should be not only proprioceptively rich, but also safe, challenging, and aimed to involve movements in multiple movement planes. Of importance is also incorporation of a multisensory environment and activities that are specificly aimed to improve the dynamic postural control. Therefore, achievement of appropriate muscular balance and joint arthrokinematics in the lumbo-pelvic-hip complex associated with the increase in neuromuscular efficiency throughout the entire body should lead to long term pain reduction and smaller incidence of pain recurence.

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CASE REPORTS

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Lipoma of the sigmoid colon

Lipom sigmoidnog kolona

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Abstract

Introduction. Lipoma is a benign tumor of adipose tissue, the most common tumor of the human body soft tissues. As such, it can be found almost anywhere in the human body including the gastrointestinal system (incidence below 0.5%), but rarely in the sigmoid colon. **Case report.** This is a case report on symptomatic polyp of the sigmoid colon, which after one year, at control colonoscopy, caused suspicion to malignancy. Endoscopically diagnosed polipoid lesion was laparoscopically removed. The pathohistological diagnosis determined benign, submucosal, incapsulated lipoma of the sigmoid colon. **Conclusion.** Although lipomas of the gastrointestinal tract are rare, this case clearly indicates that we should not prematurely and without histological confirmation of malignancy do more extensive resection for a suspected malignancy.

Key words:
lipoma; sigmoid neoplasms; gastrointestinal neoplasms; diagnosis; diagnosis, differential; laparoscopy; treatment outcome.

Apstrakt

Uvod. Lipom je benigni tumor poreklom iz masnog tkiva i najčešći je tip tumora mekih tkiva. Lipom se može naći u skoro svakom delu tela, nekada i u gastrointestinalnom sistemu (incidencija ispod 0,5%), ali veoma retko u sigmoidnom kolonu. **Prikaz bolesnika.** U radu je prikazan bolesnik sa simptomatskim polipom sigmoidnog kolona. Godinu dana nakon prvog pregleda, kontrolni kolonoskopski pregled izazvao je sumnju u postojanje maligne promene. Endoskopski dijagnostikovana polipolika promena laparoskopski je odstranjena. Patohistološkom analizom utvrđeno je postojanje submukoznog, benignog, inkapsulisanog lipoma sigmoidnog kolona. **Zaključak.** Iako su lipomi gastrointestinalnog trakta retki, ovaj slučaj jasno ukazuje da bez patohistološke verifikacije ne treba preduzimati preuranjene i obimnije resekcije creva u slučaju kliničke sumnje na malignitet.

Ključne reči:
lipom; sigma, neoplazme; gastrointestinalne neoplazme; dijagoza; dijagnoza, diferencijalna; laparoskopija; lečenje, ishod.

Introduction

Lipoma is a benign tumor and the most common tumor of soft tissues in human [1, 2]. Histologically, lipoma consists of encapsulated mature, white adipose tissue [3].

Lipoma can be found almost anywhere in human body, but most frequent localization is subcutaneous tissue of upper parts of the body, especially trunk and neck [1, 2]. Cases of rare (atypical) lipoma localization have been reported – intracranial [1, 2], liver [4], myometrium uteri [5], oral cavity [6], and different parts of gastrointestinal system starting from pharynx to anal zone [7].

Inside the gastrointestinal system, the highest incidence of lipoma is in the colon, where it represents the second most frequent benign tumor, after adenomas of colon [3, 8].

Gastrointestinal lipomas usually have no symptoms (unless greater than 2 cm) and are discovered accidentally [8, 9].

Case report

A 64-year-old female patient with body mass index 23.79 kg/m^2 was admitted to the Clinic for Abdominal, Endocrine and Transplantation Surgery, Clinical Center of Vojvodina, Novi Sad. A year before the surgery, due to abdominal pain and occult blood in the stool the patient underwent colonoscopy, and was diagnosed with polypus of sigmoid colon. Colonoscopy after one year showed changes in the part of the intestinal epithelium suspicious for malignancy. After preoperative preparation and analyses, polypus was laparoscopically removed. The patient went through a regular postoperative course.

The removed colon was 13 cm long, and 3 cm from the proximal end and 10 cm from the distal end, a sessile polypoid change with dimensions 1.8 × 1 × 1 cm was detected. Cross section revealed grey to yellow, homogenous struc-

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ture. Polipoid structure and deeper parts of intestinal wall were sampled, fixated in formalin, dehydrated, paraffin embedded and permanent paraffin blocks were formed. Paraffin blocks were sectioned to a thickness of 5 micrometers and stained for hematoxylin and eosin (H&E).

The examined material in some sections showed normal intestinal wall structure, while in others colonoscopically registrated, polipoid structure was observed, coated with intestinal mucosa. In submucosal layer there was demarcated, encapsulated tissue of the tumor, composed only of mature adipocytes without cellularity or atypia (Figure 1). The described histological feature was typical of lipoma. Tumor tissue was elevating mucosa and forming macroscopically described polipoid formation. Mucosal surface and crypts of mucosa above the polyp were lined with mildly hyperplastic epithelium. The lamina propria contained diffuse, moderate inflammatory infiltrate and erythrocytes.

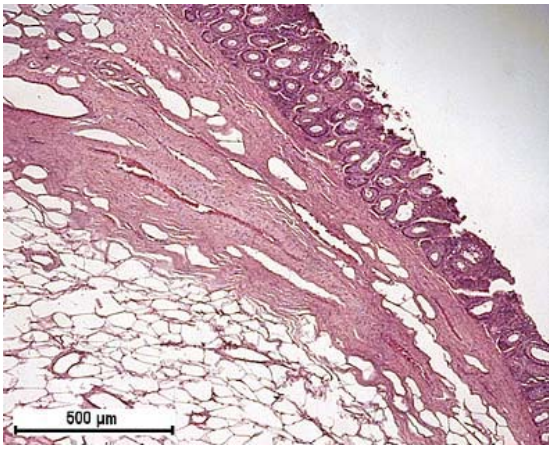

Fig. 1 – Encapsulated tissue of the lipoma (HE, ×40)

Discussion

Lipomas are frequently diagnosed in soft tissues, and are most common in people aged 40–60 years, more frequently in females [3, 10].

Of all lipomas in the gastrointestinal system, 65% is located in the colon, 20%–25% in the small intestine and it is extremely rare in the gaster and the esophagus [11, 12]. Most common lipomas are present in the ascending colon (coecum included), transverse colon (including hepatic and splenic flexure), and rarely at the descending and sigmoid colon and rectum [7, 8]. Lipomas of the gastrointestinal system are mostly located in submucosa, less in subserosa. The first description of colonic lipoma was given by Bauer in 1757 [13].

The appearance of clinical symptoms is related to the dimension of the tumor. Tumor size can range from 1.8 to 3.5 cm, and as symptomatic are generally considered those larger than 2 cm [8, 9]. Symptoms may include: abdominal pain (diffused or localised), mechanical obstruction, hemorrhage, constipation [7, 12, 14, 15]. There is a report on a case of gastric, antral lipoma prolapsing into duodenum, causing duodenal ulcer [16]. Although the patient in this case came with symptoms frequent in lipoma, it did not lead to proper diagnosis.

Most of lipomas do not require treatment, except for those which rapidly grow or painful symptomatic ones. Available methods for their treatment are endoscopic removal of lipoma (diameter less than 2 cm), surgical extraction (diameter > 2 cm, subserosal location or uncertain diagnose), steroid injections and liposuction [10, 13].

