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Dr Mihajilo Mika Petrović (1863–1934), prvi srpski ratni hirurg, prvi sanitetski general Srpske vojske, univerzitetski profesor, zaslužan je za razvoj medicinske struke i nauke u tadašnjoj Srbiji. Budući da je srcem bio posvećen svom radu, zaveštao je da mu se srce ugradi u zid hirurške sale Glavne vojne bolnice u Beogradu. Na njegovoj urni zapisano je: "Dr Petrović predaje dušu Bogu, telo srpskoj zemlji, a srce srpskoj medicini."
Povodom obeležavanja 167 godina postojanja Vojnomedicinske akademije (VMA) u Beogradu, 2. marta, na Dan VMA, u njenom krugu biće otkrivena bista dr Mihajla Mike Petrovića.

Dr. Mihajilo Mika Petrović (1863–1934), the first Serbian war surgeon, the first Serbian Army Medical Corps general, a university professor, is meritorious for the development of medical profession and science in Serbia of that time. Since he was truly devoted to his work from the bottom of his heart, it was his will to let his heart be built into a wall of the operating room in the Central Military Hospital, Belgrade. His burial urn was written as follows: "Dr. Petrović presents his soul to God, his body to the soil of Serbia, but his heart to the medicine of Serbia."
On the occasion of the Military Medical Academy (MMA) 167th Anniversary Celebration, on March 2, the Day of MMA, a bust of Dr. Mihajilo Mika Petrović will be unveiled in its yard.

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

Povodom 167 godina tradicije – Vojnomedicinska akademija: juče, danas, sutra

On 167 years of tradition – Military Medical Academy then, now and in the future

Elizabeta Ristanović

Vojnomedicinska akademija, Odeljenje za moral i odnose sa javnošću, **Beograd, Srbija**

Pređeni put

Tradicija Vojnomedicinske akademije (VMA) duga je 167 godina, a njen istorijski put veoma je sadržajan i ispunjen najsvetlijim znamenjima medicinske struke i nauke, velikim podvizima časti, humanizma, profesionalizma, u službi čoveka, zdravlja i otadžbine, uvek u korak sa svetom, uz poštovanje prošlosti, ali pogleda uvek uprtog u budućnost. O pređenom putu VMA, od 1844. godine do danas, uglavnom je sve poznato. Svi koji vole i poštuju VMA znaju najvažnije datume iz njene istorije ispunjene surovom balkanskom stvarnošću u kojoj je bitka za svetinju života često morala da se vodi na istinskom bojnom polju, a odanost i posvećenost domovini morala uvek iznova da se dokazuje.

Menjala su se vremena i prilike, a VMA je opstajala i uzrastala i danas, na početku trećeg milenijuma, postala prepoznatljiv simbol Beograda i Srbije, ne samo po svom arhitektonskom, velelepnom zdanju, već i po rezultatima koji ovu ustanovu, po mnogo čemu, svrstavaju u nespornog lidera u brojnim oblastima medicine, stomatologije i farmacije i koja je pouzdan oslonac naše Vojske i države na putu međunarodne saradnje i integracija.

VMA danas: i dela i reči

Vreme u kome živimo i godina za nama obeleženi su teškom ekonomskom krizom i brojnim izazovima savremenog doba koji od nas zahtevaju da dobro premerimo učinjeno, racionalno sagledamo svoje mogućnosti i da sa mnogo mudrosti projektujemo svoje ciljeve i zadatke u vremenu koje dolazi.

Uprkos krizi i brojnim teškoćama, period između dva rođendana, za sve pripadnike VMA i upravni tim na čelu sa general-majorom prof. dr Miodragom Jevtićem, bio je veoma uspešan i može se s pravom nazvati periodom ostvarenih vizija.

Brojniji smo za 141 novog pripadnika, lekara i medicinskih tehničara, koji su primljeni u stalni radni odnos u VMA, zahvaljujući podršci i razumevanju pretpostavljenih u sistemu odbrane čiji smo integrativni deo.

Uspesi u dijagnostici i lečenju: najbolja zdravstvena ustanova u Srbiji

Prošle godine u Dijagnostičko-polikliničkom centru VMA ambulantno je pregledano oko pola miliona ljudi, 40 000 ljudi zbrinuto je u našem Centru hitne pomoći, stacionarno je u VMA lečeno oko 30 000 bolesnika i urađeno je oko 27 000 hirurških intervencija. Iako je briga o vojnim osiguranicima primarni zadatak i prioritetna obaveza svih zaposlenih u VMA, među našim pacijentima je veliki broj civilnih osiguranika, građana naše zemlje koji u VMA dolaze sa uputnicom svoga lekara, shodno ugovoru koji je pre tri godine potpisan sa Republičkim zavodom za zdravstveno osiguranje (RZZO) i koji se uspešno sporovodi. Ugovori o saradnji postoje i sa fondovima zdravstvenog osiguranja Crne Gore i Republike Srpske i oni se uspešno realizuju, a veliki broj pacijenata iz nekadašnje Jugoslavije brigu o svom zdravlju, takođe, poklanja VMA.

Od 3. marta 2010. godine preuzeli smo još jedan zadatak u službi zdravlja naših građana, a to je da jedan dan u nedelji, sredom, budemo urgentni centar srpske medicine (slika 1). I taj zadatak uspešno izvršavamo!

Broj izvršenih medicinskih usluga povećan je 10–15%, uvedene su brojne nove metode dijagnostike i lečenja, npr. u domenu grudne i kardiohirurgije - ugradnja veštačke plućne arterije, u domenu vaskularne hirurgije – visceralna rekonstrukcija aneurizme grudne i trbušne aorte, ortopedije – metode revizione hirurgije kuka i kolena sa velikim koštanim defektima primenom modularnih revizionih endoproteza, oftalmologije – mikroinciziona operacija katarkate, otorinolaringologije – ugradnja kohlearnog aparata, interventne radi-

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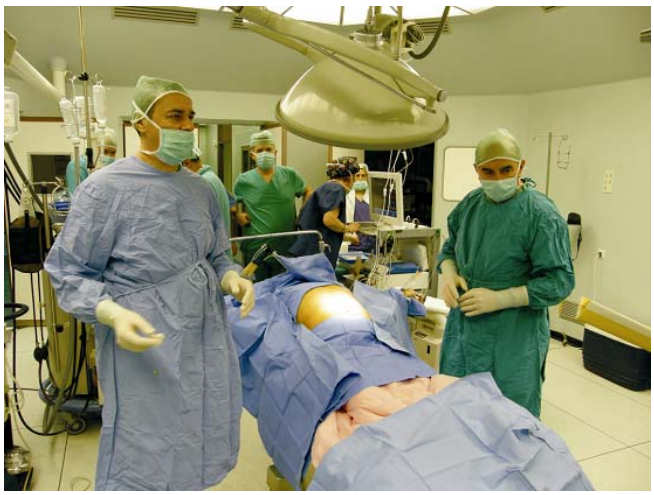
Sl. 1 – Centar hitne pomoći VMA – urgentni centar srpske medicine

ologije – intraarterijska tromboliza kod pacijenata sa akutnim infarktom mozga, balon dilatacija jugularnih vena kod bolesnika sa multiplom sklerozom, embolizacija aneurizmi... Naši neurohirurzi nastavili su sa uspešnim sprovođenjem programa stabilizacije kičme, uveli metodu operativne korekcije idiopatske skolioze, učinjeno je 70 procedura afereze alogenih i autologih matičnih ćelija hematopoeze i 17 alogenih i 48 autologih transplantacija matičnih ćelija hematopoeze. Izvršena je i hirurška aplikacija matičnih ćelija u miokard.

Zajedno sa našim kolegama iz ostalih zdravstvenih ustanova u Srbiji i novoformiranom Upravom za biomedicinu nastojali smo da primerom i delom damo svoj kvalitativni doprinos programu „*Srbijatransplant*“ i nacionalnoj akciji „*Produži život*“. Tokom prethodne godine učinjeno je u VMA ukupno 12 transplantacija jetre (11 kadaveričnih i jedna sa živog davaoca), kao i 21 transplantacija bubrega (14 *living* i 7 kadaveričnih). Bilans do sada učinjenih transplantacija iznosi: 21 transplantacija jetre i 304 transplantacije bubrega, što, uz činjencu da su naši stručnjaci obučili kolege iz Kliničkog centra Niš za sprovođenje programa transplantacije bubrega i otpočeli program obuke transplantacionog tima u Kliničkom centru Banja Luka, zajedno čini značajnu referencu koja VMA ozbiljno kandiduje za nacionalni referentni centar za transplantaciju solidnih organa (slika 2).



Sl. 2 – Transplantacioni tim Vojnomedicinske akademije

I ne samo u hirurškim granama, stručnjaci VMA postižu podjednako velike uspehe i u oblasti interne medicine – kardiologiji, pulmologiji, gastroenterologiji, endokrinologiji, dermatologiji, neurologiji, preventivnoj medicini itd. – mnogo bi bilo nabrajati sve pojedinačne uspehe i vredne doprinose srpskoj medicini.

U skladu sa imperativima savremene medicine i strateškim opredeljenjima menadžmenta VMA, uz jasnu podršku Ministarstva odbrane Srbije, odvija se proces ubrzane tehnološke obnove naše ustanove. Ministar odbrane, g. Dragan Šutanovac 27. decembra 2010. godine pustio je u rad novi 128-slajsni skener koji će značajno unaprediti sprovođenje brojnih dijagnostičkih procedura i smanjiti liste čekanja (slika 3). Tokom prošle godine puštena je u rad i nova angiosala za sprovođenje interventnih procedura, uskoro će početi sa radom komora za hiperbaričnu medicinu, a napravljeni su i precizni planovi za nova strateška ulaganja u periodu koji dolazi.

Sl. 3 – Ministar odbrane Republike Srbije g. Dragan Šutanovac pušta u rad novi 128-slajsni skener u Vojnomedicinskoj akademiji

Postignuti vredni rezultati u domenu Službe lečenja krunisani su i nagradom za najbolju zdravstvenu ustanovu u 2010. godini, „Sunčani sat“, koja je dodeljena VMA u Kliničkom centru Srbije (slika 4). Ima li vrednijeg i prestižnijeg priznanja od onog koje dolazi iz ruku kolega?

Sl. 4 – Sunčani sat – priznanje za najbolju zdravstvenu ustanovu u Srbiji koje je u 2010. godini dobila Vojnomedicinska akademija

Obrazovanje i nauka

Svi stručni izazovi proveravaju se u VMA naučnim metodima, a rezultati naučnoistraživačkog rada primenjuju se u svakodnevnoj medicinskoj praksi. Istraživanja se sprovode u okviru dva meganaučna projekta sa 62 naučnoistraživačka zadatka iz različitih oblasti medicine na kojima je angažovan veliki broj stručnjaka koji su referisali o postignutim rezultatima na brojnim naučnim skupovima. U toku ove godine naši lekari učestvovali su na 159 skupova u zemlji i 97 kongresa u inostranstvu.

Multidsciplinarni projekat VMA pod naslovom „Klinički, patofiziološki i molekularni aspekti povreda i bolesti“, u čiju realizaciju je uključen veliki broj istraživača i nastavnika sa VMA i iz civilnih institucija u zemlji sa kojima VMA sarađuje, a bave se fundamentalnim kliničkim istraživanjima, proglašen je najboljim u sistemu odbrane u toku protekle godine, a njegov rukovodilac, pukovnik akademik prof. dr Miodrag Čolić, v.d. dekana Visoke škole medicine VMA dobitnik je specijalne godišnje nagrade za naučnoistraživački rad Ministarstva odbrane Srbije.

Akreditovali smo doktorske studije i programe akademskih specijalizacija. Ovih dana privodi se kraju proces akreditacije naučnoistraživačkog rada VMA, čime bi se nakon funkcionalne integracije u sistem javnog zdravstva i akreditacije nastavnih programa zaokružio proces pozicioniranja naše ustanove u akademskom i naučnom sistemu države Srbije**.**

Šest pripadnika VMA usavršavalo se tokom godine na višemesečnim kursevima širom planete od SAD do Japana, a u našoj ustanovi svoje znanje unapređivalo je i usavršavalo 13 pripadnika Međunarodne organizacije za zabranu hemijskog oružja (OPCW) iz Haga, kao i 90 kolega iz naše zemlje. Pripravnički staž završilo je 186 lica, a studentsku praksu njih 65. Ukupno 203 Programa kontinuirane medicinske edukacije akreditovao je Zdravstveni savet Srbije.

Uspešna saradnja sa Medicinskim fakultetima u Beogradu, Kragujevcu, Nišu, Novom Sadu, Kosovskoj Mitrovici krunisana je potpisivanjem novih protokola o saradnji kao i istorijskim sastankom dekana svih medicinskih fakulteta održanom u VMA 12. novembra 2010. godine (slika 5). Ovim smo još jednom pokazali da je medicina jedna i nedeljiva i da svi zajedno služimo zdravlju građana Srbije.

Sl. 5 – Doprinos akademskoj zajednici Srbije – dekani svih medicinskih fakulteta Srbije u VMA

Izuzetna saradnja postoji i sa Biološkim fakultetom, Tehnološko-metalurškim, Stomatološkim fakultetom, brojnim naučnim institutima i sa kolegama iz ostalih zdravstvenih ustanova u našoj zemlji, kao i u Republici Srpskoj, Crnoj Gori, Makedoniji itd. Tako potvrđujemo i tezu da smo regionalni lider u brojnim oblastima medicinske struke i nauke.

Naši kadeti, studenti Prve klase Visoke škole medicine, uspešno su završili prvu godinu studija sa prosečnom ocenom 9,14 i pokazali da su opravdali naša očekivanja i da su razumeli naš poziv: „Vreme je za mlade i ambiciozne“. U Drugu klasu upisano je ukupno 30 kadeta, a interesovanje je bilo veliko – čak po 10 odlikaša „borilo“ se za jedno mesto. Ima li boljeg priznanja za VMA, vojno zdravstvo, vojno školstvo i sistem odbrane u celini (slika 6).

Sl. 6 – Kadeti Visoke škole VMA – budućnost vojnog saniteta države Srbije

za zbrinjavanje povređenih i obolelih u uslovima masovnih katastrofa.

Medicina bez granica: i Zapad i Istok

Medicina ne poznaje granice, a samo komunikacijom i razmenom znanja i iskustava služi se zdravlju vojske i naroda. Vođeni tim svetim ciljem, uspostavili smo mostove saradnje sa najvećim vojnomedicinskim i zdravstvenim centrima u svetu i gradimo nove. U ovoj ustanovi tokom proteklih 12 meseci boravili su komandant Nacionalne garde Ohaja, general Vejt, ministar odbrane Mađarske gospodin Imre Sekereš, kao i najviši predstavnici MO Kraljevine Norveške, Kraljevine Belgije, Portugala, Španije, Turske, Danske, Italije, Ukrajine, Egipta, Libije, Irana, Namibije, Svetske zdravstvene organizacije, kao i kolege profesori Tomas Džon sa Lajola Univerziteta iz Čikaga, Jordan Saveski iz Skoplja, Džon Volf iz Londona, Čabo Džimić iz Mađarske, Said Sirin iz Turske itd.

Svi oni žele ravnopravnu saraduju i razmenjuju iskustvo sa nama, da od nas uče, ali i mi želimo da njihova znanja pretočimo u našu svakodnevnu praksu i zato smo i ove godine više naših mladih doktora-ortopeda, grudnih, vaskularnih hirurga, kliničkih farmakologa, internista poslali na školovanje i usavršavanja širom sveta. Velike i značajne aktivnosti VMA ostvaruje u okviru Balkanskog i Svetskog komiteta vojne medicine (slika 7). Važan aspekt te saradnje je i naše učešće u međunarodnim vežbovnim aktivnostima i u mirovnim misijama UN, gde naši pripadnici u okviru sanitetskih timova Vojske Srbije predstavljaju čast, ugled, profesionalizam i humanost srpskog oficira i lekara u Čadu i Kongu.

Sl. 7 – Članovi Balkanskog komiteta vojne medicine (Solun, Grčka, 2010)

Naša Škola rezervnih oficira sanitetske i veterinarske službe odškolovala je svoju 98. i 96. klasu, kao i prvu klasu lekara i veterinara na osposobljavanju za profesionalnu vojnu službu. Ova škola uskoro će biti transformisana u Regionalni centar za obuku u kome će se osposobljavati i školovati naše kolege iz okolnih zemalja za različite oblasti medicine, kao i

Zdravlje kao stanje duha

Da je zdravlje i stanje duha, a da je zdravo telo preduslov za fizičko i duhovno zdravlje poznato je odavno i možda je, upravo, to osnov za sve bolju saradnju VMA sa brojnim sportistima i sportskim udruženjima koja je tokom protekle

godine krunisana potpisivanjem protokola o saradnji sa Atletskim savezom Srbije, sa Fudbalskim savezom Srbije, Olimpijskim komitetom Srbije, medicinskim obezbeđenjem takmičenja kao što su bili teniski turnir „*Serbia-Open*“, svetska prvenstva u rvanju i karateu, Evropsko prvenstvo u atletici i još mnogo toga.

Brigu o svom zdravlju poverili su našoj ustanovi i direktori najvećih srpskih kompanija, a uspešna saradnja sa Srpskom pravoslavnom crkvom, Narodnim pozorištem u Beogradu i sa ostalim nacionalnim, javnim i kulturnim ustanovama potvrđuje da smo institucija posvećena svim sadržajima ljudskog duha koji doprinose telesnom i duševnom zdravlju.

Medicina i mediji

Mediji i medicina su prirodni partneri na istom zadatku promocije i afirmacije ljudskog zdravlja. Tačnost ove činjenice primerom i delom potvrđuje se kroz uspešnu saradnju VMA sa medijima, o čemu svedoči i podatak da je samo tokom 2010. godine u domaćim štampanim i elektronskim medijima objavljeno 3 022 priloga o ovoj ustanovi. Tonalitet objavljenih priloga govori da se srpski mediji pozitivno odnose prema našoj ustanovi. Odlična saradnja postoji i sa medijskim servisima u okruženju (Crna Gora, Republika Srpska/BiH, Makedonija) koji redovno objavljuju priloge o VMA. Sajt VMA zabeležio je ukupno 338 574 poseta iz 163 zemlje sveta.

VMA sutra: jasna vizija

U 2011. godinu VMA je zakoračila sa porukom: I juče i sutra. Ponosni smo na ostvarene rezultate, na svoju dugu tradiciju, ali gledamo smelo u budućnost. I u vremenu koje je pred nama želimo da nastavimo istim putem sa željom da ostanemo nacionalni i regionalni lideri u mnogim oblastima medicinske struke i nauke, radeći po najvišim standardima kvaliteta i stalno unapređujući naše dijagnostičke i terapijske mogućnosti, da nastavimo sa intenzivnom tehnološkom obnovom institucije i ulaganjem u kadrovske resurse, investicijom u njihovo znanje i obrazovanje. I dalje cilj nam je jačanje međunarodne saradnje sa najprestižnijim medicinskim centrima u svetu. Želimo da damo svoj puni doprinos zdravstvenom i akademskom prostoru države Srbije i da spremno izvršavamo sve zadatke koje pred nas postavlja sistem odbrane Srbije, naše državno i vojno rukovodstvo.

Obeležavanje 167 godina tradicije

Obeležavanje godišnjice neke ustanove prilika je da se zastane, da se podseti na sve što je učinjeno i da se ukaže na zadatke koji su pred nama. Povodom Dana VMA i ove godine će biti dodeljene nagrade i priznanja najuspešnijoj organizacijskoj celini VMA, autoru godine časopisa Vojnosanitetski pregled, medalje dr Vladan Đorđević za doprinose srpskoj hirurgiji, kao i povelje za uspešnu saradnju instutucijama i pojedincima. U krugu VMA biće postavljena bista dr *Mihajila Mike Petrovića*, prvog srpskog ratnog hirurga i prvog sanitetskog generala Srpske vojske. Životu i delu ovog humaniste biće posvećena i odogovarajuća monografija, kao i naučna konferencija čiji su organizatori VMA i Akademija medicinskih nauka Srpskog lekarskog društva (slika 8). Povodom Dana VMA biće objavljen i treći broj almanaha vesti – *Ljudi i događaji,* kao i monografija *Zdravlje – više od zlata*, posvećena medicinskom zbrinjavanju Univerzijade 2009. i vredan priručnik za buduće organizatore ovakvih manifestacija.

Sl. 8 – Bista dr Mihajila Mike Petrovića koja će biti postavljena u krugu VMA, 2. marta 2011.

U slavu 167 godina VMA, duga i sadržajna istina o njenom razvoju i rezultatima, misijama i vizijama pretočena je u monografiju koju mi, koji sada stvaramo i gradimo ovaj hram zdravlja, poklanjamo precima i potomcima. Svoj vrednosni sud o ovoj monografiji na svečanoj promociji koja će biti upriličena povodom Dana VMA daće njeni recenzenti rektor Univerziteta u Beogradu prof. dr Branko Kovačević i predsednik Srpskog lekarskog društva akademik prof. dr Radoje Čolović i brojni drugi profesori i akademici.

U službi čoveka, zdravlja i otadžbine: VMA – juče, danas i sutra!

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

Autor godine Vojnosanitetskog pregleda za 2010.

The Author of the Year 2010 by Vojnosanitetski Pregled

Silva Dobrić

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

Prema savremnom shvatanju nauke, rezultati naučnoistraživačkog rada i naučne informacije proistekle iz njih nisu relevantni ako se ne objave i, na taj način, stave na uvid naučnim krugovima kako bi se mogli neposredno koristiti u praksi ili biti putokaz za dalja istraživanja. Osnovna uloga naučnih publikacija, dakle, jeste prenos rezultata naučnih istraživanja što širem krugu korisnika, ali one imaju veoma značajnu ulogu i u proceni rezultata rada i vrednovanju samih istraživača. Od ovih procena, neretko, zavisi položaj naučnih radnika i njihovo napredovanje u akademskim i naučnim krugovima, a, samim tim, i ugled među kolegama.

Postoji više načina za vrednovanje naučnog opusa jednog istraživača, a jedan od njih je broj radova koje je objavio, kao i njihova citiranost. Posebni značaj imaju radovi objavljeni u časopisima sa recenzijom, a pogotovo onima koje prate citatne baze instituta *Thomson Reuters* (bivši Institut za naučne informacije) iz Filadelfije, SAD, jer se na osnovu citiranosti pojedinih časopisa referisanih u ovim bazama i izračunava njihov impakt faktor. Preduslov za ulazak u sistem praćenja ovih baza ili popularnije rečeno, ulazak na *Science Citation Index* (SCI) listu je, između ostalog, i kvalitet objavljenih radova, pa uredništva časopisa koji se nalaze na toj listi, prilikom donošenja odluke o objavljivanju nekog rada u svom časopisu, itekako vode računa o tome. Pri tome se posebno ocenjuje originalnost, aktuelnost, primenjena metodologija istraživanja, način prezentacije i diskusije rezultata, kao i aktuelnost i poreklo literaturnih navoda korišćenih u tom radu, jer ovo su elementi koji garantuju kvalitet rada. Kada rad, prethodno ocenjen od strane recenzenata kao kvalitetan, bude objavljena u časopisu sa SCI liste, velika je verovatnoća da će biti zapažen u naučnoj zajednici kojoj je namenjena, što će se, kasnije, moći proveriti i preko citiranosti te publikacije od strane drugih autora.

Uredništvo i izdavač Vojnosanitetskog pregleda (VSP) oduvek su poklanjali posebnu pažnju kvalitetu radova koji su objavljivani na njegovim stranicima. Stoga, ne čudi što je upravo VSP 2008. godine, kao prvi medicinski časopis iz Srbije, uvršten na proširenu SCI listu (*Science Citation Index Expanded* – SCIE). Uz urednike i recenzente časopisa, najzaslužniji za ovaj uspeh, svakako, jesu autori koji su proteklih godina objavljivali svoje radove u VSP.

U želji da istakne ulogu i značaj publikovanja u naučnim časopisima, ali i da nagradi autore koji svojim radovima promovišu časopis i podižu njegov ugled, uredništvo i izdavač VSP od 1995. godine, po tačno utvrđenim kriterijumima koji uzimaju u obzir redosled autora (samo prva tri autora) i vrstu rada (tabela 1), proglašava Autora godine VSP. To je autor koji je u prethodnoj godini objavio najviše radova na njegovim stranicama. Tradicionalno, proglašenje Autora godine VSP vrši se na proslavi obeležavanja Dana Vojnomedicinske akademije (VMA), 2. marta, budući da se Redakcija VSP od 1961. godine nalazi u zgradi ove vrhunske medicinske, naučnonastavne ustanove.

Tabela 1

Kriterijumi za bodovanje autora i članaka u VSP

Kategorija rada	Broj bodova		
	prvi autor	drugi autor	treći autor
Originalni članak	12	6	3,6
Prethodno saopštenje	5	2,5	1,5
Pregledni članak	10	2,5	1,5
Aktuelna tema	8	4	2,4
Kazuistika	4	2	1,2
Istorija medicine	5	2,5	1,5
Uvodnik	5	2,5	1,5

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U izbor za Autora godine VSP za 2010. godinu ušao je 401 autor iz zemlje i inostranstva sa ukupno 164 rada, a njih ovo bodovanje izvršeno je prema kriterijumima navedenim u tabeli 1. Iako je najveći broj radova, a time i autora, prošle godine, kao i u nekoliko prethodnih, bio iz civilnih zdravstvenih i akademskih institucija, ipak Autor godine VSP za 2010. godinu dolazi iz naučnostručnog miljea vojnog sanitеta. To je prof. dr Gordana Dedić, neuropsihijatar i psihoanalitički psihoteraput iz Klinike za psihijatriju VMA kojoj su, u protekloj godini, kao prvom autoru, na stranicama VSP objavljena tri rada iz kategorije *Orginalni članci* (tabela 2). To joj je donelo 36 bodova i titulu Autora godine VSP za 2010. godinu (tabela 3).

Uz čestitke na ovom priznanju, uredništvo i izdavač VSP žele prof. dr Gordani Dedić mnogo uspeha u budućem radu i još mnogo kvalitetnih radova koje će, nadamo se, i dalje objavljivati u našem časopisu.

Prof. dr Gordana Dedić – Autor godine VSP za 2010.

Tabela 2

Radovi prof. dr Gordane Dedić objavljeni u VSP u toku 2010. godine

Redni broj	Autori i naziv rada
1.	Dedić G, Đurđević S, Golubović B. *Psychological assessment of persons following suicide attempt by self-poisoning*. Vojnosanit Pregl 2010; 67(2): 151–8.
2.	Dedić G, Panić M. Faktori rizika od samoubistva kod profesionalnih vojnih lica u Vojsci Srbije. Vojnosanit Pretgl 2010; 67(4): 303–12.
3.	Dedić G, Panić M. Faktori rizika od samoubistva kod vojnika Vojske Srbije. Vojnosanit Pretgl 2010; 67(7): 548–57.

Tabela 3

Redosled prvih pet autora VSP u 2010. godini

Redni broj	Prezime i ime autora	Ustanova autora	Broj bodova
1.	**Dedić Gordana**	**VMA, Klinika za psihijatriju, Beograd**	**36**
2.	Dobrić Silva	VMA, Institut za naučne informacije, Beograd	30
3.	Kuljić-Kapulica Nada	VMA, Institut za mikrobilogiju, Beograd	24
4.	Stolić Radojica	Medicinski fakultet, Interna klinika, Priština/ Kosovska Mitrovica	22
5.	Jovanović Milan	VMA, Klinika za abdominalnu i endokrinu hirurgiju, Beograd	19,2

Napomena: Navedena su imena samo prvih pet autora budući da se na pozicijama od 6. do 10. mesta nalazi veći broj autora (npr, na 9. mestu isti broj bodova ima, čak, 105 autora).

Čestitke i želje za uspešan rad, s nadom da će neko od njih u narednim godinama biti Autor godine VSP, upućujemo i ostalim autorima čiji su radovi prošle godine objavljeni u VSP. Verujemo da će nam oni i dalje slati svoje radove. Nadu za to pružaju nam podaci bodovanja za Autora godine VSP za 2010. iz kojih se vidi da mnogi autori imaju više od jednog rada objavljenog u protekloj godini. Zbog toga se i desilo da više autora deli jedno mesto. Tako, npr, na 9. mestu po bodovima za Autora godine VSP u protekloj godini nalazi se, čak, 105 autora! Možda će, upravo, neko od njih sledeće godine biti Autor godine VSP. Do tada, mnogo uspeha i sreće i mnogo, mnogo, kvalitetnih radova!

Kratka biografija Autora godine VSP za 2010.

Prof. dr sc. med. Gordana Dedić rođena je 1956. godine u Leskovcu. Osnovnu školu i gimnaziju završila je u Beogradu, a na beogradskom Medicinskom fakultetu diplomirala je 1982. godine. Na istom fakultetu magistrirala je 1989. godine odbranivši rad iz oblasti neurofiziologije „Određivanje brzine provodljivosti *n. medianus*-a i *n. ulnaris*-a kod dece uzrasta 1–3 godine“.

Specijalizaciju iz neuropsihijatrije završila je na VMA u Beogradu 1991. godine sa odličnim uspehom, a sedam godine kasnije, 1998, doktorirala je, takođe, na VMA na temu „Osobine ličnosti i manifestacije maladaptivnog ponašanja vojnika u periodu adaptacije na vojnu sredinu“.

Nakon specijalizacije, 1994. godine, završila je dvogodišnji kurs iz analitički orijentisane psihoterapije na Institutu za mentalno zdravlje u Beogradu, a 2008. i supspecijalizaciju iz psihoanalitičke psihoterapije na Medicinskom fakultetu u Beogradu.

Za vanrednog profesora za predmet Psihijatrija u VMA izabrana je 2006 godine.

Kao specijalista neuropsihijatar od 1991. do 2000. godine radila je u Kabinetu za neuropsihijatrijske bolesti u voj-

nomedicinskim centrima „Slavija“ i „Karaburma“ u Beogradu. Od 2000. godine obavljala je dužnosti načelnika Odseka za zdravstveno prosvećivanje u Odeljenju za mentalno zdravlje i vojnu psihologiju VMA, a od 2009. godine nalazi se na dužnosti načelnika Dnevne bolnice Klinike za psihijatriju VMA.

Rukovodilac je nekoliko naučnoistraživačkih projekata, od kojih su dva već završena: „Suicid u vojnoj sredini“ (2006–2010), i „Prevencija AIDS-a u vojnoj sredini (2008–2010), dok se projekat „Psihološko-psihijatrijski aspekti transplantacije organa i tkiva“ trenutno nalazi u fazi realizacije (2010-2014).

U Visokoj školi integrisanih akademskih studija medicine VMA rukovodilac je u nastavi predmeta Medicinska etika, Veština komunikacije I, Veština komunikacije II i Psihijatrija, a u školskoj 2009/2010 bila je ko-rukovodilac u nastavi predmeta Medicinska psihologija. Takođe, učestvovala je i u izvođenju nastave za slušaoce Škole rezervnih oficira sanitetske službe, kao i za lekare na specijalizaciji u VMA.

Prof. dr Gordana Dedić aktivno učestvuje i u radu strukovnih udruženja. Član je predsedništva Psihoterapijske sekcije Srpskog lekarskog društva, a u Savezu psihoterapeuta Srbije obavlja funkciju potpredsednika.

Bogata publicistička delatnost prof. dr Gordane Dedić ogleda se u preko 140 radova, knjiga, poglavlja u knjigama, i rezimea sa domaćih i inostranih kongresa. Autor je sedam knjiga i 13 poglavlja u knjigama, od čega su tri objavljene u inostranstvu. Od većeg broja radova objavljenih u časopisima, njih osam je publikovano u časopisima sa SCI liste.

Prof. dr Gordana Dedić počela je da objavljuje radove u VSP od 1992. godine i do danas ih je objavila ukupno 19 (još jedan, dakle 20, prihvaćen je za štampu i biće objavljen u toku 2011. godine). Ovo je još jedan pokazatelj da je titula Autora godine VSP došla u prave u ruke!

ORIGINALNI ČLANCI

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Analiza glasa pre i posle vokalnog zamora

Voice analysis before and after vocal tiredness

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Kliničko-bolnički centar „Zvezdara“, Klinika za otorinolaringologiju, **Beograd, Srbija**

Apstrakt

Uvod/Cilj. Profesija nastavnika je jedna od vokalno najzahtevnijih profesija. Vokalni zamor odražava se na akustičke karakteristike glasa i dovodi do promene akustičkog kvaliteta tokom vokalne produkcije. Cilj ovog rada bio je da se ispita uticaj vokalnog zamora na akustičke karakteristike glasa kod nastavnika. **Metode.** Ispitivanje je obuhvatilo 36 nastavnika (16 ispitanika muškog i 20 ispitanika ženskog pola), starosti 27–58 godina. Vokalni zamor pratili smo analizom akustičkih parametara glasa (foniranjem vokala /a/), primenom kompjuterske laboratorije za glas „*Kay Elemetrics*“. Kod ispitanika je sniman glas pre prvog časa, na početku radne nedelje i po završetku poslednjeg časa, na kraju radne nedelje. Obrađeni su parametri signala, šuma i tremora. U obradi podataka primenjene su metode deskriptivne statistike i analitičke statistike (Studentov *t*-test za zavisne uzorke, χ^2 test, Man Vitnijev *U*-test i Spirman-ov koeficijent korelacije ranga – ϱ). **Rezultati.** Dobijeni rezultati pokazali su da se statistički značajne razlike u prosečnim vrednostima ispitivanih parametara glasa javljaju kao posledica vokalnog zamora ($p < 0,01$), dok pol, starost i pušački status nisu imali značajan uticaj na akustičke karakteristike glasa kod naših ispitanika ($p > 0,05$). **Zaključak.** Rezultati ovog istraživanja govore u prilog postojanju uzročno-posledične veze između vokalnog zamora i kvaliteta glasa kod vokalnih profesionalaca.

Ključne reči:
glas, poremećaji; glas, kvalitet; govor, produkcija, merenje; faktori rizika; profesionalna izloženost.

Abstract

Background/Aim. A school teacher's occupation is one of the most vocal demanding professions. Vocal tiredness affects acoustic characteristics of voice, leads to the change in acoustic quality during vocal production. The aim of this study was to examine the influence of vocal tiredness on voice acoustic characteristics of school teachers. **Methods.** The study included 36 school teachers (16 male and 20 female) of 27–58 years of age. Vocal tiredness was evaluated by analyzing acoustic parameters of voice, using computerized laboratory "Kay Elemetrics". The voices were recorded before the first class on the beginning of a working week and after the last class at the end of a working week. Signal, noise and tremor parameters were processed. In their analysis the methods of descriptive statistics, as well as the analytical statistics (Student's *t*-test for paired samples, χ^2 test, Mann Whitney *U*-test and Pearson's correlation coefficient) were applied. **Results.** The obtained results showed statistically significant differences in average values of parameters as a consequence of the vocal tiredness ($p < 0.01$), while gender, age and being smoker or not, did not have a significant effect on voice acoustic characteristics in this group of examinees ($p > 0.05$). **Conclusion**. The results of the study suggest a casual relationship between vocal tiredness and voice quality in vocal professionals.

Key words:
voice disorders; voice quality; speech production measurement; risk factors; occupational exposure.