On the first colonoscopy polipoid structure was detected in our patient, but after a year, on control colonoscopy the same polipoid structure brought to misapprehension and suspicion to malignantly altered polypus.

Colonoscopy reveal the condition of the superficial mucosa above a lipoma, which in case of erosion, hyperplasia (as in the presented case) or dysplasia of the epithelia may appear to be malignant, and cause repeated colonoscopies and extraction of polypus in spite of biopsies which confirmed benign nature of the mucosal lesion [9].

From histopathological point of view, a common problem in the diagnosis is the distinction between true lipomas from simple multiplication of adipose tissue. This multiplication is particularly common in the coecum, which is the most common site of lipomas. It is characterized by hypertrophy of adipose tissue in the submucosal intestine wall, which is not encapsulated [3]. In the presented case, a lipoma was localized in the sigmoid colon, in which the literature claims, lipomas are rare [7, 8]. Tumor in the presented case is clearly demarcated and encapsulated which removed the doubt on simple multiplication and hypertrophy of adipose tissue.

Magnetic resonance is considered to be the best imaging method for diagnostic of lipoma, but it is not a part of standard diagnostic algorithm, so most reliable, precise and definitive diagnosis is obtained by histological examination [5].

Typical chromosome abberations were found in lipoma tissue in recent years, but it was impossible to run these tests because all the material from surgery underwent histological procedures.

Although lipomas of the gastrointestinal tract are rare (incidence below 0.5%), the presented case clearly indicates that we should not prematurely and without histological confirmation of malignancy, do more extensive intestine resection for suspected malignancy. In particular, caution should be taken in patients with a history of lipomas at other sites, in obese patients, patients suffering from dyslipidemia and females in menopause [5].

Conclusion

All of the stated above show the difficulties of preoperative diagnostics of benign lipomas and other malignant lesions of the colon. Concerning clinical signs and symptoms they are often similar in appearance. Even with abdomen radiography and colonoscopy, it is not possible to make a precise differential diagnostic of these states. Only prompt pathohistological examination give a clear insight into the nature of the change and prevents further more aggressive conservative or surgical treatment in case of suspicion of malignancy.

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CASE REPORT

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A rare case of retroperitoneal malignant Triton tumor invading renal vein and small intestine

Redak slučaj retroperitonealnog malignog tumora Triton sa invazijom renalne vene i tankog creva

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Abstract

Introduction. Malignant Triton tumor is a very rare malignant peripheral nerve sheath tumor with rhabdomyosarcomatous differentiation. Most of those tumors occur in patients with von Recklinghausen's disease or as a late complication of irradiation and commonly seen in the head, neck, extremities and trunk. **Case report.** We reported retroperitoneal malignant Triton tumor in a 57-year-old female patient. Skin lesions were not present, and there was no family history of neurofibromatosis or previous irradiation. The presented case is one of a few recorded in the specialized literature that occurs in the retroperitoneal space in sporadic form. In this case, tumor consisted of a multilobular mass was in close relation with the abdominal aorta and inferior vena cava and involved the renal vein with gross invasion of the small intestine. The patient underwent total resection of the tumor and left nefrectomy was performed. The small intestine 10 cm in length was also resected and end-to-end anastomosis was conducted. The postoperative course was uneventful and the patient was discharged from the hospital ten days after the surgery. **Conclusion**. Diagnostically, it is crucial to recognize this uncommon histological variant because malignant Triton tumor has a worse prognosis than classic malignant peripheral nerve sheath tumor does. The use of the immunohistochemistry is essential in making the correct diagnosis. Only appropriate pathological evaluation supported by immunostaining with S-100 protein and desmin confirmed the diagnosis. Aggressive surgical management treatment improves the prognosis of such cases with adjuvant radiotherapy.

Key words:
peripheral nervous system neoplasms; diagnosis; immunohistochemistry; surgical procedures, operative; treatment outcome.

Apstrakt

Uvod. Maligni tumor Triton je veoma redak maligni tumor omotača perifernih nerava sa rabdomiosarkomatoznom diferencijacijom. Većina ovih tumora javlja se kod bolesnika sa Recklinghausen-ovom bolešću ili kao kasna komplikacija zračenja i najčešće se viđa na glavi, vratu, ekstremitetima i trupu. **Prikaz bolesnika.** Prikazan je retroperitonealni maligni Triton tumor kod bolesnice starosti 57 godina. Kožne lezije nisu bile prisutne i nije bilo porodične anamneze neurofibromatoze ili prethodnog zračenja. Prikazana bolesnica jedna je od retkih koji su zabeleženi u specijalizovanoj literaturi sa tumorom u retroperitonealnom prostoru u sporadičnoj formi. Kod ove bolesnice tumor se sastojao od multilobularne mase, bio je u tesnoj vezi sa abdominalnom aortom i donjom šupljom venom sa makroskopski vidljivom invazijom tankog creva. Urađena je totalna resekcija i leva nefrektomija. Takođe, urađena je i resekcija tankog creva dužine 10 cm i anastomoza *end-to-end*. Postoperativni tok je protekao regularno i bolesnik je otpušten deset dana posle hirurške intervencije. **Zaključak.** Dijagnostički, prepoznavanje ove retke histološke varijante ima poseban značaj, jer maligni tumor Triton ima goru prognozu od klasičnog malignog tumora omotača perifernih nerava. Korišćenje imunohistohemije važno je za postavljanje tačne dijagnoze. Jedino adekvatna patološka procena sa imunohistohemijskim bojenjem S-100 proteina i desmina potvrđuje dijagnozu. Agresivno hirurško lečenje sa adjuvantnom radioterapijom može poboljšati prognozu ovakvih slučajeva.

Ključne reči:
živci, periferni, neoplazme; dijagnoza; imunohistohemija; hirurgija, operativne procedure; lečenje, ishod.

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Introduction

Malignant Triton tumor (MTT) is a malignant peripheral nerve sheath tumor (MPNST) with rhabdomyosarcomatous differentiation. MTT constitutes about 5% of all MPNSTs. MTT arises in two principal forms: sporadic or in association with neurofibromatosis type 1 [von Recklinghausen's disease (NF-1)]. Slightly more than half of the cases of MTT have been reported in conjunction with NF-1. MTT is commonly seen in the head, neck, extremities and trunk [1]. The fact that the presence of this unusual tumor in the retroperitoneal space is extremely rare has prompted the authors to report this case. We presented a 57-year-old female patient in whom a retroperitoneal paravertebral mass was postoperatively diagnosed as MTT and describeed the histomorphological and immunohistochemical features of this uncommon tumor. In this case, tumor developed outside the setting of NF-1.

Case report

A 57-year-old female patient presented with a 2-month history of abdominal pain radiating to the back. Physical examination revealed a painful abdomen in the region of umbilicus. Full blood cell count, serum urea levels, and electrolyte levels were within normal limits. Chest X-ray was normal. At laparotomy, a multilobular paravertebral mass the size of two male fists was found occupying the left abdominal region. Tumor was in close relation with the abdominal aorta and inferior vena cava and appeared to involve the left renal vessels (artery and vein) with gross invasion of the small intestine. The patient underwent total resection of the tumor and left nefrectomy was performed. Upon resection, thrombosis was present on part of a renal artery and there was no need for further pathological analysis. The small intestine 10 cm in length was also resected and end-to-end anastomosis was conducted. The postoperative course was uneventful and the patient was discharged from the hospital ten days after the surgery**.**

On the basis of histological findings and immunohistochemistry, a malignant Triton tumor, an uncommon subtype of peripheral nerve sheath tumor with rhabdomyosarcomatous elements, was diagnosed. Thereafter, the patient was referred to the Oncology Department for Radiotherapy.

During the 8-month follow-up, the patient showed no evidence of recurrence or metastasis.

Macroscopically, the tumor was received in three fragments measuring 7, 5 and 4.5 cm. The cut sections showed solid, firm and yellow whitish tissue with areas of necrosis (Figure 1). The left kidney measured 11 x 6 x 5 cm. Cut section showed no gross abnormalities. Samples of left renal vein measured 0.6 and 0.7 cm, and part of small intestine was 10 cm in length.

Microscopically, the tumor was composed of spindle cells arranged in a fasciculated pattern and whorls (Figure 2). Spindle cells showed wavy, hyperchromatic nuclei with indistinct light staining cytoplasm. Hypercellular and hypocellular zones with areas of palisading necrosis and myxoid stroma were also present. Scattered large round cells with eosinophilic cytoplasm and hyperchromatic nuclei were seen admixed with neoplastic spindle cells.

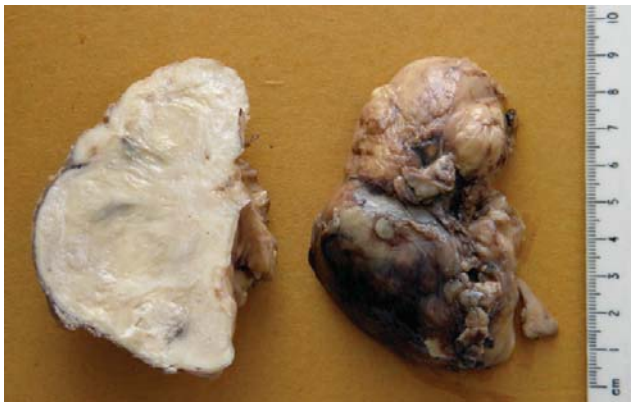

Fig. 1 – A fragment of primary malignant Triton tumor. The cut surface was solid, firm and yellow whitish with the areas of necrosis

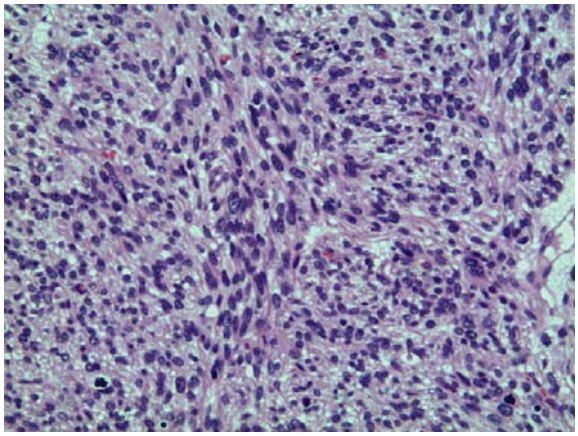

Fig. 2 – Malignant Triton tumor (spindle cells arranged in interlacing fascicles, sheaths and whorls; H&E, ×100)

On histology, the kidney showed no significant morphological abnormalities. The lesion involved renal vein and a part of the small intestine were similar, displaying poorly differentiated spindle cells.

Immunohistochemically, the spindle cells were focally positive for S-100 (Figure 3), strongly positive for vimentin, and negative for cytokeratin 7, EMA, HMB-45, and CK AE1/AE3. The large, round eosinophilic pleomorphic cells

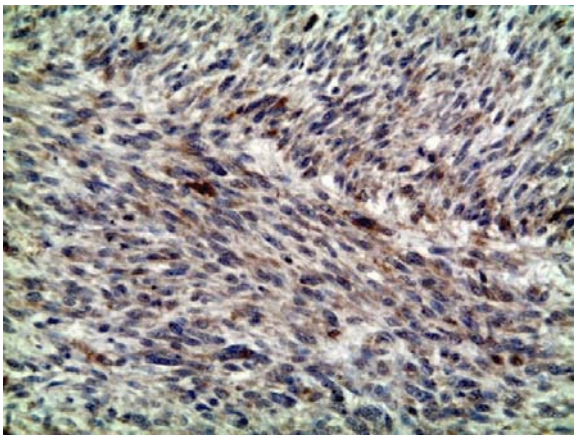

Fig. 3 – Focal staining of spindle cells for S-100 protein (peroxidase-antiperoxidase technique, ×200)

were immunoreactive for muscle-specific actin and desmin (Figure 4). Immunohistochemical staining with S-100 and desmin indicated that the tumor cells originated from Schwann cells and showed rhabdomyosarcomatous differentiation. Ki-67 was expressed in a large number of cells (30%).

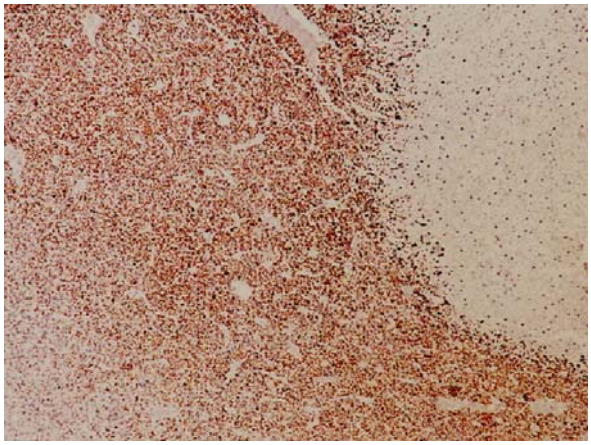

Fig. 4 – Staining for desmin was strongly positive in the area of malignant Triton tumor (peroxidase-antiperoxidase technique, ×100)

Based on these findings, the histopathological diagnosis was malignant peripheral nerve sheath tumor with rhabdomyosarcomatous differentiation, namely malignant Triton tumor.

Discussion

MPNSTs are neoplasms derived from the cellular constituents of the peripheral nerve sheath. This term replaces the earlier terms malignant schwannoma, neurofibrosarcoma, and neurogenic sarcoma [1]. The majority arise from Schwann cells, but some could develop from fibroblasts and supporting cells known as perineural cells. The capacity of MPNSTs to undergo focal divergent differentiation to rhabdomyosarcoma, chondrosarcoma, osteosarcoma, angiosarcoma, epithelial elements, or a combination thereof is well known [2–6]. MTT is a variety of this type of tumors which presents a rhabdomyoblastic differentiation. This composite neoplasm was first described in 1938 by Masson and Martin, who suggested that the neural elements in the tumor induced differentiation of skeletal muscle in much the same fashion as normal nerve was believed to induce the regeneration of skeletal muscle in the Triton salamander [1]. This tailed amphibian displays the ability to regenerate limbs after the cut end of the sciatic nerve is implanted into the soft tissue of its back. Although Masson believed that one cell line induced the other, it seems more likely that both cell lines originate from less well-differentiated neural crest cells [1]. The term "malignant Triton tumor" was first introduced by Woodruff et al. [7] in 1973.

MTTs are extremely rare, with less than 100 cases documented world-wide to date [8–10]. Regarding location, MTT occurs predominantly in the head, neck, trunk regions and lower extremities [1, 3]. To the best of our knowledge, there are only a few reports of these tumors developing in the retroperitoneal space [11–14].