Uvod

Oštećenje glasa kod vokalnih profesionalaca predstavlja veliki zdravstveni problem kome se još uvek ne pridaje dovoljan značaj u poređenju sa profesionalnim oštećenjima sluha i drugim profesionalnim bolestima [1]. Poznato je da su nastavnici gotovo najčešći bolesnici s poremećajem glasa. Prema statističkim podacima iz drugih zemalja, među bolesnicima s poremećajima glasa, oko 20% su nastavnici. Istraživanja u svetu pokazala su da oko 22–38% vokalnih profesionalaca ima najmanje jednom godišnje ozbiljnih problema s glasom [2].

Ljudski glas je specifičan pokazatelj fizičkog i emocionalnog stanja pojedinca, njegove osobenosti i identiteta [3]. Poremećaji glasa vremenom izazivaju psihosocijalne probleme jer onemogućavaju efikasnost u profesiji, dovode do gubitka stečenih pozicija u društvu, izazivaju strah od gubitka karijere i ugroženosti egzistencije.

Normalan glas koji obezbeđuje efektivnu govornu komunikaciju treba da bude prijatan za slušanje, da poseduje odgovarajuću ravnotežu usnog i nosnog rezonatora, da bude dovoljno visok. Osnovna frekvencija govora treba da odgovara uzrastu i polu [4]. Svaka neravnoteža ovog složenog sistema utiče na kvalitet glasa. Izvesne promene kvaliteta ili

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trajanja glasa ukazuju na prisustvo oboljenja i zahtevaju adekvatnu dijagnozu i rehabilitaciju.

Prvi simptomi problema s glasom su nadraženost grla, potreba za kašljanjem, osjećaj bola u grlu, promuklost i umor glasa ili njegov potpuni gubitak [5–8]. Vokalni zamor nastaje kada su vokalni zahtevi veći nego što je sposobnost pojedinca da ispuni te zahteve. Vokalnim izvođačima je potreban visok nivo vokalne fleksibilnosti, gipkosti i sposobnost da izvršavaju brze manevre kao što je vikanje ili šaputanje. Profesija nastavnika zahteva dug period govorenja. Često se tome pridodaje i buka sredine, neadekvatna ventilacija, retke prilike za odmaranje glasa i dodatno naprezanje glasa, kao što su roditeljski sastanci. Posebno treba istaći pušenje i konzumiranje alkohola, kao faktore koji dovode do poremećaja u radu fonatornog sistema.

Istraživanja u svetu pokazuju da su vokalni problemi kod nastavnika povezani sa kontinuiranom vokalnom produkcijom, tako da se vokalni zamor odražava na akustičke karakteristike govora i dovodi do promene akustičkog kvaliteta tokom vokalne produkcije. Dakle, postoji značajna korelacija između vokalne patologije i promena u akustičkim karakteristikama glasa [9]. Podaci iz literature pokazuju da se vokalni simptomi kod nastavnika za vreme raspusta ne javljaju, dok za vreme nastave dolazi do njihove pojave pri kontinuiranoj upotrebi glasa [10].

Cilj rada bio je da se ispita kvalitet glasa kod nastavnika pre i posle vokalnog zamora, ispitaju razlike kvaliteta glasa pre i posle vokalnog zamora u odnosu na pol, starost i pušački status.

Metode

Ispitivanjem koje je sprovedeno u Klinici za otorinolaringologiju Kliničko-bolničkog centra „Zvezdara“ i u osnovnoj školi „Jelena Ćetković“ u Beogradu bilo je obuhvaćeno 36 ispitanika, 16 muškog i 20 ženskog pola. Starost ispitanika bila je 27–58 god.

Vokalni zamor pratili smo tako što smo kod ispitanika snimali glas pre prvog časa u ponedeljak i na kraju radne nedelje, nakon završenog poslednjeg časa. Pre snimanja glasa svim ispitanicima bio je urađen pregled larinksa indirektnom laringoskopijom, pri čemu su u istraživanje uključeni samo oni sa urednim nalazom. Ispitanici su smireno i spontano, u sedećem položaju, upućeni da normalnim glasom izgovore vokal /a/ izolovano, izvan konteksta. Akustička struktura vokala svakog ispitanika analizirana je u realnom vremenu. Analiza vokala /a/ snimana je kompjuterizovanom laboratorijom za glas firme „*Kay Elemetrics*“. Kompjuterizovana laboratorija za glas „*Kay Elemetrics*“ ima za cilj da obezbedi objektivne podatke analize glasa i služi kao podrška subjektivnoj proceni glasa. Omogućava dobijanje dokumentovanog zapisa predterapijske i postterapijske analize glasa, kada se bolesnik podvrgava programu vokalne terapije. Ove analize pomažu u procesu procene uspešnosti terapije i potrebom za nastavljanjem iste. Laboratorija za glas ima i značajnu ulogu u procesu dijagnostike, ali to nikako ne sme biti jedina metoda u procesu dijagnostikovanja poremećaja glasa, kao jedne veoma kompleksne oblasti. Multidimenzionalni vokalni program (MDVP) danas je vodeći u svetu za analizu glasa. Omogućava izdvajanje i do 33 različita parametra analize glasa koji se mogu grafički i numerički uporediti sa referentnim vrednostima, uz grafički prikaz histogramom frekvencije, histogramom amplitude i grafičkom analizom dugotrajnog spektra.

Svim ispitanicima bili su analizirani akustički parametri kratkotrajnih i dugotrajnih poremećaja frekvencije. Prosečna fundamentalna frekvencija (Fo) predstavlja srednju vrednost osnovne frekvencije izraženu u Hz za sve izdvojene vrednosti momenta osnovne frekvencije. Srednja vrednost Fo normalnog ženskog glasa iznosi 233,828 Hz, a muškog 125,591 Hz. Varijacije u visini fundamentalne frekvencije – Jitt (%) predstavljaju promenljivost osnovne frekvencije. Srednja vrednost Jitt (%) za normalan ženski glas iznosi 0,288%, a za muški glas 0,449%. Parametar kratkotrajnih i dugotrajnih poremećaja amplitude predstavlja varijacije u amplitudi osnovnog laringealnog tona – Shim (%) (obično ovaj tip varijacija je nasumičan i dovodi se u vezu sa promuklim i zadihanim glasom). Nepravilnosti amplitude od ciklusa do ciklusa mogu se povezati sa nesposobnošću glasnica da održe periodične vibracije u posmatranom periodu i sa prisustvom turbulentnog šuma u signalu glasa. Vrednost ovog parametra za normalan ženski glas iznosi oko 1,974%, a za muški 1,829%. Parametar procene šuma jeste odnos intraharmonijskog šuma i harmonika (NHR) i predstavlja opštu procenu prisutnog šuma u analiziranom signalu. To je srednja vrednost odnosa spektralne energije šuma i spektralne energije harmonika u frekventnom opsegu od 70–4 200 Hz. Normalne vrednosti ovog parametra za muški glas, u proseku iznose 0,143, a za ženski 0,102.

U opisivanju i analizi dobijenih podataka korišćene su metode deskriptivne i analitičke statistike. Od metoda deskriptivne statistike u radu su primenjene mere centralne tendencije, mere varijabiliteta, i tabeliranje. U analitičkoj statistici za procenu značajnosti razlike parametarskih podataka korišćen je Studentov *t*-test za zavisne uzorke, a χ^2, Man Vitnijev (Mann-Withney) *U*-test i korelacija ranga ρ za neparametarske podatke. U obradi podataka korišćen je statistički paket SPSS 14.0.

Rezultati

U istraživanju je učestvovalo 36 ispitanika, od toga 20 (55,6%) ženskog i 16 (44,4%) muškog pola. Razlika u polnoj zastupljenosti ispitanika nije bila statistički značajna ($\chi^2 = 0,444$; df = 1; $p > 0,05$). Prosečna starost ispitanika bila je 40,22 ± 9,01 godina, pri čemu je najmlađi ispitanik imao 27, a najstariji 58 godina.

Iako je u istraživanju bilo više pušača (22 : 14), razlika između ispitanika u odnosu na pušenje nije bila statistički značajna ($\chi^2 = 1,778$; df = 1; $p > 0,05$). U grupi ženskih ispitanika polovina je pripadala grupi pušača, a polovina grupi nepušača. U grupi ispitanika muškog pola bilo je 12 (75%) pušača, i 4 (25%) nepušača ($\chi^2 = 4$; df = 1; $p < 0,01$).

Analiza rezultata Studentovim *t*-testom za zavisne uzorke pokazala je da statistički značajne razlike u prosečnim vrednostima parametara pre i posle vokalnog zamora glasa postoje kod svih ispitivanih parametara (tabela 1). Prosečna fundamentalna frekvencija – Fo bila je značajno viša ($p < 0,01$), a prosečna vrednost varijacije u amplitudi osnovnog laringealnog tona – Shim (%) značajno niža posle vokalnog zamora

($p < 0,01$). Vrednost parametra procene šuma – NHR povećala se posle vokalnog zamora. Uočena razlika bila je visoko statistički značajna ($p < 0,01$). Posle vokalnog zamora vrednost parametra visine fundamentalne frekvencije – Jitt (%) smanjivala se, a razlika se pokazala kao statiskički značajna ($p < 0,05$).

Ispitanici muškog i ženskog pola razlikovali su se značajno po prosečnoj fundamentalnoj frekveniciji – Fo i varijaciji u amplitudi osnovnog laringealnog tona pre i posle vokalnog zamora – Shim: žene su imale statistički značajno višu fundamentalnu frekvenciju ($p < 0,01$) i značajno nižu vrednost varijacije u amplitudi osnovnog laringealnog tona ($p < 0,01$) (tabela 2). Razlike u prosečnoj vrednosti NHR i Jitt (%) pre i posle vokalnog zamora, nisu se statistički razlikovale u odnosu na pol ($p > 0,05$).

Analizom prosečnih vrednosti parametara glasa pušača i nepušača, pre i posle vokalnog zamora (tabela 3), nije uočena statistički značjana razlika ($p > 0,05$).

Starost ispitanika nije značajno uticala ($p > 0,05$) na ispitivane parametre glasa ni pre, niti posle vokalnog zamora (tabela 4).

Tabela 1

Parametari glasa pre i posle vokalnog zamora

Parametar	Vreme merenja	AS ± SD	*p*
Fo (Hz)	pre zamora	199,610 ± 50,435	< 0,01
	posle zamora	208,052 ± 53,799	
Jitt (%)	pre zamora	0,473 ± 0,209	< 0,05
	posle zamora	0,383 ± 0,209	
Shim (%)	pre zamora	1,876 ± 0,209	< 0,01
	posle zamora	1,572 ± 0,209	
NHR	pre zamora	0,116 ± 0,209	< 0,01
	posle zamora	0,136 ± 0,209	

AS – aritmetička sredina; SD – standardna devijacija; Fo – prosečna fundamentalna frekvencija; Jitt – promenljivost osnovne frekvencije; Shim – varijacije u amplitudi osnovnog laringealnog tona; NHR – odnos intraharmonijskog šuma i harmonika

Tabela 2

Parametri glasa pre i posle vokalnog zamora u odnosu na pol

Parametar	Pol	Pre vokalnog zamora		Posle vokalnog zamora	
		AS ± SD	*p*	AS ± SD	*p*
Fo (Hz)	muški	145,110 ± 6,079	< 0,01	150,287 ± 11,456	< 0,01
	ženski	243,210 ± 4,858		253,984 ± 4,798	
Jitt (%)	muški	0,419 ± 0,184	> 0,05	0,327 ± 0,075	> 0,05
	ženski	0,511 ± 0,225		0,402 ± 0,171	
Shim (%)	muški	2,410 ± 0,398	< 0,01	2,184 ± 0,188	< 0,01
	ženski	1,401 ± 0,401		0,970 ± 0,257	
NHR	muški	0,114 ± 0,058	> 0,05	0,141 ± 0,033	> 0,05
	ženski	0,117 ± 0,074		0,136 ± 0,079	

AS – aritmetička sredina; SD – standardna devijacija; Fo – prosečna fundamentalna frekvencija; Jitt – promenljivost osnovne frekvencije; Shim – varijacije u amplitudi osnovnog laringealnog tona; NHR – odnos intraharmonijskog šuma i harmonika

Tabela 3

Parametri glasa pre i posle vokalnog zamora u odnosu na pušački status

Parametar	Pušački status	Pre vokalnog zamora		Posle vokalnog zamora	
		AS ± SD	*p*	AS ± SD	*p*
Fo (Hz)	nepušač	183,502 ± 51,595	> 0,05	192,334 ± 54,072	> 0,05
	pušač	219,831 ± 43,878		227,349 ± 49,503	
Jitt (%)	nepušač	0,467 ± 0,227	> 0,05	0,380 ± 0,179	> 0,05
	pušač	0,485 ± 0,186		0,355 ± 0,073	
Shim (%)	nepušač	1,938 ± 0,670	> 0,05	1,757 ± 0,571	> 0,05
	pušač	1,658 ± 0,707		1,199 ± 0,662	
NHR	nepušač	0,115 ± 0,051	> 0,05	0,143 ± 0,069	> 0,05
	pušač	0,110 ± 0,090		0,132 ± 0,055	

AS – aritmetička sredina; SD – standardna devijacija; Fo – prosečna fundamentalna frekvencija; Jitt – promenljivost osnovne frekvencije; Shim – varijacije u amplitudi osnovnog laringealnog tona; NHR – odnos intraharmonijskog šuma i harmonika

Tabela 4

Korelacija parametara glasa (ρ) pre i posle vokalnog zamora u odnosu na starost

Parametar	Pre vokalnog zamora	Posle vokalnog zamora
	ρ	*ρ*
F0 (Hz)	-0,333	-0,067
Jitt (%)	0,279	-0,062
Shim (%)	0,026	0,124
NHR	0,288	0,172

AS – aritmetička sredina; SD – standardna devijacija; Fo – prosečna fundamentalna frekvencija; Jitt – promenljivost osnovne frekvencije; Shim – varijacije u amplitudi osnovnog laringealnog tona; NHR – odnos intraharmonijskog šuma i harmonika; *ρ* – Spirmanov koeficijent korelacije

Diskusija

Broj i težina oštećenja glasa poslednjih godina naglo se povećavaju i na taj način najvažnije sredstvo komunikacije čoveka biva ugroženo. Dugotrajna fonacija kod glasovno needukovanih vokalnih profesionalaca povećava rizik od glasovnog zamora, što može dovesti do patoloških promena na larinksu [11].

Vokalni zamor je rezultat prekomerne upotrebe glasa usled preopterećenja brojnim ponavljanjima pokreta glasnica. Opisana su dva potencijalna aspekta zamora glasa: zamor laringealne muskulature i zamor laringealnog tkiva sa oštećenjem lamine proprie usled eksplozivne fonacije [11, 12]. Biomehanički stres usled eksplozivne i dugotrajne fonacije dovodi do ošetećenja tkiva, epitelijalnih ćelija, odvajanja kolagenih i elastičnih vlakana. Tako nastaju izmenjene vibratorne karakteristike glasnica. Istraživanja potvrđuju da se kod vokalnih profesionalaca mišići glasnica u položaju abdukcije i adukcije kontrahuju i više od 1 800 puta na sat [13].

U oblasti analize glasa u poslednjih deset godina, sproveden je veći broj istraživanja čiji se rezultati međusobno razlikuju [11–14]. Brojni autori su objavili povećanu vrednost Fo, NHR parametra i smanjene vrednosti *jitter*-a i *shimmer*-a, posle zamora glasa [14]. Izmenjene vrednosti parametra posle zamora glasa uglavnom nisu u korelaciji sa simptomima, već su posledica povećene mišićne aktivnosti [10, 15].

Fundamentalna frekvencija – Fo je parametar koji je u većini studija korišćen u analizi glasa. Kod naših ispitanika vrednost Fo je na kraju radne nedelje značajno porasla. Uočena promena zapažena je kod ispitanika oba pola. Slične rezultate objavili su i drugi autori [11, 14]. Međutim, prosečne vrednosti ovog parametra u objavljenim istraživanjima dosta se razlikuju. Stemple i sar. [16] i Rantala i sar. [17] snimanjem u prirodnom okruženju (učionici), dobili su prosečnu vrednost Fo pre vokalnog zamora od 236 Hz, a posle zamora 263 Hz. U našem istraživanju prosečna vrednost ovog parametra bila je pre vokalnog zamora 199 Hz, a posle 208 Hz. Prema podacima iz literature opseg ovog parametra kreće se od 192 do 213 Hz [18]. Moguće objašnjenje razlika u rezultatima je i različit način uslova ispitivanja. Nedostatak nekih studija je sprovođenje ispitivanja zamora glasa u kontrolisanim laboratorijskim uslovima. Većina studija ukazuje na prednosti ispitivanja glasa u radnoj sredini ispitanika. Naše istraživanje je, shodno tome i sprovedeno u radnoj sredini ispitanika.

U normalim fiziološkim uslovima između osnovne frekvencije Fo i amplitude osnovnog laringealnog tona Shim (%) muškog i ženskog pola postoji razlika. Larinks muškaraca je fiziološki veći od ženskog i iz tih razloga osnovna frekvencija glasa je niža, dok je vrednost amplitude osnovnog laringealnog tona viša. Ova razlika održala se i nakon vokalnog zamora u našem istraživanju. Kod naših ispitanika, prosečne vrednosti parametra varijacije u visini fundamentalne frekvencije – Jitt (%) i varijacije u amplitudi osnovnog laringealnog tona – Shim (%) smanjile su se posle vokalnog zamora. Naši rezutati slažu se sa rezultatima drugih isptraživača [11, 14, 19]. Niže vrednosti Jitt (%) i Shim (%) posle zamora glasa posledica su povećanog mišićnog tonusa vokalne muskulature usled hiperfunkcije. Analizirani paremetar procene šuma – NHR posle vokalnog zamora se povećao. Vokalni zamor je uticao na povećanu količinu šuma tokom produkcije glasa koja je posledica nemogućnosti potpune okluzije glasnica prilikom fonacije [19]. Drugi autori objavili su slične rezultate [20, 21].