MTT shows marked male predominance with more predilections for younger age groups. The sporadic forms mostly occurring in females of older age groups [15], as the case reported herein. These tumors may also arise in sites of previous radiation therapy. We reported the case of paravertebral MTT occurring in the patient without clinical setting of NF-1 or previous irradiation.

MPNST is one of the most histologically variable soft tissue tumors, and use of immunohistochemistry is essential in making a correct diagnosis [1, 3, 16, 17]. The fasciculated, spindle cell growth pattern may cause confusion with leiomyosarcoma, fibrosarcoma, or monophasic synovial sarcoma. In addition, MPNST must be distinguished from melanoma malignum. In the present case, histology and immunohistochemical staining revealed a typical pattern of MPNST with the additional features of rhabdomyoblastic differentiation supported by positive staining with desmin and muscle-specific actin [3, 4, 8].

Retroperitoneal localization MTT has the most unfavorable prognosis due to the delayed diagnosis but also due to the relation to adjacent organs [13]. This case of MTT was presented as a large abdominal mass with invasion of the left renal vein and the small intestine since these retroperitoneal tumors are often asymptomatic in the earlier stages [12, 14]. The natural history of MTT is much more aggressive than MPNST [3, 15, 18]. The tumor has a high propensity for early local recurrence, rather than metastatic disease. The prognosis is poor with a 5-year survival rate around 12% [15]. Location has been correlated with survival [11]. Tumors occurring in the head and neck, upper and lower extremities have a better prognosis than tumors located in the retroperitoneum, buttocks or trunk. Cytogenetic studies have revealed a breakpoint in 11p15, considered a region of myogenic differentiation. Amplification of c-myc oncogene is probably responsible for aggressive biologic behavior of MTT [3]. As MTT is a very aggressive tumor, behaving like a high grade sarcoma, it is believed that to obtain the best outcome a full surgical resection with as wide a margin as possible is vital followed by adjuvant radiotherapy [19].

Conclusion

Retroperitoneal malignant Triton tumor is extremely rare, but an important pathological condition. This uncommon histological variant has the worse prognosis than classic malignant peripheral nerve sheath tumor does. Immunohistochemistry is an essential tool for ruling out differential diagnostic considerations. Radical surgical excision of the tumor followed by radiation therapy is the treatment of choice.

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CASE REPORT

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Sclerosing mesenteritis as a rare cause of upper ileus

Sklerozirajući mezenteritis kao redak uzrok visokog ileusa

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Abstract

Introduction. Sclerosing mesenteritis is a rare pathological entity characterized by non-specific tumor-like expansion in mesentery. Accurate diagnosis of this disease is rarely made preoperatively. Surgery takes place in diagnosis, as well in treatment of the disease. We presented a case of sclerosing mesenteritis that affected the final portions of duodenum and initial part of jejunum with clinical picture of upper gastrointestinal obstruction. **Case report.** A 46-year-old man without previous medical history was presented with vomiting and loss of weight in the last 6 months. Due to suspicion of parapancreatic tumor by CT examination and clinical presentation of the disease, the patient underwent laparotomy. A mass infiltrated mesenteric root, initial part of superior mesenteric artery, the fourth duodenum portion and the ligament of Treitz, while the stomach and duodenum were dilatated. The intraoperative biopsy indicated a benign process. The mass was reduced with desobstruction of the duodenum. Definitively, histopathological finding showed fibromatosis in different phases of activity. Postoperative course passed without complications. The patient continued to receive an immunosuppressive drug therapy. After a 6-month treatment the patient showed no gastrointestinal problems. **Conclusion.** Sclerosing mesenteritis that affects the duodenum and the proximal part of the jejunum with subacute upper gastrointestinal obstruction is an extremely rare condition. In the presented case a surgical procedure was necessary for marking the diagnosis and treatment as well.

Key words:
panniculitis, peritoneal; intestinal obstruction; diagnosis; surgical procedures, operative; treatment outcome.

Apstrakt

Uvod. Sklerozirajući mezenteritis je retki patološki entitet koji karakteriše nespecifičnu infiltracija u predelu mezenterijuma, nalik tumoru. Tačna dijagnoza ove bolsti retko se postavlja preoperativno. U cilju dijagnoze, kao i terapije, hirurgija zauzima značajno mesto. Prikazali smo bolesnika sa sklerozirajućim mezenteritisom sa zahvatanjem završnih delova dvanaestopalačnog creva i početnog dela jejunuma koji je imao kliničku sliku opstrukcije gornjeg gastrointestinalnog trakta. **Prikaz bolesnika.** Prethodno zdrav muškarac, star 46 godina, javio se zbog povraćanja i gubitka telesne mase u poslednjih šest meseci. Klinička slika i nalaz na CT pregledu abdomena, izazvali su sumnju na parapankreasni tumor, te je bolesnik operisan. Nađena je masa koja je infiltrisala koren mezenterijuma, početne delove gornje mezenterične arterije, četvrtu porciju dvanaestopalačnog creva i Treitz-ov ligament, sa dilatacijom dvanaestopalačnog creva i želuca. Intraoperativna biopsija promene ukazivala je na to da se radilo o benignom procesu. Masa je redukovana sa dezopstrukcijom dvanaestopalačnog creva. Definitivni histopatološki nalaz pokazao je da se radilo o fibromatozi u različitim fazama aktivnosti. Postoperativni tok protekao je uredno, bez komplikacija. Nastavljena je imunosupresivna terapija, a na kontrolnom pregledu nakon šest meseci bolesnik nije imao gastrointestinalne tegobe. **Zaključak.** Sklerozirajući mezenteritis sa zahvatanjem dvanaestopalačnog creva i proksimalnog dela jejunuma sa subakutnom opstrukcijom gornjeg gastrointestinalnog trakta je izuzetno retko stanje. Kod prikazanog bolesnika hirurška intervencija bila je neophodna za postavljanje dijagnoze, ali i kao terapijska procedura.

Ključne reči:
paniculitis, peritonealni; creva, opstrukcija; dijagnoza; hirurgija, operativne procedure; lečenje, ishod.

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Introduction

Sclerosing mesenteritis (SM) (or retractile mesenteritis) is a rare, benign and chronic fibrosing disease with inflammatory etiology of unknown origin, which affects the mesentery of the small bowel. Rarely, the mesentery of the transversal colon, peripancreatic region, omentum, retroperitoneum or the pelvic region can be affected, as well [1]. Three different histopathological changes are described in this process which include fat tissue necrosis, chronic nonspecific inflammation and fibrosis [2, 3]. Due to a very different course of the disease many different names for SM were used such as: mesenteric lipodistrophy, retractile or liposclerotic mesenteritis, mesenteritic Weber-Christian disease, xantogranulomatosis mesentiritis, mesenteric lypogranuloma and system nodular panniculitis [3]. If inflammation or fat tissue necrosis are predominant features, the disease is considered to be mesenteric panniculitis; if otherwise fibrosis with retraction is predominant feature the disease is called retractile mesentiritis. However, the presence of fibrosis in any degree, makes SM the most accurate term in a large number of cases [3, 4].

The disease more commonly affects middle-aged male adults [1]. Due to different atypical and nonspecific manifestations of the disease (abdominal pain, loss of weight, intestinal obstruction, fever, chylous ascites, palpable abdominal mass, constipation or diarrhea), preoperative diagnosis of SM is difficult in most cases [3–7]. Diagnosing this disease is complicated, posing a great problem and a challenge for radiologists, gastroenterologists and surgeons, even for pathologists who encounter this disease very rarely, with only 300 cases described in the literature so far [8]. In order to avoid misdiagnosis, one should think about this disease, even so the finall diagnosis demands biopsy and histopathological examination. With an no clearly defined treatment modalities of SM, surgery can take place in diagnosis, as well as in treatment of the disease [1, 3].

We reported a patient presented with an upper bowel obstruction caused by a retroperitoneal mass, which seemed to be pancreatic or parapancreatic tumor, and turned out to be SM on histopathological examination.

Case report

A 46-year-old male was admitted to our institution with vomiting and weight loss (7 kg for a month and 15 kg in a 6-month period). Problems started in the last six months with dyspepsia, anorexia and occasional pain in epigastrium, which in time grew to be stronger. For instance, vomiting was deteriorating and led to anorexia in the last l5 days. During admission the patient had light pain in the epigastrium with a palpable mass in that region. All laboratory parameters including tumor markers were in physiological ranges, except for the proteins whose value was 53 g/L.

Esophagogastroduodenoscopy (EGDS) showed dilatation of the bulb and the second duodenal portion with extraluminal compression in the region of the second duodenal knee, which was almost completely narrowing it's lumen. Endoscope ultrasound (EUS) showed heterogeneous echo change with hypoechogenic fields 4 cm in diameter in the region of Treitz ligament next to the duodenal wall which was infiltrated. X-ray of gastroduoduodenum showed almost complete obstruction of the lumen of the third and the fourth duodenal portion with the preserved mucosa relief and a significant dilatation of the proximal duodenal segment and moderate gastrectasis (Figure 1). Multislice computed tomography (MSCT) of the abdomen showed tumor formation bordered by the wall of the third and the fourth duodenal portion extended to the ligament of Treitz with thickening of the bowel wall, enlarged lymph nodes around superior mesenteric artery (SMA) and dilatation of the proximal segment of the duodenum and the pylorus (Figure 2).

Fig. 1 – X-ray of gastroduodenum – almost a complete obstruction of the duodenal lumen with proximal duodenal dilatation

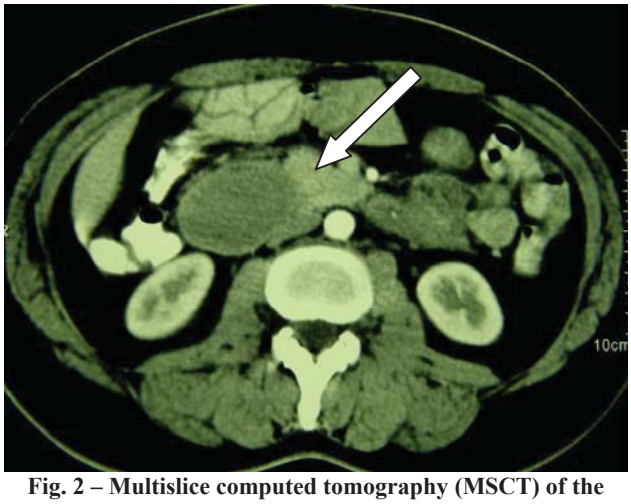

Fig. 2 – Multislice computed tomography (MSCT) of the abdomen – a tumor formation in pancreatic and parapancreatic region with dilatation of the second duodenal portion

The patient was presented on a meeting of gastroenterologists, surgeons and radiologists. They decided that surgical treatment should be applied, since the tumor formation which led to almost complete obstruction of the duodenum

and ileus, was the cause of the patient's condition. After short preparations, the patient underwent laparotomy, and retroperitoneal tumor was found with a remarkably firm consistency, unclearly bordered, which infiltrated mesenteric root, initial part of SMA, the fourth duodenal portion and the ligament of Treitz. The duodenum and almost a complete stomach were dilatated. A tumor formation was retracting proximal part of jejunum and pulled initial part of the descending colon. Using the transgastrocolic approach, we performed meticulous preparation of the mesenteric root and SMA with preparation and dissection of tumor tissue. During dissection a couple of excision bioptats were taken for the intraoperative histopathological examination and showed no malign cells. The operation was finished with a significant tumor reduction and duodenal desobstruction. Postoperative course was with no complications. The patient was introduced to *per os* food intake on the 3rd postoperative day with intact intestinal passage. The definitive histopathological finding showed fibromatosis in different phases of activity with a small degree of fat necrosis (Figures 3–5).

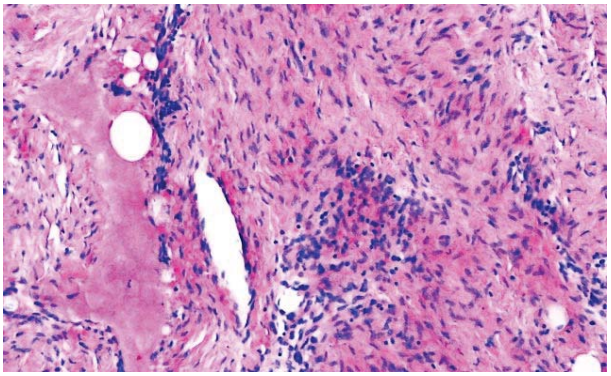

Fig. 3 – Proliferation of the cellular connective tissue with vascular compartments and bar of mononuclear inflammatory infiltrate (HE, ×40)

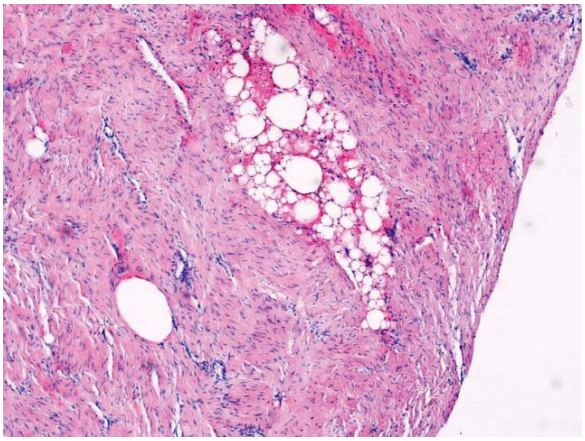

Fig. 4 – The islands of a mature fat tissue with fields of steatonecrosis surrounded with the cellular and acellular connective tissue (HE, ×10)

Seven days after the surgery MSCT angiography of the abdomen showed a significantly lower level of fibrotic mass compared with the period before the operation, without duodenal obstruction (Figure 6) and the normal trunk of SMA (Figure 7). After a full recovery of the patient, the same physicians, including pathologists, decided to start treatment with oral methotrexate and prednisone. After a six-month treatment the patient had no gastrointestinal problems. The next examination with radiological assessment was scheduled in 6 months.