Podaci iz literature ukazuju na povezanost vokalnog zamora i pušenja [4]. U našem istraživanju pušenje nije imalo uticaja na zamor glasa, što objašnjavamo činjenicom da se radilo o malom uzorku ispitanika. Nedostatak naše studije je i što nismo uzimali u obzir dužinu pušačkog staža kao ni broj popušenih cigareta.

Poznato je da glas sa fiziološkim procesom starenja menja svoje akustičke karakteristike. Ove promene sa progresijom starosti nisu samo posledica anatomskih i fizioloških promena larinksa već su uslovljene i otežanim kontrolisanjem glasa zbog oštećenja sluha. Starenje glasa individualno varira i u skladu je sa načinom života. Kod naših ispitanika, starost nije značajno uticala na ispitivane parametre glasa niti pre, ni posle vokalnog zamora. Ovo objašnjavamo činjenicom da je uzorak naših ispitanika bio relativno mlad: prosečna starost bila je 40 godina.

Zaključak

Uprkos inovacijama u nastavničkoj metodologiji, glas i dalje ostaje najvažnije sredstvo rada. Rezultati našeg istraživanja potvrdili su da je zamor glasa kod nastavnika najevidentniji na kraju radne nedelje. Shodno tome, ističemo potrebu uvođenja vokalne edukacije za osobe koje profesionalno angažuju glas u cilju prevencije poremećaja glasa. Uvođenjem multidimenzione akustičke analize glasa dobijena je moćna, objektivna, veoma osetljiva dijagnostička procedura za kvantitativno i kvalitativno praćenje kvaliteta glasa, koja omogućava otkrivanje početnih patoloških promena i pre nego što postanu klinički uočljive.

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Evaluation of a prevention programme efficiency for patients with fixed orthodontic appliances

Procena efikasnosti preventivnog programa za pacijente sa fiksnim ortodontskim aparatima

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Abstract

Background/Aim. Orthodontic treatment enables the establishment of functional occlusion and improvement of oral health, however, it increases the risk of periodontal disease development. The aim of this paper was to examine the efficiency of the applied programme for the prevention of gingivitis in children undergoing the fixed orthodontic appliance therapy and to determine the most efficient devices and techniques for maintaining oral hygiene during orthodontic treatment. **Methods.** The study included 80 patients of both genders – 60 patients comprised the experimental group and 20 patients comprised the control group. All of them were patients of the Clinic for Orthodontics at the School of Dentistry in Belgrade, aged between 13 and 18. The Silness-Löe Plaque Index (PI) was utilised for the assessment of oral hygiene quality and Silness-Löe Gingival Index (GI) and Mühlemann Papilla Bleeding Index (PBI) were utilised for the assessment of gingival state. Checkups were conducted as a single-blind study at the beginning and after the first, the third and the sixth month of the preventive and prophylactic programme. **Results.** During the observed period, a statistically significant change in PI, GI and PBI values was noticed ($p < 0.005$), as well as the difference in the dynamics of value changes during the periods between the observed groups. **Conclusion.** The preventive programme, applied to children undergoing the fixed orthodontic appliance therapy, had a positive effect both on oral hygiene quality and gingival state. The values of the examined parameters of the patients from the experimental group were significantly lower in comparison with those of the patients from the control group. The most efficient combination of devices for oral hygiene during orthodontic treatment was: a Curaprox CP5460 toothbrush, CD Ortho 60 orthodontic toothbrush and Curaprox CPS 14 interdental brush.

Key words:
orthodontic appliances; preventive dentistry; oral hygiene; periodontal index; dental plaque index; adolescent.

Apstrakt

Uvod/Cilj. Ortodontsko lečenje omogućava uspostavljanje funkcionalne okluzije, poboljšanje oralnog zdravlja, ali nosi i povećan rizik od nastanka parodontalnih oboljenja. Cilj rada bio je da se ispita efikasnost primenjenog programa za prevenciju gingivitisa kod dece koja su pod terapijom fiksnim ortodontskim aparatima i da se utvrdi koja su najefikasnija sredstva i tehnike za održavanje oralne higijene tokom ortodontskog tretmana. **Metode.** Ispitivanjem je obuhvaćeno 80 ispitanika oba pola, od kojih je 60 činilo eksperimentalnu, a 20 kontrolnu grupu. Svi ispitanici bili su pacijenti Klinike za ortopediju vilica, Stomatološkog fakulteta Univerziteta u Beogradu, uzrasta od 13 do 18 godina. Za procenu oralne higijene primenjivan je plak indeks (PI) prema Silnes-Lö-u, a za procenu stanja zdravlja gingive primenjivani su gingivalni indeks (GI) prema Lö-Silnes-u i indeks krvarenja gingive (IKG) prema Milemanu. Pregledi ispitanika rađeni su kao jednostruko slepo istraživanje. Pregledi su obavljeni na početku, posle prvog, trećeg i šestog meseca preventivnoprofilaktičkog programa. **Rezultati.** Utvrđena je statistički značajna promena vrednosti PI, GI i IKG ($p < 0,005$) tokom posmatranog vremenskog perioda, kao i razlika u dinamici promena vrednosti tokom vremena između posmatranih grupa. **Zaključak.** Primenjeni preventivni program kod dece koja su pod terapijskim fiksnim ortodontskim aparatima pozitivno je uticao na kvalitet izvođenja oralne higijene, kao i na stanje zdravlja gingive. Smanjenje vrednosti ispitivanih parametara ispitanika eksperimentalne grupe bilo je značajno u odnosu na ispitanike kontrolne grupe. Kombinacija sredstava za izvođenje oralne higijene tokom ortodontskog tretmana koja je dala najbolje rezultate je: četkica za zube Curaprox CP5460, ortodontska četkica CD 0rtho 60 i interdentalna četkica Curaprox CPS14.

Ključne reči:
ortodontski aparati; stomatologija, preventivna; higijena, oralna; periodontalni indeks; zub, indeks plaka; adolescenti.

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Introduction

Orthodontic treatment is widely acknowledged and accepted in everyday dental practice due to the positive effects it has on dentofacial complex. With fixed orthodontic appliances, clinicians can offer patients the establishment of functional occlusion, improvement of oral health and aesthetic improvement of dentofacial complex. Anomalies in development of the face and jaws, as well as orthodontic treatment, can influence oral health. Deviations from an ideal arrangement and position of teeth (lack of space, tooth rotation or open bite, a deep bite and cross-bite) facilitate dental plaque accumulation. It has to be pointed out that malocclusion is not a primary etiological factor, but an auxiliary factor which facilitates dental plaque accumulation. The main principle of orthodontic therapy is to correct tooth and jaw position and thus indirectly improve the health of parodontium and durability of teeth [1].

By accepting an orthodontic treatment, a patient makes a firm commitment to maintain oral hygiene regularly and thus prevent potential iatrogenic damages which may occur during therapy. Numerous studies show a significant increase in the quantity of dental plaque as well as in the occurrence of gingivitis in patients with fixed orthodontic appliances because they make removal of dental plaque difficult [2]. Fixed orthodontic appliances, such as orthodontic braces, arches and rings, increase the number of retention places for dental plaque accumulation. All these factors make it even more difficult to maintain oral hygiene [3]. Self-cleaning is also more difficult because of the reduced effect of mechanical chewing and rinsing the food residues off by saliva [4]. All preventive programmes referring to prevention and treatment of an gingivitis and parodontopathy include regular removal of dental plaque as a part of an adequate daily oral hygiene.

The following factors are necessary for adequate oral hygiene: adequate devices (equipment), correct technique of using those devices, regular toothbrushing and sufficient length of brushing every single tooth. Recommendations for adequate devices for oral hygiene maintenance include the following factors: specific needs of patients (disease predisposition or state of the mouth) and individual characteristics (age, affinities, manual dexterity or lifestyle). All these factors should be adjusted to individual patients in order to enable perfect oral hygiene at home. Individual preventive programmes should be implemented for patients with fixed orthodontic appliances and they should, apart from health education, include education about the importance of regular and correct oral hygiene maintenance and checkups. Patients need to be demonstrated the correct technique and frequency of toothbrushing. They also need to learn about the right toothbrushes, interdental and orthodontic brushes, as well as about auxiliary devices for oral hygiene maintenance (adequate toothpaste and mouthwash) [5].

During a fixed orthodontic appliance therapy, the technique and duration of toothbrushing and constant motivation of patients are key factors of oral hygiene maintenance. Before the beginning of treatment, patients should be informed about the increased risk of caries and parodontium and they should be instructed about the necessity of regular oral hygiene maintenance in order to minimise the risks [6]. The choice of patients, education and training about a regular and correct oral hygiene maintenance together with preventive and prophylactic measures and patients' motivation will increase the comfort of patients undergoing orthodontic therapy and contribute to the functional and aesthetic success of it. A regular oral hygiene maintenance is of great importance for the preservation of gingival health until the end of orthodontic therapy as well as after its ending. Apart from having a regular dental arch, the habit of regular oral hygiene will help preserve the health of gingiva and contribute to lifelong oral health.

The aim of this paper was to examine the efficiency of the applied programme for the prevention of gingivitis in children undergoing the fixed orthodontic appliance therapy and determine the most efficient devices and techniques for maintaining oral hygiene during orthodontic treatment.

Methods

The study included 80 patients of both genders – 60 patients comprised the experimental group and 20 ones the control group. The experimental group was subdivided into three groups consisting of 20 patients each and they received different devices for oral hygiene maintenance. For oral hygiene maintenance, the patients from the experimental group 1 used Curaprox CP5460 toothbrush and Curasept ADS 205 mouthwash, patients from experimental group 2 used Curaprox CP5460 toothbrush, CD Ortho 60 orthodontic toothbrush and Curaprox CPS14 interdental brush and the patients from the experimental group 3 used Curaprox CP5460 toothbrush, Curaprox CPS14 interdental brush and Curasept ADS 205 mouthwash. All of them were patients of the Clinic for Orthodontics at the School of Dentistry in Belgrade, aged between 13 and 18. Random sampling was applied as a method. All the patients had the written consent of their parents and all of them had been previously fully informed, both orally and in a written form, about the objectives of the research. During the research, 10% of the whole sample (8 patients) were re-examined in a four-hour interval and the compared data were processed. The acquired Kappa value of 0.84 denotes excellent concordance and verifies the fact that individual error of the examiner is within the acceptable limitations [7].

The Silness-Löe Plaque Index (PI) was utilised for the assessment of oral hygiene quality. The Silness-Löe Gingival Index (GI) and Mühlemann Papilla Bleeding Index (PBI) were utilised for the assessment of gingival state.

PI values were assessed from 0 to 3 according to the following criteria:

0 – There is no dental plaque on the gingival third of the tooth crown. The research was conducted by pulling the tip of the probe over the tooth surface at the entry into the gingival sulcus after a tooth had been adequately dried. The surface of the tooth is considered clean if no materia alba is adherent to the tip of the probe;

1 – Dental plaque cannot be recognised with a naked eye on the examined surface of a tooth, but it becomes visible on the tip of the probe after it has been pulled over the tooth surface at the entry into the gingival sulcus. In these situations, solutions for the visualisation of plaque can be used;

2 – A gingival third of the tooth crown is covered with a thin or moderately thick layer of dental plaque. Plaque deposit is visible to the naked eye;

3 – There is an abundance of dental plaque which is 1–2 mm thick and covers the gingival edge and the surface of the neighbouring tooth and fills the gingival sulcus, i.e. the pocket. Interdental area is filled with debris.

An average PI was calculated by adding individual PI for every single tooth and dividing the acquired sum by the number of examined teeth. The acquired value is divided by four because four surfaces of a tooth are examined: vestibular, oral, mesial and distal.

This index is mostly used for the assessment of gingival state and examination of those parts of the tooth where the PI has been determined. The assessment is based on the change in color and consistency and gingival swelling. GI values were assessed in the following way:

0 – Healthy gingiva;

1 – Mild inflammation – gingival edge is slightly redder than normally, there is a mild oedema and an increased secretion of gingival exsudates from the sulcus and gingiva does not bleed when provoked by a blunt probe;

2 – Moderate inflammation – gingiva is red, there is a pronounced oedema and enlargement of free gingiva and gingiva bleeds when a blunt probe is gently pressed against it;

3 – strong inflammation – gingiva is very red and enlarged, there is a strong tendency towards spontaneous bleeding and there are gingival ulcers.

A total GI is acquired by adding all values of the gingival state from vestibular, mesial, oral and distal surfaces of examined teeth and by dividing the acquired sum by four and then by the number of examined teeth. Mild gingival inflammation refers to GI values 0.5–1.0, whereas moderate gingival inflammation refers to GI values 1.1–2.0. In case mean GI values range from 2.1 to 3.0, gingival inflammation is assessed as serious.

Clinical assessment of color, form and surface structure of gingiva is based on the subjective assessment of an examiner, whereas gingival bleeding is an objective diagnostic sign of inflammation linked to several periodontal diseases. In this study, Mühlemann PBI from gingival sulcus was used as a precursor and the first sign of gingival inflammation. Gingival bleeding is the earliest sign of inflammation occurring even before the change in form and colour. Bleeding index is determined by gingival bleeding provoked by a blunt periodontal probe. The probe first examines distal and then mesial surface of the sulcus, from the base of interdental papilla to its top. Intensity of bleeding is assessed in the following way:

0 – There is no bleeding 20–30 seconds after using a probe;

1 – After using a probe, there is bleeding at only one place;

2 – There are several traces of blood from a papilla in the form of spots and threads;

3 – Interdental area is filled with blood immediately after a probe has been used (blood from papilla in the form of drops);

4 – Bleeding is profuse after a probe has been used. Interdental area is immediately filled with blood which flows over into gingival sulcus and out of it.

Mühlemann PBI is a reliable indicator of gingival state and it is utilised in a relatively fast and simple way. While determining the index, a patient alone can monitor the intensity of bleeding (i.e. the degree of gingival inflammation), which can motivate him/her to maintain a regular and appropriate oral hygiene. Bleeding provoked by a probe is the first sign of gingivitis because the beginning of inflammation is connected with the sulcus side of gingiva invisible to the examiner.

Checkups were conducted as a single-blind study. During checkups, PI, GI and PBI values acquired by an examination with a periodontal probe and a dental mirror with artificial light were recorded first, whereas the technique of conducting oral hygiene and remotivation were monitored later. Checkups were conducted at the beginning and after the first, third and sixth month of the preventive and prophylactic programme. During checkups, PI, GI and PBI were recorded into special study reports in accordance with the described methodology. In the control group, checkups were conducted and values acquired by measuring anticipated indexes in determined time intervals were recorded. The patients from the control group were not included in the preventive and prophylactic programme. Instead, they were advised on methods of maintaining oral hygiene and on proper nutrition by orthodontists who had installed the fixed appliances on their teeth. They also used a standard orthodontic toothbrush for maintaining oral hygiene.

The patients who met all criteria for inclusion into the study were included into the experimental model of the preventive programme after the first checkup and they became a part of the experimental group. After they had been thoroughly acquainted with the causes of the disease of gingiva and the supporting apparatus of teeth through health and education work, they were instructed how to prevent or slow down such diseases. They were explained that the key factor for preventing gingival disease is the control of dental plaque. The patients from all three experimental groups received Curaprox CP5460 ultrasoft toothbrushes. They demonstrated how they brushed their teeth and then their toothbrushing technique was assessed. Afterwards, the Bass technique of toothbrushing was demonstrated and practised (a technique which enables removal of dental plaque from gingival thirds of teeth). Techniques of some patients were corrected in terms of adapting movements during toothbrushing in certain areas due to the specific position of teeth and the fixed orthodontic appliances. The patients from the experimental groups 2 and 3 got Curaprox CPS 14 interdental toothbrushes. The procedure for using this toothbrush was demonstrated and practised – this toothbrush is intended for brushing the area around braces and between orthodontic braces, arches and vestibular surfaces of teeth. Apart

from getting toothbrushes and interdental toothbrushes, the patients from the experimental group 2 were instructed to use properly a CD Ortho 60 orthodontic toothbrush. They were told about its role in maintaining braces and the area around orthodontic braces clean. The patients from the experimental groups 1 and 3 got Curasept ADS 205 mouthwash for a longterm use, containing 0.05% of fluoride and 0.05% of chlorhexidine, and accompanied by written instructions for use. The importance of using mouthwash and its role in preventing plaque accumulation were explained, as well as the fact that chemical agents can never replace toothbrushing [8]. All patients got tablets of erythrosine for dental plaque colouring and visualisation so that they could check at home whether they had brushed their teeth properly and correct their brushing techniques in case plaque was not removed from all surfaces.

During the next checkup, clinical parameters (PI, GI and PBI values) were measured and recorded. The patients spoke about their impressions in terms of toothbrushing techniques and potential difficulties during brushing. Afterwards, dental plaque was identified (by erythrosine) and the toothbrushing technique was monitored. The toothbrushing technique was practised again, as well as the position of an arm and head while brushing inaccessible surfaces due to the specific position of the tooth. The patients from experimental groups 2 and 3 were monitored while using interdental brushes and the techniques were corrected when necessary.

Considering different levels of manual dexterity of patients of this age range and their previous toothbrushing skills, some of them should be given more time for practice until they learn to use properly mechanical devices for oral hygiene maintenance. The patients were motivated by repeated lecture from the previous visit on preserving oral health – the health of teeth and gingiva and duration of the fixed orthodontic appliance therapy depend on how much patients adhere to the given advice on maintaining oral hygiene and proper nutrition. During the third checkup, clinical parameters (PI, GI and PBI values) were measured and the level of oral hygiene was monitored just like in previous visits. Since the level of oral hygiene decreases in time, even with the best trained children, patients were remotivated and the toothbrushing technique was revised. During the fourth checkup conducted six months after the beginning of the programme, the values of monitored clinical indexes were recorded.

Statistical package SPSS was used for the statistical analysis of data which included the calculation of descriptive statistical parameters (mean values with dispersion measures), as well as the statistical check of hypotheses established during the research. The single-factor and a double-factor analyses of variance were utilised for analysis of both, PI and GI, whereas Mann-Whitney and Kruskall-Wallis tests were utilised for analysis of the PBI. Each value $p < 0.05$ was regarded as a statistically significant difference.

Results

During the observed 6-month period, a statistically significant change in PI, GI and PBI values was noticed after conducting a double-factor analysis of variance, as well as the difference in the dynamics of changes in value during the periods in-between the observed groups.

Table 1 shows the results of comparison of PI between the observed grous during a 6-month period of monitoring.

Arithmetic mean values of PI at the beginning of measuring were significantly different (single-factor analysis of variance, $p = 0.022$). There was also a statistically significant difference in the second period of measuring which took place a month later (single-factor analysis of variance, $p = 0.001$). Arithmetic mean values of PI in all three experimental groups decreased, whereas PI values of the control group indicated a slight growth. The trend carried on even three and six months later (single-factor analysis of variance, $p = 0.000$). Compared with the other two experimental groups, the experimental group 2 indicated the lowest values of arithmetic mean of PI. Three months later, the control group maintained the similar level as one month later, whereas six months later there was a slight decrease in the values of arithmetic mean of PI.

The results of comparison of GI values are presented in table 2.

Table 1

Comparison of plaque index (PI) values of the observed groups during a 6-month period of monitoring

Time (months)	CG ($\bar{x} \pm SD$)	EXP1 ($\bar{x} \pm SD$)	EXP2 ($\bar{x} \pm SD$)	EXP3 ($\bar{x} \pm SD$)	*p*
0	0.416 ± 0.159	0.635 ± 0.322	0.494 ± 0.144	0.501 ± 0.213	0.022
1	0.545 ± 0.189	0.458 ± 0.216	0.301 ± 0.117	0.407 ± 0.173	0.001
3	0.579 ± 0.174	0.326 ± 0.155	0.193 ± 0.094	0.307 ± 0.119	0.000
6	0.501 ± 0.185	0.218 ± 0.118	0.086 ± 0.062	0.208 ± 0.057	0.000

CG – the control group; EXP 1 – the experimental group 1; EXP 2 – the experimental group 2; EXP 3 – the experimental group 3; $\bar{x}$ – mean value; SD – standard deviation

Table 2

Gingival index (GI) values of the observed groups during a 6-month period of monitoring

Time (months)	CG ($\bar{x} \pm SD$)	EXP1 ($\bar{x} \pm SD$)	EXP2 ($\bar{x} \pm SD$)	EXP3 ($\bar{x} \pm SD$)	*p*
0	0.506 ± 0.152	0.776 ± 0.379	0.567 ± 0.154	0.622 ± 0.221	0.006
1	0.641 ± 0.189	0.602 ± 0.278	0.414 ± 0.125	0.508 ± 0.187	0.003
3	0.668 ± 0.158	0.436 ± 0.180	0.303 ± 0.092	0.396 ± 0.125	0.003
6	0.577 ± 0.186	0.307 ± 0.133	0.161 ± 0.090	0.260 ± 0.081	0.000

CG – the control group; EXP 1 – the experimental group 1; EXP 2 – the experimental group 2; EXP 3 – the experimental group 3; $\bar{x}$ – mean value; SD – standard deviation

A single-factor analysis of variance at the beginning of the research does not indicate any statistically significant differences in GI values among the examined groups: $p = 0.006$. After a month, there was a statistically significant difference in GI values among examined groups (a single-factor analysis of variance, $p = 0.003$). Arithmetic mean values of GI for all the three experimental groups indicate a decrease, whereas GI values for the control group indicate a growth. After three months, there was a statistically significant difference in GI values among the examined groups (a single-factor analysis of variance, $p = 0.000$). The values of arithmetic mean for the experimental groups were decreased – the experimental group 2 had the lowest values, next came the experimental group 3 and finally the experimental group 1. After three months, GI values for the control group indicated growth, whereas after six months they indicated a slight decrease.

The obtained PBI values for both groups within a 6-month period are compared and presented in Table 3.

Table 3

Papilla bleeding index (PBI) values during a 6-month period of monitoring

Time (months)	CG ($\bar{x} \pm SD$)	EXP1 ($\bar{x} \pm SD$)	EXP2 ($\bar{x} \pm SD$)	EXP3 ($\bar{x} \pm SD$)	*p*
0	0.219 ± 0,103	0.326 ± 0,176	0.249 ± 0,101	0.289 ± 0,132	0.155
1	0.278 ± 0,128	0.204 ± 0,123	0.148 ± 0,051	0.199 ± 0,102	0.003
3	0.258 ± 0,113	0.144 ± 0,077	0.047 ± 0,053	0.134 ± 0,065	0.000
6	0.188 ± 0,104	0.093 ± 0,055	0.019 ± 0,030	0.086 ± 0,030	0.000

CG – the control group; EXP 1 – the experimental group 1; EXP 2 – the experimental group 2; EXP 3 – the experimental group 3; $\bar{x}$ – mean value; SD – standard deviation

After comparing PBI values among the groups, it was determined that arithmetic mean values at the beginning of registration were not significantly different in statistical terms (Kruskall-Wallis test, $p = 0.155$). Arithmetic mean of PBI value was the lowest at the beginning of measuring for the control group. After one month, PBI values were significantly different in statistical terms (Kruskall-Wallis test, $p = 0.003$). At the beginning, PBI values for the control group indicated a growth and after three months they indicated a decrease which was continued even after six months. PBI values for the experimental groups indicated a decrease during all checkups. After a month, PBI values of the experimental group 2 were lower than PBI values of all the other groups and the trend carried on until the last checkup, *i.e.* after six months. Arithmetic mean values of PBI were significantly different in statistical terms after three and six months ($p = 0.000$).

Discussion

The experimental model of the preventive programme, whose elements have been mentioned in the methodology, has shown positive effects on the removal of dental plaque and prevention of its reaccumulation. The patients from the experimental group 2 had the lowest values of dental plaque, which can be explained by the fact that they had used three different types of toothbrushes which had helped them remove dental plaque from the least accessible surfaces. The experimental group 2 indicated a bigger and statistically more significant difference from the experimental group 1 than from the experimental group 3. For oral hygiene maintenance, the patients from the experimental group 3 used a Curaprox CP5460 toothbrush, Curaprox CPS 14 interdental brush and Curasept ADS 205 mouthwash, whereas the patients from the experimental group 1 used a Curaprox CP5460 toothbrush and Curasept ADS 205 mouthwash. The results are in accordance with the research conducted by Kilicoglu et al. [9], where they compared oral hygiene of patients undergoing the fixed orthodontic appliance therapy using two different types of toothbrushes. PI and PBI values were measured at the beginning of the research and after a month and it was concluded that utilising several types of mechanical devices (classical, orthodontic and interdental toothbrushes) for maintaining oral hygiene was more effective in removing dental plaque.

Bulajić [10] conducted a six-month research with 32 patients and she got the following results: during the first three months after the fixed appliance had been installed, PI values tended to grow; after that they stabilised and finally they started decreasing towards the end of a sixth-month period. These findings are in accordance with the results of the current research as far as the control group is concerned. Regardless of the type of fixed orthodontic technique (ring or braces), adolescents experience much higher plaque accumulation and more serious gingival inflammation than adults before, during and after the orthodontic treatment.

The results are also in accordance with the research conducted by Wang et al. [11], which included 57 patients with fixed orthodontic appliances. The patients from the experimental group were a part of the preventive programme which included health and education work, identification of plaque with plaque-colouring devices and the training about using orthodontic, single-tuft and interdental brushes as well as dental floss for oral hygiene maintenance. Both, PI and GI were examined during checkups, which were conducted every three weeks in the course of six months. The patients were remotivated and instructed how to perform oral hygiene properly. At the beginning of the research, there were no statistically significant differences in PI and GI values between the control and the experimental groups. After the checkups, however, there was a statistically significant difference in PI and GI values between the groups, which goes to say that the preventive programme was fruitful. The authors conclude that the state of oral health of patients undergoing the fixed orthodontic appliance therapy can be improved by imple-

menting measures such as health education and practising, revising and monitoring techniques of oral hygiene maintenance, along with permanent motivation of patients. Good oral hygiene and appropriate devices for its maintenance produce good results in terms of oral health, but the importance of instructions and trainings should not be overlooked either.

Ay et al. [12] have proven the thesis that oral instructions are insufficient for achieving a satisfactory level of oral hygiene – orthodontists and dental hygienists must make a point of improving the level of oral hygiene of orthodontic patients. They conducted the study with 150 orthodontic patients divided into five groups and they compared the efficiency of verbal motivational methods for oral hygiene maintenance with auxiliary devices or without them under the supervision of dentists. After four weeks, there were significant differences in GI values among experimental groups.

It takes a lot of patience, effort and time for the patients with fixed orthodontic appliances to master a quality technique of toothbrushing. At the beginning, it takes up to 15 or 20 minutes to brush teeth if three different brushes are used. In time, when patients master the technique of performing oral hygiene, the duration of toothbrushing shortens. According to this research, results of the preventive programme in the experimental group (lower PI, GI and PBI values) show that a good preventive programme, based on motivation, health education and good trainings about performing oral hygiene, enables preservation of periodontal tissue health, which is in accordance with researches of other authors who have studied effects of preventive programmes including motivation, trainings about oral hygiene maintenance and health and education work [13].

Conclusion

During the research, there were statistically significant decreases in PI, GI and PBI values of the patients from all the three experimental groups, which proves that the applied programme for the prevention of gingivitis in children undergoing the fixed orthodontic appliance therapy had a positive effect on the quality of performing oral hygiene, as well as on the gingival state. The values of the examined parameters of patients from the experimental group were significantly lower in comparison with the examined parameters of the patients from the control group. The most efficient combination of devices for oral hygiene during orthodontic treatment was: Curaprox CP5460 toothbrush, CD Ortho 60 orthodontic toothbrush and Curaprox CPS14 interdental brush. Good oral hygiene can be achieved by using a Curaprox CP5460 toothbrush, Curaprox CPS14 interdental brush and Curasept ADS 205 mouthwash for a longterm use.

Motivation, adherence to all measures proposed by the preventive programme and their implementation, patience, persistence, practice and mastering the techniques of performing oral hygiene prevent gingival diseases and enable successful implementation of acquired knowledge and skills regarding oral hygiene maintenance both after the orthodontic treatment and throughout life.

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Clinical characteristics of respiratory syncytial virus infection in neonates and young infants

Kliničke karakteristike infekcije respiratornim sincicijalnim virusom kod novorođenčadi i odojčadi

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Abstract

Introduction/Aim. Infection with respiratory syncytial virus (RSV) occurs during the first year of life in 50% of children and 20%–40% of them have signs of lower respiratory tract infection (bronchiolitis or pneumonia). There is an increased risk for complicated course and death from RSV infection in premature infants, especially those with bronchopulmonary dysplasia (BPD) or congenital heart disease. The aim of our study was to analyze clinical characteristics of laboratory confirmed RSV infection in order to evaluate the need for preventive measures in neonates and young infants. **Methods.** The prospective study included children under age of 12 months admitted to our hospital in the period November 2008–March 2009 who were positive for RSV by enzyme immunoassay membrane test. The course of disease was assessed by clinical score and radiographic findings. **Results.** Infection with RSV was confirmed in 91 patients: 21 (23.0%) were under the age of 30 days, 37 (40.7%) were between 31–60 days, and 33 patients (36.3%) were older than 60 days ($p > 0.05$). The highest hospitalization rate was in January – 33 patients (36.3%; $p < 0.01$). Disease severity score in these age groups (AG) were: 8.4 ± 0.4 (AG 0–30 days); 9.0 ± 0.3 (AG 31–60 days) and 8.3 ± 0.3 (AG > 60 days), without statistically significant difference among the groups ($p > 0.05$). Clinical scores in patients with and without risk factors were 10.5 ± 0.5 and 8.3 ± 0.2, respectively ($p < 0.01$). Pathological radiographic findings were observed in 72 (79.1%) and complications (apnea, significant atelectasis, encephalopathy) occured in 15 (16.5%) patients. The average length of hospital stay in complicated and uncomplicated course of the disease was 9 days and 6 days, respectively ($p < 0.01$). Therapy in 85 (93.4%) patients included bronchodilators, while systemic glucocorticoids and oxygen therapy were used in 51 (56.0%) and 44 (48.4%) patients, respectively. Death occured in 2 (2.2%) patients, both from a high risk group (the patient with BPD and the other one with congenital heart disease and Down syndrome). **Conclusion.** Infection with RSV in our settings showed marked seasonal characteristics with highest hospitalization rate in January. Although the course and outcome of the disease were favorable in the majority of our patients, the need for hospitalization and administration of therapy with possible side effects warrants that general measures for prevention of respiratory infections are followed especially in the first year of life. Severe disease and death are more probable in neonates and infants with risk factors. In these children passive immunisation with specific monoclonal antibody (e.g. palivizumab) during RSV season should be considered.

Key words:
respiratory syncytial viruses; infection; infant, newborn; child, preschool; immunologic tests; drug therapy; prognosis.

Apstrakt

Uvod/Cilj. Respiratornim sincicijalnim virusom (RSV) inficira se 50% dece do navršene prve godine života, a 20–40% obolelih ima znakove zahvatanja periferijskih disajnih puteva (bronhiolitis ili pneumonija). Poseban rizik od komplikacija i smrtnog ishoda usled infekcije RSV postoji kod prevremeno rođene dece, odojčadi sa bronhopulmonalnom displazijom (BPD) i urođenim srčanim manama. Cilj ovog rada bio je analiza kliničkih karakteristika laboratorijski potvrđene infekcije RSV i procena potrebe za uvođenjem preventivnih mera kod novorođenčadi i odojčadi. **Metode.** Prospektivnom studijom bili su obuhvaćeni bolesnici do navršenih 12 meseci života hospitalizovani u periodu novembar 2008 - mart 2009. godine, kod kojih je imunoenzimskim testom dokazana infekcija RSV. Procena toka bolesti vršena je na osnovu kliničkog skora i radiografskog nalaza. **Rezultati.** Infekcija RSV dokazana je kod 91 bolesnika od kojih je 21 (23,0%) imalo manje od 30 dana života, dok se uzrast 37 (40,7%) bolesnika nalazio u rasponu 31–60 dana života. Više od 60 dana imalo je 33 (36,3%) obolele odojčadi ($p > 0,05$). Najveća stopa

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hospitalizacije bila je u januaru – 33 bolesnika (36,3%; $p < 0,01$). Težina ispoljavanja procenjena je na osnovu kliničkog skora koji je u navedenim uzrasnim grupama iznosio 8,4 ± 0,4 (0–30 dana); 9,0 ± 0,3 (31–60 dana); 8,3 ± 0,3 (> 60 dana), a razlika nije imala statističku značajnost ($p > 0,05$). U zavisnosti od prisustva ili odsustva faktora rizika klinički skor iznosio je 10,5 ± 0,5, odnosno 8,3 ± 0,2 ($p < 0,01$). Patološki radiografski nalaz imalo je 72 (79,1%) dece, a komplikacije (krize apneje, opsežne atelektaze, encefalopatija) postojale su kod 15 (16,5%) bolesnika. U slučaju komplikovanog toka bolesti prosečna hospitalizacija trajala je 9 dana, a kod dece bez komplikacija 6 dana ($p <0,01$). U lečenju su primenjivani bronhodilatatori kod 85 (93,4%) bolesnika, dok je sistemska terapija glukokortikoidima i kiseonikom primenjena kod 51 (56,0%), odnosno 44 (48,4%) obolele dece. Smrtni ishod nastupio je kod dva (2,2%) bolesnika koji su pripadali grupi sa faktorima rizika (bolesnik sa BPD i bolesnik sa urođenom srčanom manom i Dounovim sindromom). **Zaključak.** Infekcija RSV u našoj sredini ima izraziti sezonski karakter sa najvećom učestalošću hospitalizacija tokom januara. Mada su tok i ishod bolesti kod većine bolesnika bili povoljni, neophodnost hospitalizacije i primene terapijskih postupaka sa mogućim neželjenim dejstvima nameću potrebu za doslednom primenom opštih mera prevencije respiratornih infekcija, naročito tokom prve godine života. Teži oblik i nepovoljan ishod bolesti mogu se očekivati kod novorođenčadi i odojčadi sa faktorima fizika. Kod te dece u toku sezone infekcije RSV opravdano je razmatranje primene pasivne zaštite specifičnim monoklonskim antitelom (palivizumab).

Ključne reči:
respiratorni sincicijalni virusi; infekcija; novorođenče; deca, predškolska; imunološki testovi; lečenje lekovima; prognoza.

Introduction

Respiratory syncytial virus (RSV) is the one of the most common causes of acute respiratory tract infections in children. Infection with this virus occurs during the first year of life in 50% of children and 20%–40% of them have signs of lower respiratory tract infection (bronchiolitis or pneumonia). There is an increased risk for complicated course and lethal outcome in premature infants, especially those mechanically ventilated due to the respiratory distress syndrome (RDS), infants with chronic lung disease, in particular bronchopulmonary dysplasia (BPD) and infants with hemodynamically significant congenital heart diseases [1].