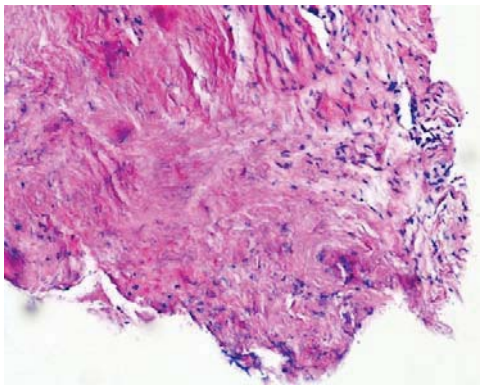

Fig. 5 – Proliferation of the acellular connective tissue, dezmoid like (HE, ×40)

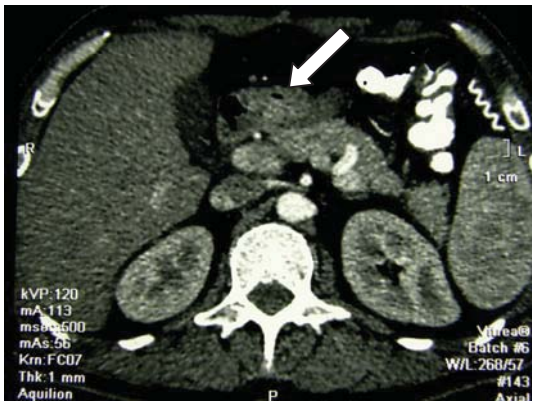

Fig. 6 – Postoperative multislice computed tomography (MSCT) – lower level of a fibrotic mass without duodenal dilatation

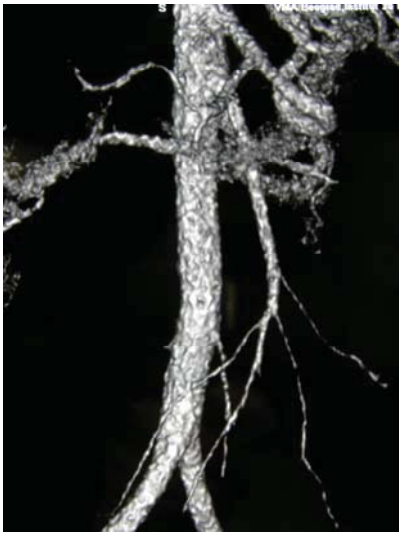

Fig. 7 – Postoperative multislice computed tomography (MSCT) angiography – the normal trunk of superior mesenteric artery

Discussion

SM presents a rare disease of unknown etiology firstly described by Jura [9] in 1921. Until today the literature has described about 300 cases [8]. It presents nonspecific tumor-like expansion in the mesentery, characterized with a different grade of chronic inflammation, fibrosis and fat necrosis [2, 3]. Various names were used to describe this disease focusing on histopathological features: fibrosis (retractile mesenteritis), inflammation (mesenteric panniculitis) or fat tissue necrosis (mesenteric lipodistrophy). It was acknowledged that these states represent only different histological types of the same clinical entity known as SM, which is being used as the most appropriate term for describing this disease [10].

SM can be associated with an autoimmune diseases, mesenteric ischemia, cancers (especially lymphoma), tuberculosis, lymphadenitis, previous abdominal surgeries and trauma [5]. It is by two times more common in men, white race, while very rare in children [11, 12].

Preoperative diagnosis of SM is usually difficult and rarely exact [3, 5–8]. The most common symptoms are abdominal pain and vomiting, while constipation, diarrhea and hematochezia are less common [5, 6, 13]. In around 50% of patients there is palpable abdominal mass[14]. Symptoms of acute or subacute upper obstruction of the small intestine are rare, but nevertheless described in the literature [5]. Laboratory findings are usually normal, although normocytic anemia may be present [15]. Radiological examinations can be helpful in reaching the correct diagnosis. X-rays with contrast can show different stages and levels of obstruction of the intestinal tract. In case of fibrosis predominance, the level of obstruction is in the region of jejunum, ileum, left or right colon, very rarely in the duodenal region [14]. Lumen obstruction is mainly partial and very rarely complete or almost complete [16–18]. Preservation of the bowel mucosa during the contrast examinations is crucial in differentiation between SM and cancers [13, 18–20]. MSCT can show tumor mass in the mesentery with fat tissue density, which surrounds blood vessels and suppresses the bowel without any signs of it's infiltration [15, 17]. If the fibrosis is predominant in the mesentery, MSCT scan may suggest a malign tumor of the connective tissue or pancreatic or parapancreatic tumor [11], just like in our patient. CT scan is an important diagnostic procedure when the localization of the disease is in the region of small bowel mesentery. Two CT findings are considered more specific for the diagnosis of SM [12]: a) the presence of the tumour pseudo-capsule, which is a hyperattenuated stripe surrounding the mass in the mesentery of the small bowel (this is seen in 60% of cases); b) the "fat ring" – sign of hypodense fatty halo surrounding mesenteric nodules and vessels. This is seen in up to 75% of cases. It should be emphasized that if the mass is localized in the region of intestinal loops closer to mesenteric side, it suggests SM. On the other hand, if the mass is located in the peripancreatic region, cancer of pancreas or the tumor of non-pancreatic origin is more probable [1, 19]. Differentiation of SM and sarcoma presents a great diagnostic problem. In that case an open surgical or laparoscopy exploration with biopsy should be done [19–22]. Only in few so far described cases the diagnosis of SM was made before the surgery [3, 5–8, 10, 23]. However, histopathological finding is necessary to confirm diagnosis [16].

There is no specific treatment or the treatment protocols for SM. In the study from the Mayo Clinic which included 92 patients with any form of SM and different treatment modalities, the results suggested that symptomatic patients might benefit from medical therapy, particularly tamoxifen and prednisone combination treatment. Only 10% of patients respond to surgery alone, and 20% to additional medical treatment after surgery [1]. Also, there have been reports on the response to antibiotics [24], irradiation [25], and cyclophosphamide [26]. Some literature data indicated that SM may regress spontaneously after laparotomy (especially in cases of fat necrosis predominance) [4, 27]. If chronic inflammation predominates various immunosuppressive therapies are suggested [1, 26]. In cases of bowel obstruction, partial resection, bypass, and colostomy may be necessary [10]. It is suggested to reserve surgery for unsuccessful medical treatment and complications of SM [28], but in cases when the diagnosis cannot be established with certainty and/or when a patient's clinical condition requires emergency treatment, surgery is indicated. The complications of SM requiring surgery are: shortening and retraction of the mesentery with compression of the mesenteric blood vessels, followed or not with intestinal ischemia and/or partial or complete intestinal obstruction [13, 19, 20]. Frequently, surgery is required for excision biopsy, but compression of the vessels will limit any further dissection of the mesentery for exposure or resection [27, 29].

In the available medical literature, in the Medline database, there is no case of SM with duodenal obstruction and clinical presentation of acute and/or subacute upper ileus [1, 5, 6, 8, 14, 18].

Our patient had no known exposure to toxic agents and did not use any medications. Abdominal trauma or previous abdominal surgery could not be implicated. Also, our patient had no previous history of any disease. Surgery was necessary to resolve duodenal obstruction and to confirm SM. In the same act the reduction of fibrotic tissue without resection of the gut was performed. Due to inconclusive preopertive and intraoperative diagnosis, and a significant reduction of fibrotic tissue followed by duodenal desobstruction, there was no need to do gastroenterostomy and expose the patient to additional risks. A postoperative prednisone and methotrexate administration resulted in the complete resolution of symptoms and pathological clinical findings.

Conclusion

SM can affect any part of the small intestine and colon, including the retroperitoneum in the form of different inflammatory diseases and abdominal tumors, with diverse clinical pictures. Etiology and pathogenesis are unknown. There are still no clear criteria in making certain diagnosis preoperatively or the defined treatment protocols for different forms of SM. It seems that the only certain are states in

which surgery is the primary option. Perennial follow-ups of treated patients, are necessary to answer to at least a few questions: Is surgery without resection of the small intestine sufficient for some forms of the disease? In which cases only medical treatment should be applied? What forms of SM demands specific type of therapy?