Infection with RSV is transmitted by droplets or direct contact. This virus preserves contagiousness for a few hours on objects as far as 6.6 m from the patient [2, 3]. Immunity after primary infection is short-term and reinfections occur frequently during childhood [4]. In temperate climate RSV infection shows marked seasonability with peak incidence during winter and early spring [5]. Every year between 75,000 to 125,000 hospitalizations in the USA and more than 600,000 deaths worldwide are connected to the RSV infection [6, 7].

According to our knowledge there aren't sufficient data regarding RSV infection in neonates and young infants in Serbia. The aim of our study was to analyze clinical characteristics of laboratory confirmed RSV infection in order to evaluate the need for preventive measures in neonates and young infants.

Methods

The prospective study included children under the age of 12 months admitted to the Mother and Child Health Institute "Dr Vukan Čupić" in the period 1st November 2008 – 31st March 2009 with laboratory confirmed RSV infection. Informed consents were obtained from parents or guardians for all children enrolled. The enzyme immunoassay membrane test (BD Directigen™ RSV Test Kit, Becton Dickinson, USA) was used for confirmation of RSV infection by qualitative detection of RSV antigen in nasopharyngeal aspirates within 24 h of hospital admission. The participation in the study did not affect routine management or the length of hospital stay.

The children enrolled were assessed for gender, age, gestational age, month of admission and course of disease in the presence of risk factors (prematurity, neonatal RDS and/or mechanical ventilation, BPD, congenital heart disease). The course of disease was assessed by clinical score with six criteria including transcutaneous oxygen saturation measured by a pulse oxymeter (SaO2) (Table 1) [8]. Some other evaluated parameters included patient's axillary temperature, radiographic findings, white blood cell (WBC) count and C-reactive protein (CRP) level measured immunoturbdimetrically (Turbox®, Orion Diagnostica), type of complication, therapy administered and length of hospital stay.

Table 1

Parameters of clinical score used for assessment of respiratory distress severity

Parameter	Score		
	1	2	3
Heart rate (beats/min)	< 120	120–160	> 160
Respiratory rate (breaths/min)	< 40	40–60	> 60
Wheezing	absent	expiratory	audible without auscultation
Skin color	normal	mild cyanosis	moderate to severe cyanosis
Feeding difficulties	absent	mild	serious
SaO_2 (%)	> 98	94–98	< 94

SaO_2 – oxygen saturation of hemoglobin

Statistical analysis was performed by SPSS v.12.0 for Windows. The Student's *t*-test, ANOVA and χ^2 test were

used and the difference was considered statistically significant when $p < 0.05$.

Results

Respiratory syncytial virus infection was confirmed in 91 patients, with even distribution by gender and predominance of term neonates and infants born by vaginal delivery with average body mass of 3.140 ± 75 g (Table 2). The monthly distribution of RSV infection was the following: in November and March there were 6 (6.6%) and 8 (8.8%) patients, respectively; in December and February, 25 (27.5%) and 19 (20.9%) patients, respectively ($p > 0.05$); while in January the hospitalization rate was the highest with 33 (36.3%) patients, which was statistically highly more significant than in the previous months ($p < 0.01$) (Figure 1).

Table 2
Characteristics of patients with respiratory syncytial virus (RVS) infection (n = 91)

Characteristics	n (%)
Age (days)	
< 30*	21 (23.0)
31–60	37 (40.7)
> 60	33 (36.3)
Gender	
male	47 (51.6)
female	44 (48.4)
Gestational age (weeks)	
> 36	79 (86.8)
32–36	7 (7.7)
≤ 32	5 (5.5)

***the youngest patient = 10 days**

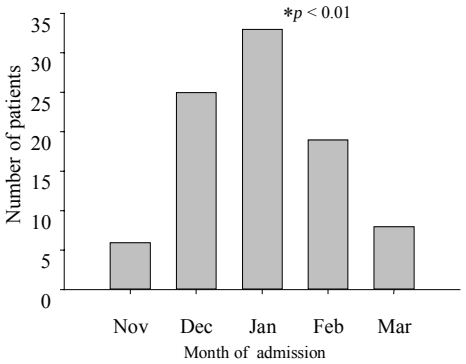

Fig. 1 – Monthly distribution of hospitalized patients with confirmed respiratory syncytial virus (RSV) infection (n = 91)

Body temperature was normal on admission and/or during hospitalization in 63 patients (69.2%), while fever with average value of 38.3 ± 0.1 °C was noted in 28 (30.8%) of the patients. Pathological radiographic findings were present in 72 (79.1%) of the patients with hyperinflation seen in 50 (54.9%) of the patients, infiltrates in 13 (14.3%), consolidation in 5 (5.5%) and atelectasis in 4 (4.4%) of the cases. The median of WBC count was 11.3×10^9/L, and the median of CRP level was 2.5 mg/L.

The clinical score for the whole group had the average value of 8.6 ± 0.2 without statistically significant difference between age groups, or between patients born before and after 36 weeks of gestation. The clinical score for those born before 32 weeks of gestation was 10.6 ± 0.7 and was highly statistically greater than for the patients born after this gestational age (Table 3).

Table 3
Clinical score, age and gestational age of patients with respiratory syncytial virus (RSV) infection (n = 91)

Parameters	Clinical score	*p*
Age (days)		
0–30	8.4 ± 0.4	
31–60	9.0 ± 0.3	> 0.05
> 60	8.3 ± 0.3	
Gestational age (weeks)		
> 36	8.5 ± 0.2	
32–36	9.0 ± 0.3	> 0.05
≤ 32	10.6 ± 0.7	≤ 0.01

Risk factors for more severe disease were present in 12 (13.2%) of the patients with clinical score of 10.5 ± 0.5, while in the patients without these risk factors clinical score was 8.3 ± 0.2. This difference was highly statistically significant ($p < 0.01$).

The median length of hospital stay in the presence of risk factors or in complicated disease was 10 and 9 days, respectively, while in the absence of risk factors the average length of hospital stay was 6 days. This difference was highly statistically significant ($p < 0.01$).

The prevalence of various therapeutic procedures (the use of bronchodilators, systemic glucocorticoids, oxygen therapy) is shown in Table 4.

Table 4
Therapeutic procedures in patients with respiratory syncytial virus (RSV) infection (n = 91)

Therapeutic procedure	n (%)
Brochodilators	85 (93.4)
Systemic glucocorticoids	51 (56.0)
Oxygen therapy	40 (44.0)

The course of the disease was complicated by apnea, significant atelectasis and/or encephalopathy in 15 (16.5%) patients, while death occurred in 2 infants, so that mortality rate in our patients was 2.2%.

The discharge diagnosis was bronchiolitis in 77 (84.6%) of the patients. Ten (11.1%) patients were discharged with the diagnosis of pneumonia and 4 (4.4%) with the diagnosis of nonspecific respiratory infection.

Discussion

According to the available literature this is the first prospective study in our country including patients under the age of 12 months with laboratory confirmed RSV infection. The enzyme immunoassay test with two monoclonal antibodies (BD Directigen™ RSV Test Kit, Becton Dickinson, USA) was used for confirmation of RSV infection. This test is simple, reliable, has high specificity of 97.5% and preva-

lence of false-positive results of only 0.7% [9]. The results of testing were available in a very short period of time (< 1 h). Besides, RSV and bacterial co-infection occur in less than 2% of previously healthy infants. Therefore, the confirmation of RSV infection by this test excludes with high probability the suspicion of systemic bacterial infection, which enhances the safety and rationality of diagnostic and therapeutic procedures especially in children of the youngest age [10].

Our results also confirm the seasonal character of RSV infection with the increase in hospitalization rate from November until January when the highest prevalence was reached. Afterwards, there was slow decline in hospitalization rate, so there were no confirmed cases in these age groups after the end of March. Large epidemiological studies have shown that the regional season pattern of RSV infection distribution does not change significantly over time [11, 12].

Our youngest patient was 10 days old on admission, and RSV infection in the first week of life was also described [13]. Since the incubation period lasts 2–8 days, from the epidemiological point of view it is important that the infection with RSV can occur in, or shortly after discharge from maternity ward [14]. The most important preventive measure against the spread of nosocomial infection is the appropriate hand hygiene of the staff. It should be also bared in mind that infected persons eliminate virus in 3 to 8 days, and in infants it takes up to four weeks [15].

Similarly to the previously published results there was a slight predominance of male gender in our group as well, while the rate of 13.2% of patients born before 36 weeks of gestation was twice as high as the general rate of premature delivery in our country [16]. This result is in agreement with the finding that premature infants are more often hospitalized due to RSV infection than term infants. The need for hospitalization in these infants is explained by higher prevalence of severe forms of bronchiolitis due to the slow and incomplete increase of small airways diameter during the first year of life [14, 15]. Also, in our patients hyperinflation was the most common radiographic finding, while infiltrations and consolidations were less prevalent. Although there is an evidence that the presence of atelectasis does not complicate the course of disease, it has been described that in more than 5% of infants there is a whole lobe consolidation with respiratory failure and the need for mechanical ventilation [17].

The majority of our patients did not have fever on admission or during hospital stay which supports the view that RSV infection is an "afebrile illness" [4]. There was not a significant rise in WBC count nor in CRP level which is in agreement with previous studies and indicates that RSV infection is rarely complicated by bacterial infections [18].

Since usually there is involvement of small airways in RSV infection leading to bronchoobstruction, we used clinical score for assessment of disease severity that was originally designated for use in acute asthma attacks [8, 11]. The advantage of this score lies not only in quantification of respiratory distress severity and early recognition of hypoxemia but also in possibility of comparison with results from different authors. For example, the consistency of our criteria for hospital admission is confirmed by the fact that the average clinical score in our group (8.6 ± 0.2) was very similar to that of Constantopoulos et al. (8.7 ± 1.7) [12]. The lack of a significant difference in our age groups probably comes from standardized criteria for hospital admission. Opposite to this, the higher score was obtained in premature infants born before 32 weeks of gestation and is most probably caused by before mentioned morphological characteristics of airways. The higher clinical score was present in high-risk group of infants for severe disease and unfavorable outcome of RSV infection due to the chronic lung disease (BPD) and hemodynamically significant congenital heart disease [18]. In these situations, according to our results as well, there is higher rate of complications and greater length of hospital stay, but one can also expect unfavorable course with lethal outcome [7]. In a group of serious, early complications of disease common are central apneas which can be seen in up to 10%–26% of patients [19]. The risk for their occurrence is higher in premature, young infants and in infants with apneas of prematurity [20], but they can be the first sign of disease in previously healthy children. Taking this into account current recommendations for hospitalization include all infants under the age of 3 months with RSV lower respiratory tract infection [21]. The signs of encephalopathy were present in one of our patients, but this rare, previously described complication most probably is not related to the structural changes in the CNS [22].

The average length of hospital stay in our group was 6 days in case of uncomplicated disease which is consistent with previously published results [23], while in the case of complicated disease the length of hospital stay was significantly increased (on average for 3 days).

When compared to other respiratory viral infections, RSV infection treatment in neonates and infants is based on more extensive approach and the cost of treatment per patient in USA goes up to 3,000 US dollars [24]. Symptomatic, mostly empiric therapy is used. The exception is the need for oxygen therapy when oxygen saturation of hemoglobin is lower than 90% [15]. Inhalations with beta-2 agonists are used in up to 85% of patients with positive effect on clinical score, but they do not affect the length of hospital stay [25]. Similarly to our experience, hospitalized patients with RSV bronchiolitis receive glucocorticoids as strong anti-inflammatory medications in up to 60% of cases [26]. But recent systematic analysis has shown that treatment with systemic glucocorticoids does not have impact on clinical score or the length of hospital stay [27]. Although certain authors suggest the use of nebulized epinephrine as more effective treatment, new studies show that isotonic and hypertonic (3%) NaCl solution are equally effective [28].

Death has occurred in two of our patients at the age of 3 months. Both patients had known risk factors for unfavorable outcome of RSV infection. The first patient was born at 28th week of gestation with body mass of 1,100 g, and as a result of mechanical ventilation due to the RDS suffered from severe form of BPD. The second patient had congenital heart disease (ventricular septal defect) and Down syndrome.

Lethal outcome of RSV infection is a problem in a group of children with risk factors for severe disease form. Therefore, in most countries with developed healthcare system passive immunization with palivizumab, recombinant monoclonal antibody, is performed in specially defined groups. Recom-

mendations for the use of palivizumab in high-risk groups of children were recently published in our country, as well [29].

Conclusion

According to our study, the first of this kind in our country, we can conclude that the course and outcome of RSV infection in hospitalized neonates and young infants are favorable in most cases. The average length of hospital stay in uncomplicated disease course is six days. Serious complications (apnea, significant atelectasis and encephalopathy) prolong hospital stay for three days on average. Severe disease and unfavorable outcome are more probable in children with risk factors. In these children passive immunisation with specific monoclonal antibody (palivizumab) during RSV season should be considered.

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Poređenje efekata primarne medikamentne terapije i primarne argon-laser trabekuloplastike na regulaciju intraokularnog pritiska i stabilnost perimetrijskog nalaza kod glaukoma otvorenog ugla

Comparison of primary medicament therapy effects and primary argon laser trabeculoplasty on regulation of intraocular pressure and stability of perimetry findings in open angle glaucoma

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Apstrakt

Uvod/Cilj. Argon-laser trabekuloplastika (ALT) je priznata metoda sniženja intraokularnog pritiska (IOP) kod bolesnika sa glaukomom otvorenog ugla. Cilj rada bio je da se uporede efekti inicijalne medikamentne terapije i primarne ALT na regulaciju IOP i stabilnost perimetrijskog nalaza kod glaukoma otvorenog ugla. **Metode.** Ukupno 50 očiju 35 bolesnika lečeno je primarnom ALT, dok je 50 očiju 36 bolesnika tretirano primarnom medikamentnom terapijom (timololom 0,5% 20 očiju, latanoprostom 0,005% 18 i dorzolamidom 2% 12 očiju). Intraokularni pritisak kontrolisan je na tri meseca, a vidno polje na šest meseci tokom 30-mesečnog perioda praćenja. **Retultati.** Tokom prva 24 meseca nije utvrđena statistički značajna razlika u procentu očiju sa uspešno regulisanim IOP. Međutim, 27. i 30. meseca u grupi primarno lečenih medikamentima utvrđen je statistički značajno viši procenat uspešno regulisanog IOP i to 98% i 96% očiju sukcesivno, dok je u grupi primarno lečenih ALT utvrđeno opadanje procenta uspešno regulisanog IOP i to kod 78%, odnosno 76% očiju (χ^2-test, $p = 0{,}002$, odnosno $p = 0{,}140$). Obe terapijske grupe pokazale su stabilnost perimetrijskog nalaza bez statistički značajne razlike u vrednostima indeksa prosečne devijacije (MD) do kraja posmatranog perioda. Dinamika promene vrednosti indeksa MD pokazala je statistički značajno veći pad vrednosti indeksa MD kod ispitanika koji su primarno lečeni medikamentima u poslednjih šest meseci praćenja (dvofaktorska analiza varijanse sa ponovljenim merenjem, faktor vreme × vrsta terapije; $p = 0{,}030$). **Zaključak.** Primarna ALT jednako uspešno, kao i primarna medikamentna terapija, reguliše IOP i postiže stabilnost perimetrijskog nalaza kod bolesnika sa glaukomom otvorenog ugla.

Ključne reči:
glaukom; lečenje; lekovi; lečenje laserom; trabekulektomija; lečenje, ishod.

Abstract

Introduction/Aim. Argon Laser Trabeculoplasty (ALT) is a recognized method for reducing intraocular pressure (IOP) in patients with open angle glaucoma. The aim of this study was to compare the effects of primary medicament therapy and primary ALT on IOP regulation and stability of perimetry findings. **Methods.** A total of 50 eyes of 35 patients were treated with primary ALT while 50 eyes of 36 patients were treated with primary medicament therapy with 0.5% timolol with 20, 0.005% latanoprost 18 and with 2% dorzolamid 12 eyes. IOP was controled at 3 months, and the visual field at 6 months during a 30-month follow-up period. **Results.** In the first 24 months of follow-up there was no statistically significant difference in percentage of eyes with successfully regulated IOP. At 27th and 30th month, in the group primarily treated with medicaments a statistically significant higher percentage of successfully regulated IOP was observed in 98%, and 96% of the eyes, respectively, while in the group primarily treated with ALT the decline in the percentage of successfully regulated IOP was observed in 78% and 76% of the eyes, (χ^2-test, $p = 0.002$, $p = 0.140$). Both therapy groups showed stability of perimetry findings without statistically significant difference in the values of mean deviation (MD) index until the end of the monitoring period. The dynamics of change in MD index value showed a statistically significant greater decline in this parameter in subjects who had been primarily treated with medications during the last six months of follow-up, (two-factor analysis of variance with a repeated measurment, factor of time × type of therapy, $p = 0.030$). **Conclusion.** Primary ALT equally successfully regulates IOP and restores stability of perimetry findings in patients with open angle glaucoma like the primary medicament therapy.

Key words:
glaucoma; therapeutics; pharmaceutical preparations; laser therapy; trabeculectomy; treatment outcome.

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Uvod

Argon-laser trabekuloplastika (ALT) je priznata metoda fotokoagulacije za sniženje intraokularnog pritiska (IOP) kod bolesnika sa glaukomom otvorenog ugla. Iako se prvo pominjanje ALT vezuje za Krasnova [1] 1973. i Worthen-a i Wickham-a [2] 1974, može se reći da su ALT u širu upotrebu uveli Wise i Witter [3] 1979. godine. Ranija teorija da mikro ožiljci na mestima fotokoagulacijske tkivne nekroze dovode do redukcije prečnika unutrašnjeg trabekularnog prstena, širenja kolabirane trabekularne mreže i povećanja lakoće oticanja očne vodice [4] danas je dopunjena saznanjem da fotokoagulacijski procesi dovode do specifičnog pokretanja biološke kaskade događaja, stimulacije deobe trabekularnih ćelija i aktivacije endotelnih ćelija sa obnavljanjem ekstracelularnog matriksa, što rezultira povećanjem lakoće oticanja očne vodice [5–7]. Bolesnicima kod kojih nije postignuto zadovoljavajuće sniženje IOP, uprkos maksimalnoj medikamentnoj terapiji, pre donošenja odluke o izvođenju filtracione operacije, predlagana je ALT. Svoje mesto ALT, danas, sve više nalazi kao primarna terapija, posebno kod starijih bolesnika, ako postoje kontraindikacije za primenu lekova i loša komplijansa, čime se izbegava neželjeno dejstvo medikamenata i rizik od hirurške intervencije [8, 9]. Cilj rada bio je da se uporede efekti primarne medikamentne terapije i primarne ALT na sniženje IOP i analizira stabilnost perimetrijskog nalaza kod bolesnika sa glaukomom otvorenog ugla.

Metode

Analizirano je 100 očiju 71 bolesnika sa utvrđenom dijagnozom glaukoma otvorenog ugla lečenih u Klinici za očne bolesti Kliničkog centra u Kragujevcu. Metodom slučajnog izbora ispitanici su podeljeni u dve grupe. Prva grupa od 35 bolesnika, odnosno 50 očiju, lečena je primarnom ALT. Kod 15 bolesnika urađena je primarna ALT obostrano, dok je kod 20 bolesnika sa pseudoeksfolijativnim glaukomom (XFG) i pigmentnim glaukomom lečeno samo jedno oko. Druga grupa od 36 bolesnika, odnosno 50 očiju, lečena je primarnom medikamentnom terapijom. Kod 14 bolesnika terapija je uvedena obostrano, dok je kod 22 bolesnika (XFG i pigmentni glaukom) lečeno samo jedno oko. Obavljen je detaljan oftalmološki pregled koji je obuhvatio određivanje vidne oštrine, pregled na biomikroskopu, aplanacionu tonometriju, gonioskopiju, stereoskopski pregled papile vidnog živca i sloja retinalnih nervnih vlakana na biomikroskopu indirektnom tehnikom (lupa 90D) ili direktnom tehnikom (centralnim staklom Goldmanovog kontaktnog stakla), perimetriju (Humphrey perimetar, program Threshold 30–2). Utvrđeni su specifični kriterijumi za uključivanje u ispitivanje i to novotkriveni glaukom otvorenog ugla tipa primarnog glaukoma otvorenog ugla i sekundarni glaukom otvorenog ugla (XFG i pigmentni glaukom), IOP > 21 mmHg, glaukomna promena papile vidnog živca ili prisutni glaukomni ispadi u vidnom polju potvrđeni u dva uzastopna perimetrijska nalaza i starost bolesnika ≥ 50 godina.

Iz ispitivanja su bili isključeni bolesnici sa promenama kao što su uznapredovale promene na papili vidnog živca i u vidnom polju, izmerene vrednosti IOP > 28 mmHg, bolesnici sa prethodno izvedenim operacijama na oku (afakija, pseudofakija, filtracione operacije i sl), bolesnici kod kojih se očekuje neka okularna hirurška intervencija, bolesnici sa kornealnim oboljenjima koja ometaju vizualizaciju trabekularne mreže komornog ugla i precizno merenje IOP, monokularni bolesnici, oni sa ambliopijom, visokom miopijom i bolesnici na sistemskoj ili lokalnoj kortikosteroidnoj terapiji, kao i bolesnici sa oboljenjima koja bi mogla zahtevati kortikosteroidno lečenje u toku perioda praćenja.

Argon laser trabekuloplastika izvođena je na aparatu Visuals 532 (Zeiss) u lokalnoj anesteziji (tetrakain). Pečati su aplikovani uz pomoć Goldman-ovog gonioskopskog stakla sa antirefleksnim slojem na granici između prednjeg pigmentovanog i zadnjeg nepigmentovanog dela trabekuluma, neposredno ispred Schlemm-ovog kanala sa standardnim podešavanjem aparata. Veličina spota bila je 50 μm, ekspoziciono vreme 0,1 s, a upotrebljena snaga je individualno dozirana do postizanja željenog efekta (500–850 mW). Optimalnom reakcijom smatrano je nastajanje izbeljivanja ili pojava mehurića vazduha u tretiranom području trabekularne mreže. Aplikovano je po 50 pečata u donjih 180° komornog ugla i to u smeru kazaljki na satu. U cilju prevencije skoka IOP indukovanog laserom, bolesnici su na dan intervencije i sutradan dobijali *per os* tablete acetazolamida od 250 mg, 2 puta dnevno. U cilju smanjenja inflamatornog odgovora prednjeg očnog segmenta ordinirane su lokalno kortikosteroidne kapi, 4 puta dnevno, sedam dana od intervencije. Kontrola IOP, kao i pregled prednjeg segmenta oka na biomikroskopu ponovljeni su posle 24 h i 7 dana od izvođenja intervencije.

Druga grupa (36 bolesnika, odnosno 50 očiju) lečena je primarnom medikamentnom terapijom. U zavisnosti od kliničkih karakteristika bolesnika, prisustva odnosno odsustva sistemskih bolesti, prisustva, alergije na neku od komponenti leka bolesnici su primarno lečeni: 20 očiju sa 0,5% timololom dva puta dnevno, 18 očiju sa 0,005% latanoprostom u jednoj večernjoj dozi i 12 očiju 2% dorzolamidom tri puta dnevno. U obe posmatrane grupe IOP je kontrolisan na tri meseca do kraja 30-mesečnog perioda posmatranja u prepodnevnim časovima u isto vreme (razlika 1–2 sata u merenju) kako bi se izbegle velike dnevne varijacije IOP prilikom merenja. U toku posmatranog perioda beležena je pojava svih neželjenih efekata ALT i medikamenata.

Rezultati su prikazani kao aritmetička sredina, standardna devijacija i medijana. Primenom *t*-testa za nezavisne uzorke, analizirali smo srednje vrednosti dve grupe ispitanika sa graničnom vrednošću za prihvatanje hipoteze o postojanju međuzavisnosti na $p < 0,05$. Kada su se podaci ponašali prema raspodeli različitoj od normalne korišćen je Mann Whitney-ev *U*-test. Fridman-ov test korišćen je za testiranje dinamike promene vrednosti parametara. Za poređenje vrednosti parametra između dva vremena merenja korišćen je Wilcoxon-ov test ekvivalentnih parova. Pirson-ovim χ^2 testom registrovan je nivo asimptotske značajnosti za postojanje međuzavisnosti testiranog obeležja i ishoda. Granična vrednost za prihvatanje hipoteze o postojanju međuzavisnosti između testiranih varijabli postavljena je na $p < 0,05$. U cilju izvođenja neophodnih statističkih testiranja korišćen je statistički programski paket SPSS for Windows (17.0).

Rezultati

Prosečno životno doba ispitanika u grupi primarno lečenih ALT iznosilo je 64,97 ± 6,32 godina (51–74 godine), dok je u grupi primarno lečenih medikamentnom terapijom iznosilo 65,08 ± 5,03 godina (52–74 godine). Nije utvrđena statistički značajna razlika u starosti između ispitivanih grupa bolesnika (*t*-test $p = 0{,}934$). Ispitivanjem je bilo obuhvaćeno više muškaraca nego žena i to u grupi primarno lečenih ALT 22 muškarca (62,9%) i 13 žena (37,1%), a u grupi primarno lečenih medikamentnom terapijom 24 muškarca (66,7%) i 12 žena (33,3 %). Uočena razlika nije bila statistički značajna (χ^2-test, $p = 0{,}737$). Između posmatranih grupa nije utvrđena statistički značajna razlika u zastupljenosti pojedinih vrsta glaukoma. U grupi primarno lečenih ALT, 30 (60%) očiju imalo je primarni glaukom otvorenog ugla (POAG), 18 (36%) očiju XFG, a kod dva slučaja (4%) nađen je pigmentni glaukom. U grupi primarno lečenih medikamentnom terapijom 28 (58%) očiju imalo je POAG, 21 (42%) oko XFG, a u jednom (2%) slučaju postojao je pigmentni glaukom (χ^2-test; $p = 0{,}729$). U obe grupe najveći broj ispitanika imalo je POAG, a najmanje su bili zastupljeni ispitanici sa pigmentnim glaukomom.

Između posmatranih grupa nije utvrđena statistički značajna razlika u prosečno izmerenim vrednostima IOP pre započinjanja lečenja. U grupi lečenih primarnom ALT vrednost IOP je iznosila 25,20 ± 0,81 mmHg, dok je u grupi primarno lečenih medikamentima iznosila 25,46 ± 1,09 mmHg (Mann Whitney-ev *U*-test, $p = 0{,}287$). Prvih 18 meseci praćenja nije uočena statistički značajna razlika u izmerenim vrednostima IOP između posmatranih grupa. Dobijene prosečne vrednosti IOP nakon 3, 6, 9, 12, 15 i 18 meseca u grupi lečenih primarnom ALT iznosile su 17,88 ± 1,69, 17,64 ± 1,55, 17,82 ± 1,65, 18,00 ± 1,99, 18,18 ± 2,00 i 18,60 ± 1,76 mmHg, dok su u grupi primarno lečenih medikamentima iznosile 18,04 ± 1,73, 17,92 ± 1,56, 17,84 ± 2,38, 17,76 ± 1,46, 17,82 ± 1,56 i 17,94 ± 1,53 mmHg. Dve godine nakon izvođenja primarne ALT, odnosno započinjanja primarne medikamentne terapije, uočena je statistički značajna razlika u postignutim prosečnim vrednostima IOP među posmatranim grupama. Viša prosečna vrednost IOP zabeležena je u grupi primarno lečenih ALT, 18,88 ± 2,26 mmHg, dok je u grupi primarno lečenih medikamentima iznosila 17,80 ± 1,40 mmHg (Mann Whitney-ev *U*-test, $p = 0{,}028$). Statistički značajna razlika održavala se do kraja posmatranog perioda, tako da je nakon 27 meseci praćenja izmerena prosečna vrednost IOP u grupi lečenih primarnom ALT iznosila 19,14 ± 1,96 mmHg, a u grupi primarno lečenih medikamentima 17,80 ± 1,51 mmHg (Mann Whitney-ev *U*-test, $p = 0{,}000$). Nakon 30 meseci, u grupi lečenih primarnom ALT prosečna vrednosti IOP bila je 19,32 ± 2,06 mmHg, a u grupi primarno lečenih medikamentima 17,78 ± 1,67 mmHg (Mann Whitney-ev *U*-test, $p = 0{,}000$). Analizom dobijene razlike utvrđeno je da su vrednosti ovog parametra bile više kod ispitanika kod kojih je rađena primarna ALT (tabela 1).

Vrednosti IOP razlikovale su se statistički značajno između analiziranih vremena praćenja, tokom posmatranog 30-mesečnog perioda u grupi koja je lečena primarnom ALT (Fridman-ov test, $p = 0{,}000$). Tokom prvih šest meseci vrednosti IOP smanjivale su se statistički značajno (Wilcoxon-ov test, $p = 0{,}000$), a onda je zabeležen porast vrednosti IOP. U periodu 24–30 meseci zabeležen je statistički značajan porast IOP između analiziranih vremena praćenja i to u periodu do 27 meseci (Wilcoxon-ov test, $p = 0{,}012$) i do kraja 30-mesečnog perioda praćenja (Wilcoxon-ov test, $p = 0{,}001$) (tabela 1).

Kod primarno medikamentno lečenog glaukoma, zapaža se statistički značajan pad vrednosti IOP tokom 30-mesečnog perioda praćenja (Fridman-ov test, $p = 0{,}000$). Statistički značajan pad vrednosti IOP u ovoj grupi zabeležen je tokom prva tri meseca (Wilcoxon-ov test, $p = 0{,}000$). Do kraja posmatranog perioda vrednosti IOP samo su se blago menjale u odnosu na vrednosti postignute u trećem mesecu, bez statistički značajne razlike (tabela 1).

Tabela 1
Promene intraokularnog pritiska (IOP) posle određenog perioda praćenja

Period praćenja (meseci)	IOP (mmHg), $\bar{x} \pm SD$		*p*
	grupa lečena ALT	grupa lečena medikamentima	
Pre početka terapije	25,20 ± 0,81	25,46 ± 1,09	0,287
3	17,88 ± 1,69	18,04 ± 1,73	0,649
6	17,64 ± 1,55	17,92 ± 1,56	0,190
9	17,82 ± 1,65	17,84 ± 2,38	0,887
12	18,00 ± 1,99	17,76 ± 1,46	0,971
15	18,18 ± 2,00	17,82 ± 1,56	0,491
18	18,60 ± 1,76	17,94 ± 1,53	0,054
24	18,88 ± 2,26	17,80 ± 1,40	0,028*
27	19,14 ± 1,96	17,80 ± 1,51	0,000*
30	19,32 ± 2,06	17,78 ± 1,67	0,000*

***statistički značajna razlika između grupa; ALT – argon-laser trabekuloplastika**

Uspešnost lečenja definisali smo postizanjem IOP ≤ 21 mmHg. U tabeli 2 prikazan je % očiju sa uspešno regulisanim IOP, po mesecima i grupama u odnosu na zadati kriterijum. Mesec dana od započinjanja posmatranja analizirana je uspešnost lečenja samo u grupi primarno lečenih ALT. Intraokularni pritisak regulisan je samo kod 24% očiju. Tokom tri i šest meseci IOP u obe grupe bio je regulisan kod 92% očiju (χ^2-test, $p = 1{,}000$). Nakon 9, 12, 15, 18 i 24 meseca od izvođenja primarne ALT, IOP bio je regulisan kod 92%, 86%, 86% i 88% očiju, respektivno, dok je u grupi primarno

lečenih medikamentnom terapijom zabeležen veći procenat očiju sa uspešno regulisanim IOP, 94%, 96%, 94% i 96% respektivno, ali bez statistički značajne razlike prema grupi lečenoj ALT (χ^2-test, $p = 0,695$, $p = 0,081$, $p = 0,182$, $p = 0,140$ respektivno). Posle 27. meseca u grupi lečenoj medikamentno uočen je statistički značajno veći procenat očiju sa uspešno regulisanim IOP (98%), dok je u grupu primarno lečenih ALT uočeno opadanje procenta uspešno regulisanog IOP, 78% očiju; (χ^2-test, $p = 0,002$). Nakon 30 meseci IOP je bio regulisan kod 96% očiju u grupi primarno lečenih medikamentnom terapijom, što je bilo statistički značajno više u odnosu na grupu primarno lečenih ALT kod kojih je IOP uspešno regulisan kod 76% očiju (χ^2-test, $p = 0,004$) (tabela 2).

Tabela 2

Procenat očiju sa uspešno regulisanim intraokularnim pritiskom (IOP) tokom perioda posmatranja

Vreme praćenja (meseci)	Uspešno regulisan IOP	Analizirane grupe		p (χ^2-test)
		lečena ALT n (%)	lečena medikamentima n (%)	
1	Da	12 (24,0)	/	/
	Ne	38 (76,0)	/	
3	Da	46 (92,0)	46 (92,0)	1,000
	Ne	4 (8,0)	4 (8,0)	
6	Da	46 (92,0)	46 (92,0)	1,000
	Ne	4 (8,0)	4 (8,0)	
9	Da	46 (92,0)	47 (94,0)	0,695
	Ne	4 (8,0)	3 (6,0)	
12	Da	43 (86,0)	48 (96,0)	0,081
	Ne	7 (14,0)	2 (4,0)	
18	Da	43 (86,0)	47 (94,0)	0,182
	Ne	7 (14,0)	3 (6,0)	
24	Da	44 (88)	48 (96,0)	0,140
	Ne	6 (12)	2 (4,0)	
27	Da	39 (78)	49 (98)	0,002*
	Ne	11 (22)	1 (2)	
30	Da	38 (76)	48 (96,0)	0,004*
	Ne	12 (24)	2 (4,0)	

***statistički značajna razlika između grupa; ALT – argon-laser trabekuloplastika**

Efikasnost primarne ALT i primarne medikamente terapije u usporavanju i zaustavljanju progresije glaukoma otvorenog ugla procenjivana je na osnovu stabilnosti perimetrijskog nalaza. Vidno polje testirano je statičkom konvencionalnom perimetrijom na aparatu Humphrey, programom Threshold 30–2 pre započinjanja lečenja i na šest meseci do kraja posmatranog perioda. Promene vidnog polja procenjivane su na osnovu vrednosti indeksa MD. Indeks MD je vrednost prosečnog gubitka vidnog polja i predstavlja razliku između utvrđene prosečne senzitivnosti i srednje vrednosti normalne senzitivnosti za dato godište. Vrednosti indeksa MD kod 95% normalne populacije kreću se u rasponu od -2,4 dB do +2,4 dB ± 2 SD i rezultat su normalnih varijacija senzitivnosti retine. Naši rezultati prikazani su u tabeli 3.