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CASE REPORT

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Breast cancer metastasis to the conjunctiva

Metastaze karcinoma dojke u konjunktivu

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Abstract

Introduction. Conjunctival metastasis is exceedingly rare, and it is, as a rule, a sign of advanced malignant disease with poor prognosis. We presented a female patient with breast cancer metastasis to the conjunctiva. **Case report.** A 45-year-old premenopausal female patient was presented with a solitary, yellowish, thin, demarcated lesion in the superior nasal quadrant of the bulbar conjunctiva of the left eye noted by chance a week earlier. There was no sign of irritation, and no pain, and no other functional or morphological problem in either eye or orbit. Five years before the appearance of conjunctival metastasis, breast carcinoma was diagnosed and the patient underwent chemotherapy, preoperative radiotherapy and radical mastectomy. Three years later, computed tomography scan showed metastasis in the left hepatic lobe with ascites and the patient underwent chemotherapy again. But, four months prior to the appearance of conjunctival lesion body scintigraphy showed multifocal sceletal lesions and nuclear magnetic resonance revealed diffuse hepatic metastases and bilateral ovarial tumors. Paliative radiotherapy and hormonal therapy (megestrol, 160 mg) were carried out. An excisional biopsy of the observed conjunctival lesion was performed under topical anesthesia and the material was subjected to histopathological (HP) examination. HP and immunohistochemical examinations established the presence of breast infiltrating lobular carcinoma metastatic to the conjunctiva. The patient showed rapid deterioration after intervention, and died after three weeks. **Conclusion.** A survival period less than one month after the appearance of conjunctival metastasis deserves attention because it is unexpected and has never been reported previously. It is not a rule that HP presentation of a metastatic lesion is so characteristic that it is possible to determine a primary tumor.

Key words:
conjunctiva; neoplasm metastasis; diagnosis; histological techniques; breast neoplasms.

Apstrakt

Uvod. Metastaze u konjunktivu izuzetno su retke i, po pravilu, znak su uznapredovale maligne bolesti sa lošom prognozom. Prikazali smo bolesnicu sa metastazom karcinoma dojke u konjunktivu. **Prikaz bolesnika.** Bolesnica, stara 45 godina, pri dolasku imala je solitarnu, žućkastu, tanku i ograničenu leziju u gornjem nazalnom kvadrantu bulbarne konjunktive levog oka, koja je slučajno zapažena nedelju dana ranije. Nije bilo znakova iritacije niti bola, kao ni drugih funkcionalnih ni morfoloških problema u oku ili orbiti. Pet godina ranije dijagnostikovan je karcinom dojke. Bolesnica je lečena hemioterapijom, preoperativnom radioterapijom i urađena je radikalna mastektomija. Tri godine ranije, kompjuterizovanom tomografijom utvrđene su metastaze u levi hepatički lobus sa ascitesom i bolesnica je ponovo lečena hemioterapijom. Međutim, četiri meseca pre pojave konjunktivalne lezije, scintigrafijom su utvrđene multifokalne lezije u kostima dok su nuklearnom magnetnom rezonancom otkrivene difuzne metastaze u jetru i obostrano ovarijalni tumor. Sprovedena je palijativna radioterapija i hormonska terapija (megestrol, 160 mg). Urađena je ekscizijska biopsija uočene konjunktivalne lezije u lokalnoj anesteziji i materijal poslat na histopatološki pregled. Histopatološkim i imunohistohemijskim ispitivanjem utvrđena je metastaza infiltrišućeg lobularnog karcinoma dojke u konjunktivu. Stanje bolesnice nakon intervencije rapidno se pogoršavalo i umrla je nakon tri nedelje. **Zaključak.** S obzirom na to da je neočekivano i da do sada nije bilo registrovano, preživljavanje kraće od jednog meseca od pojave metastaze u konjunktivu zaslužuje posebnu pažnju. Nije uobičajeno da je histopatološka slika metastatske lezije toliko karakteristična da je na osnovu nje moguće definisati primarni tumor.

Ključne reči:
konjunktiva; neoplazme, metastaze; dijagnoza; histološke tehnike; dojka, neoplazme.

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Introduction

The exact incidence of metastatic tumors to the eye and adnexa is unknown, and the supposed incidence is probably underestimated. A certain number of these metastases are asymptomatic and remain unrecognized. Some of them are not appreciated because of the dominant problems with simultaneous tumor involvement of major organs. The systemic treatment of primary or metastatic disease may also cause regression of ocular metastases as a side effect. On the other hand, the number of tumor patients increases, their survival is prolonged, thus making the possibility of ocular metastases greater.

Among the metastases to the eye and adnexa the most common are intraocular, choroidal metastases, and orbital metastases.

Conjunctival metastases of distant solid tumors are extremely rare. In an experiment on rabbits, only one case of conjunctival metastasis was identified among 67 ocular metastases after injection of Brown-Pearce tumor cells into the left ventricle [1]. A clinical survey of 1,643 patients treated for conjunctival tumors over a 28-year-period revealed only 13 cases of metastatic tumor, less than 1% [2].

Breast carcinoma, being the most frequent malignancy in female population, is also the most frequent site of primary tumor to give ophthalmic metastases in females [3, 4].

Autopsy studies have found the presence of ocular metastases in 8.3% [5], 36% [6] and even 41% [7] of patients who died of breast carcinoma. In a clinical series the incidence of ocular metastases in patients with breast carcinoma is between 8% and 10% [8, 9]. However, screening for ophthalmic involvement in 68 visually asymptomatic patients with locally advanced or metastatic breast carcinoma after a median period of 5 years from the diagnosis of cancer, has shown only one case of orbital metastasis, a deposit in the lateral rectus muscle, three cases of ophthalmic manifestations of neurological problems, and two cases of ocular complications of treatment. The conclusion of the study was that there was, therefore, no need for routine screening [10].

Breast carcinoma is the most common malignancy to metastasize to the conjunctiva. Shields et al. [2] found that breast cancer is a primary tumor site for 39% of conjunctival metastases.

In Serbia there is only one Laboratory for Ophthalmopathology, and despite its 60-year history this was the firts diagnosed conjunctival metastasis of breast carcinoma.

Case report

A 45-year-old premenopausal female patient was presented with solitary, yellowish, thin, demarcated lesion in the superior nasal quadrant of the bulbar conjunctiva of the left eye. There was no sign of irritation, and no pain. The lesion had been noted by chance a week earlier. An ophthalmologic examination showed no other functional or morphological problems in either eye or orbit.

Five years before the patient had presented with 30 mm lump in the left breast, passive infiltration of the overlaying skin and left axillary lymphadenopathy. Tumor biopsy showed lobular infiltrative breast carcinoma with estrogen receptor (ER) and progesterone receptor (PGR) positive and human epidermal growth factor receptor (HER) 2+ negative receptors. Patient underwent IV cycles of FAC chemotherapy, preoperative radiotherapy of the left breast and radiocastration, followed by left modified radical mastectomy (Madden). Sixteen of the 17 removed axillary lymph nodes were positive. The patient received V more cycles of FAC chemotherapy to the cumulative dose and 20 mg tamoxifen daily was introduced. Three years later computed tomography (CT) scan showed metastasis in the left hepatic lobe, 20 mm in diameter with ascites. The patient underwent VIII cycles of taxol CBDCA chemotherapy followed by anastrozole 1 mg daily. Four months prior to conjunctival lesion body scintigraphy showed multifocal skeletal lesions, and nuclear magnetic resonance (NMR) revealed diffuse hepatic metastases and bilateral ovarial tumors. Palliative radiotherapy and megestrol 160 mg were carried out.

An excisional biopsy of the conjunctival lesion was performed under topical anesthesia and a material was subjected to histopathological examination.

Within conjunctival connective tissue stroma histopathology revealed the presence of small, round and ovoid tumor cells with little cytoplasm and with visible intracytoplasmic lumina. The nuclei of those tumor cells were more or less eccentrically placed with little pleomorphism. Mitoses were infrequent. Tumor cells exhibited a diffuse infiltrative pattern with a single file of “targetoid” infiltration. Conjunctival epithelium was unremarkable (Figure 1).

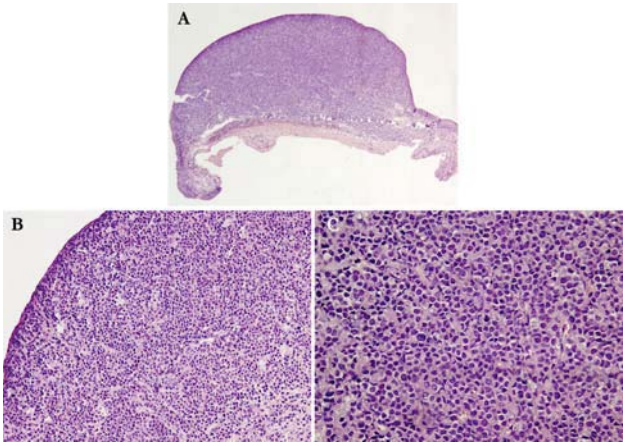

Fig. 1 – A) A conjunctival subepithelial tumor nodule. Intact overlying epithelium exibits no pathology, entire conjunctival substantia propria is diffusely involved by tumor calls, resection lines are free [Haematoxylin and Eosin (H&E), original magnification × 40]; B) Small, round and ovoid tumor cells with little cytoplasm and with visible intracytoplasmatic lumina, arranged in single files and/or cords, exhibit infiltrative pattern. A marked vascularisation of tumor nodule is also evident (H&E, original magnification × 200); C) Nuclei of the tumor cells more or less eccentrically placed with little pleomorphism are well preserved, some of them with a vesicular appearance and also with prominent nucleoli. Mitoses are infrequent. Also, there is a single file of “targetoid” pattern/infiltration (H&E, original magnification × 400)

Immunohistochemical phenotype was: ER + ; HER-2/neu (c-erB/2) -; E/cadherin - ; CK17 -; BRCA1 + ; EMA + (Figure 2).

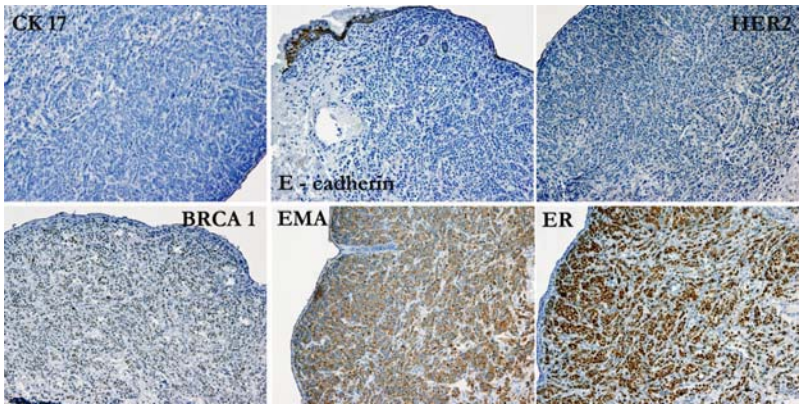

Fig. 2 – Immunohistochemical staining of tumor cells suggesting an infiltrative lobular breast carcinoma metastatised to the conjunctiva (× 100)

Histopathological and immunohistochemical examination established the presence of breast infiltrating lobular carcinoma metastatic to the conjunctiva.

The presented patient showed rapid deterioration after the intervention, and died three weeks later.

Discussion

Conjunctival metastases are most commonly localized on the bulbar conjunctiva. All 13 conjunctival metastatic tumors reported by Shields et al. [2] had bulbar localization. Three out of four metastases of breast carcinoma were on the bulbar conjunctiva [11]. Clinical presentation of conjunctival metastasis is not characteristic. It usually presents a solitary, yellowish, painless lesion not adherent to the underlying sclera with a variable amount of conjunctival irritation. The presented patient referred with an unremarkable lesion of the bulbar conjunctiva, which is typical for conjunctival metastasis.

There is currently no consensus on the treatment of conjunctival metastasis and the therapeutic modality must be individualized. Treatment modalities are excision, local radiotherapy and systemic chemotherapy. In the presented case an excisional biopsy was both a diagnostic and therapeutic procedure.

Conjunctival metastasis of breast carcinoma usually occurs after a relatively long period of time, a few years after diagnosis of the primary tumor. The interval between diagnosis of primary and secondary tumor was more than 5 years in Kiratli et al. study [11], but Skalicky et al. [12] reported a case of conjunctival metastasis after only 9 months. In the presented patient conjunctival metastasis was recognized 5 years after the diagnosis of breast tumor.

As a rule, conjunctival metastases are a part of an advanced malignant disease, with other organs or ocular structures already involved. In the study of Kiratli et al. [11] only 2 out of 10 patients with conjunctival metastasis, and only 1of 4 patients with conjunctival metastasis of breast carcinoma were free of nonocular metastases at the appearance of conjunctival metastasis. Two out of 4 patients with conjunctival metastasis of breast carcinoma had a concurrent choroidal metastasis. Benzimra et al. [13] reported a case of metastatic breast carcinoma to the anterior chambre angle and conjunctiva. The presented patient experienced no other ocular metastases, but multiple bone and liver metastases were present.

The prognosis of patients with conjunctival metastases is mainly poor. The main survival time reported for patients with conjunctival metastasis is 9 months, but for patients with conjunctival metastasis of breast carcinoma it is a little bit longer, 14 months [11]. Our patient died only three weeks after the diagnosis of conjunctival metastasis. Such a short survival period is very unusual and totally unexpected. This could reflect more aggressive tumor biology in stage IV breast cancer patient.

A histopathological picture of a metastatic tumor may recapitulate the appearance of the primary lesion, or it may appear less differentiated. It is not always possible to differentiate a primary tumor on the basis of metastasis. In the presented case the histopathologic appearance of conjunctival metastasis was typical enough to make the right diagnosis.

Conclusion

We reported exceedingly rare conjunctival metastasis of breast carcinoma. The interval between diagnosis of the primary tumor and conjunctival metastasis, the presence of synchronous or metachronous metastases, the location and clinical presentation of conjunctival lesion and local treatment methods have been discussed. Histopathologic presentation of a metastatic lesion is not by the rule so characteristic to make it possible to determine the primary tumor. A survival period less than one month after the appearance of conjunctival metastasis was unexpected and had never been reported previously.

Conjunctival metastases of breast carcinoma, although uncommon, have clinical importance as the signs of the advanced stage of a systemic malignant disease with poor prognosis. The clinical presentation of metastasis is unremarkable, neverthless it certenly should attract full attention of an ophthalmologist, and deserves appropriate treatment.

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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 _____