Vrednosti indeksa MD pre započinjanja lečenja nisu se statistički značajno razlikovale među posmatranim grupama. U grupi primarno lečenih ALT iznosile su -3,10 ± 0,51 (-2,98) dB [($\bar{x}$ ± SD (Med)], dok su u grupi primarno lečenih medikamentnom terapijom iznosile -3,09 ± 0,45 (-3,12) dB (t-test, $p = 0,875$). Vrednosti indeksa MD na 6, 12, 18, 24 i 30 meseci od izvođenja primarne ALT iznosile su -3,14 ± 0,49 (-2,98) dB, -3,14 ± 0,45 (-3,075) dB, -3,23 ± 0,46 (-3,12) dB, -3,15 ± 0,45 (-3,025) dB i -3,23 ± 0,47 (-3,24) dB, dok su u grupi primarno lečenih medikamentnom terapijom iznosile -3,16 ± 0,46 (-3,27) dB, -3,15 ± 0,42 (-3,13) dB, -3,15 ± 0,42 (-3,13) dB, -3,18 ± 0,42 (-3,15) dB i -3,39 ± 0,49 (-3,46) dB i nisu se statistički značjno razlikovale (t-test, $p = 0,840$, $p = 0,978$, $p = 0,647$, $p = 0,763$ i $p = 0,102$, respektivno). Utvrđena je stabilnost perimetrijskog nalaza u obe grupe do kraja posmatranog perioda. Posmatranjem dinamike promene indeksa MD utvrđeno je da se vidno polje u obe grupe očiju tokom 30-mesečnog perioda praćenja statistički značajno menjalo (dvofaktorska analiza varijanse sa ponovljenim merenjem, faktor vreme, $p = 0,000$). Dinamika promene vrednosti vidnog polja statistički značajno se razlikovala između posmatranih grupa (dvofaktorska analiza varijanse sa ponovljenim merenjem, faktor vreme × vrsta terapije; $p = 0,030$). Analizom dobijene razlike zapažen je statistički značajno veći pad vrednosti indeksa MD kod ispitanika koji su primarno lečeni medikamentima. Najveća razlika između grupa, u promeni vrednosti indeksa MD zapažena je tokom poslednjih šest meseci praćenja. Trideset meseci od izvođenja primarne ALT indeks MD pokazuje prosečno sniženje od -0,13 dB u odnosu na početne vrednosti, dok je u grupi primarno lečenih medikamentima prosečno sniženje indeksa MD u odnosu na početne vrednosti iznosilo -0,30 dB (tabela 3).

Tokom istraživanja praćena je i pojava neželjenih efekata ALT. Najozbiljnija komplikacija ALT je akutni skok IOP indukovan laserom. Vrednosti IOP analizirane su 24 h od intervencije. Skok IOP zabeležen je kod 56% očiju. Uočena razlika bila je statistički značajna (χ^2-test, $p = 0,000$). Prosečan skok IOP kod očiju kod kojih je zabeležen skok IOP indukovan laserom 24 h nakon intervencije iznosio je 1,18 ± 0,39 mmHg, odnosno za 4,75 ± 1,55% više od početnih vrednosti. Skok IOP je tranzitornog karaktera i ne beleži

Tabela 3

Promene vidnog polja (indeks MD) tokom perioda praćenja

Period raćenja (meseci)	Indeks MD (dB), $\bar{x} \pm SD$ (medijana)		*p* (*t*-test)
	grupa lečena ALT	grupa lečena medikamentima	
Pre početka terapije	-3,10 ± 0,51 (-2,98)	-3,09 ± 0,45 (-3,12)	0,875
6	-3,14 ± 0,49 (-3,075)	-3,16 ± 0,46 (-3,27)	0,840
12	-3,14 ± 0,45 (-2,98)	-3,15 ± 0,42 (-3,13)	0,978
18	-3,23 ± 0,46 (-3,12)	-3,19 ± 0,47 (-3,25)	0,647
24	-3,15 ± 0,45 (-3,025)	-3,18 ± 0,42 (-3,15)	0,763
30	-3,23 ± 0,47 (-3,24)	-3,39 ± 0,49 (-3,46)	0,102

Indeks MD – vrednost prosečnog gubitka vidnog polja; ALT – argon-laser trabekuloplastika

se sedam dana nakon intervencije, kada su izmerene prosečne vrednosti IOP za 0,16 ± 0,71 mmHg niže od početnih.

Analizirano je prisustvo uvealne reakcije 24 h i sedam dana nakon izvođenja primarne ALT. Uvealna reakcija uočena je kod 8% slučajeva, 24 h od intervencije, dok sedam dana od intervencije nije uočena ni u jednom slučaju.

U grupi lečenih primarnom ALT, do kraja posmatranog perioda 12 očiju (24%) imalo je potrebu za dodatnom medikamentnom terapijom radi regulacije IOP, dok je u grupi primarno medikamentno lečenih bolesnika kod 2 oka (4%) bilo potrebno uvesti još jedan leka radi regulacije IOP.

Diskusija

U ovom istraživanju poredili smo uticaj primarne ALT i primarne medikamentne terapije na sniženje IOP i stabilnost perimetrijskog nalaza kod novootkrivenih glaukoma otvorenog ugla bez uznapredovalih promena na papili vidnog živca i u vidnom polju. Naše istraživanje pokazalo je da su inicijalno obe metode jednako efikasne za sniženje vrednosti IOP, pri čemu je u grupi primarno lečenih ALT uočena pojava opadanja efikasnosti tokom perioda posmatranja. Prvih 18 meseci praćenja nije uočena statistički značajna razlika u prosečno izmerenim vrednostima između posmatranih grupa, a od 24. meseca, pa do kraja posmatranog perioda zabeleženo je statistički značajnije sniženje IOP u grupi primarno lečenih medikamentnom terapijom. Grupa primarno medikamentno lečenih ispitanika pokazala je statistički značajan pad vrednosti IOP tokom svih 30 meseci praćenja sa blagim fluktuacijama, bez statistički značajne razlike. Nasuprot tome, u grupi primarno lečenih ALT uočen je trend opadanja efikasnosti tokom perioda posmatranja. Prvih šest meseci vrednosti IOP smanjivale su se statistički značajno, da bi tokom 24–30 meseci došlo do statistički značajnog porasta IOP. Naši rezulti ukazuju na to da je primarna ALT prvih osamnaest meseci jednako efikasna kao i primarna medikamentna terapija i kao takva predstavlja dobru alternativu medikamentnoj terapiji (*Glaucoma Laser Trial/Glaucoma Laser Trial Follow up Study* [10]). Nakon tog perioda zabeleženo je opadanje efikasnosti ALT. Postignuta redukcija IOP u grupi medikamentno lečenih bolesnika u saglasnosti je sa rezulatatima van der Valka i sar. [11, 12].

Imajući u vidu činjenicu da je zadati kriterijum u postizanju IOP ≤ 21 mmHg u prvih devet meseci praćenja u obe posmatrane grupe postignut kod preko 90% bolesnika, može se zaključiti da obe posmatrane grupe inicijalno pokazuju jednaku efikasnost na sniženje IOP. Do kraja 30-mesečnog perioda praćenja, u grupi primarno lečenih medikamentima vrednost IOP ≤ 21 mmHg postignuta je kod 96% slučajeva i samo kod 2 (4%) slučaja bilo je potrebe za dodatnom medikamentnom terapijom, dok je u grupi primarno lečenih ALT vrednost IOP ≤ 21 mmHg nakon 18 meseci postignuta kod 86% slučajeva, da bi do kraja posmatranog perioda ona bila postignuta kod njih 76%, odnosno 12 (24%) očiju imalo je potrebe za dodatnom medikamentnom terapijom.

Mnoge studije potvrdile su povoljan efekat ALT na sniženje IOP kod glaukoma otvorenog ugla [13], ali i opadanje efikasnosti tokom perioda praćenja [14]. Kriterijumi uspešnosti intervencije, kao i procenat uspešnosti variraju među studijama, tako da nakon prve godine iznose 70–90% [15, 17]. Weinreb i sar. [18] nalaze da je nakon pet godina praćenja ALT efikasna kod 50% slučajeva, sa stopom opadanja od 6% do 10% godišnje. Može se zaključiti da ALT može biti dobra alternativa medikamentnoj terapiji, ali zbog slabljenja efikasnosti zahteva brižljivo kontrolisanje bolesnika nakon izvođenja terapije.

Imajući u vidu rezultate CIGTS, naši rezultati ukazuju na stabilnost perimetrijskog nalaza u obe grupe do kraja posmatranog perioda [19, 20]. Između posmatranih grupa nije uočena statistički značajna razlika u vrednosti indeksa MD ni u jednom vremenu merenja. Trideset meseci od izvođenja primarne ALT vrednost indeksa MD pokazuje prosečno smanjenje od -0,13 dB u odnosu na početne vrednosti, dok u grupi primarno lečenih medikamentima vrednost indeksa MD pokazuje prosečno sniženje od -0,30 dB u odnosu na početne vrednosti. Ako se imaju u vidu rezultati studije *Early Manifest Glaucoma Trial* [21] u kojoj je zabeležen prosečan pad vrednosti indeksa MD od 0,03 dB mesečno, odnosno 0,36 dB godišnje, kod bolesnika u početnoj fazi bolesti i na medikamentnoj terapiji, možemo zaključiti da znaci progresije razvoja defekata u vidnom polju nisu uočeni ni u jednoj od posmatranih grupa. Imajući u vidu da sniženje IOP za svaki mmHg u odnosu na početne vrednosti redukuje rizik od nastajanja progresije za 10% [21], opravdano je zaključiti da su obe metode efikasne u redukovanju rizika od nastanka progresije bolesti.

Metode ALT je bezbedna, jednostavna za izvođenje, jednokratna, ambulantna metoda koju ne prate teške komplikacije. Prednost primarne ALT u odnosu na medikamentnu terapiju je jednokratno izvođenje intervencije koja većini bole-

snika omogućava da budu nekoliko godina bez lokalne medikamentne terapije, čime se prevazilaze neželjeni efekti lekova, umanjuje cena lečenja, poboljšava kvalitet života bolesnika i prevazilaze problemi vezani za komplijansu [22–24]. U našem istraživanju uočen je tranzitorni, akutni, laserom indukovani skok IOP kod 56%, očiju 24 h nakon intervencije, koji je iznosio svega 1,18 ± 0,39 mmHg. Ovako blag skok IOP je verovatno razlog za preventivnu upotrebu tableta acetazolamida na dan inervencije i sutradan. Uvealna rekcija uočena je kod 8% očiju 24 h od intervencije uz potpuno povlačenje sedam dana nakon intervencije. Drugi neželjeni efekti nisu zapaženi.

Zaključak

I primarna medikamentna i primarna ALT jednako su efikasne za snižavanje IOP i postizanje stabilnosti perimetrijskog nalaza. Primarna ALT može biti dobra alternativa za primarnu medikamentnu terapiju kod većine novootkrivenih glaukoma otvorenog ugla jer bezbedno i efikasno snižava IOP, bez teških neželjenih efekata. Neželjene strane ALT su slabljenje efekata tokom vremena i nemogućnost ponavljanja lečenja zbog strukturnih promena trabekularne mreže komornog ugla, pa se savetuje pažljivo praćenje bolesnika nakon izvođenja intervencije.

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Evaluation of body mass index and lipid fractions levels in patients with retinal artery occlusion

Evaluacija indeksa telesne uhranjenosti i lipidnih frakcija kod bolesnika sa okluzijom retinalne arterije

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Abstract

Background/Aim. There are studies stressing out that atherosclerosis is most common associated systemic condition in patients with retinal artery occlusion. The aim of this study was to analyze values of body mass index and lipid fractions in healthy individuals and patients with retinal artery occlusion. **Methods.** This study included 90 participants during a 6-year period. The population was divided into 2 groups: the group with the diagnosed retinal artery occlusion and the group without retinal artery occlusion. The observed parameters were as follows: body mass index, low and high density lipoproteins and triglycerides. **Results.** The study revealed no significant difference regarding body mass index and triglycerides values between the two evaluated groups, while low and high density lipoproteins values were significantly higher in the group of patients with retinal artery occlusion. **Conclusions.** The study demonstrated that body mass index and triglycerides have less important role in atherogenic pathogenesis of retinal artery occlusion, while low density lipoprotein is the fraction that is shown to be most potent in such etiological processes.

Key words:
arteriosclerosis; lipids; body mass index; retinal artery; arterial occlusive diseases.

Apstrakt

Uvod/Cilj. Studije svetskih autora ističu da je ateroskleroza najčešće sistemsko stanje udruženo sa okluzijom arterijskih krvnih sudova retine. Cilj ove studije bio je analiza vrednosti indeksa telesne mase i lipidnih frakcija kod zdravih osoba i bolesnika sa okluzijom retinalne arterije. **Metode.** Ova studija obuhvatila je 90 osoba tokom 6-godišnjeg perioda. Ispitanici su bili podeljeni u dve grupe: grupu sa dijagnostikovanom okluzijom retinalne arterije i grupu bez okluzije retinalne arterije. Ispitivani su sledeći parametri: indeks telesne mase, lipoproteini male i velike gustine i trigliceridi. **Rezultati.** Dobijeni rezultati pokazali su da ne postoji značajna razlika u vrednostima indeksa telesne mase i triglicerida između ispitivanih grupa, dok su lipoproteini male i velike gustine bili značajno povišeni kod osoba sa okluzijom retinalne arterije. **Zaključak.** Indeks telesne mase i trigliceridi imaju manju ulogu u procesima aterogeneze kod okluzije retinalnih arterija, dok su lipoproteini male gustine značajan faktor u procesu koji vodi okluzivnim promenama ovih krvnih sudova.

Ključne reči:
arterioskleroza; lipidi; telesna masa, indeks; a. centralis retinae; okluzija.

Introduction

Retinal vascular occlusions (RVO) are the second frequent retinal vascular disease seen in clinical practice in ophthalmology. Its frequency is estimated to approximately 1/10,000 outpatients visits [1]. Retinal artery occlusions (RAO) are important acute retinal vascular occlusive disorders and ophthalmic emergencies, associated with sudden and massive visual loss in middle-aged and elderly people and are highly associated with hypercholesterolemia, atherosclerosis, and hypertension [2, 3].

There are studies stressing out that atherosclerosis is most common associated systemic condition in patients with RAO [4]. It is also observed that risk factors for development

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of atherosclerotic lesions including hyperlipidemia, diabetes mellitus and arterial hypertension are associated with RAO [5].

The role and impact of low density lipoprotein (LDL) cholesterol in atherosclerosis processes was described by numerous epidemiological studies [6]. Protective effects of plasma high density lipoprotein (HDL) cholesterol by promoting reverse cholesterol transport and slowing vascular disease by blocking inflammation have been studied [7, 8].

Also, it is stressed out that overweight and obesity are strongly associated with development of atherosclerotic plaques [9, 10].

However, recent studies suggest that even though overweight and obesity are cardiovascular risk factors, they are not independently associated with carotid atherosclerosis [11].

The aim of this study was to analyze values of body mass index (BMI) and lipid fractions in healthy individuals and patients with RAO.

Methods

The study evaluated 90 participants during a 6-year period. The population was divided into 2 groups: the group with diagnosed RAO (group I) and the group that did not have RAO, or any other ophthalmological disease (group II). The group I included 50 participants treated at the Ophthalmology Clinic, Clinical Center of Serbia, Belgrade, while the second group included 40 adults with no RAO. Central retinal artery occlusion (CRAO) or brench retinal artery occlusion (BRAO) was diagnosed based on abrupt visual loss accompanied by one or more of the following signs as observed by slit-lamp biomicroscopy with 90 diopter or 78 diopter lens: sluggish, thinned retinal artery flow, fragmentation of the blood column in retinal arterioles, retinal opacification combined with sluggish retinal blood flow, and the presence of a cherry-red spot. Visual acuity tests by a Snellen chart under the same standard illumination, relative afferent pupillary defect, applanation tonometry, slitlamp biomicroscopy and funduscopy were performed. Two general parameters were analyzed: BMI and lipid fractions.

As one of the important risk factors for development of atherosclerosis and therefore occlusion of retinal artery, we analyzed separately each lipid fraction: LDL cholesterol, HDL cholesterol and triglycerides. Lipid fractions were analyzed separately in both groups of participants. Blood samples were taken in the morning before meal and with last meal not less than 12 hours from taking blood samples.

The study group was presented in terms of whole numbers and percents. To compare distribution of participants between the two groups we used the chi squared test.

The values for BMI, LDL cholesterol, HDL cholesterol and triglycerides were presented as mean with standard deviation (SD), and minimal and maximal values as well. To compare values of BMI, LDL cholesterol, HDL cholesterol and triglycerides between the evaluated groups we used the Student's *t*-test. A range interval between minimal and maximal values was presented in terms of whole numbers, while difference in values between the two evaluated groups was described as percents for each parameter. Statistical significance was defined as $p < 0.05$. Analyses were assessed in part using SPSS 16.0 for Windows.

Results

The study included 50 (55.56%) patients with the diagnosed RAO and 40 (44.44%) adults without RAO. There was no significant difference between the two groups regarding number of participants ($X^2 = 2.78$; $p > 0.05$). Table 1 shows the values of BMI and lipid fractions for both evaluated groups of participants. The obtained results pointed out that there was no statistically significant difference ($p > 0.05$) for BMI between the two evaluated groups.

Table 1

Body mass index (BMI) and lipid fractions values in the evaluated and the control group

Parameters	Group with RAO	Group without RAO	*p*
	$\bar{x} \pm SD$	$\bar{x} \pm SD$	
BMI (kg/m^2)	26.16 ± 3.77	24.87 ± 2.85	n. s.
LDL-C (mmol/L)	3.92 ± 1.32	2.87 ± 0.91	< 0.001
HDL-C (mmol/L)	1.43 ± 0.29	1.29 ± 0.27	< 0.05
Triglycerides (mmol/L)	2.02 ± 0.96	1.83 ± 0.82	n. s.

RAO – retinal artery occlusion; BMI – body mass index; LDL-C – low density lipoproteins cholesterol; HDL-C – high density lipoproteins cholesterol

Since different lipid fractions have different role in occlusion etiology, LDL cholesterol, HDL cholesterol and triglycerides were evaluated separately for both groups of participants. We demonstrated that there was a statistically significant difference ($p < 0.001$) between the two observed groups regarding LDL cholesterol values. The group of participants with the diagnosed RAO had higher levels of LDL cholesterol. Regarding HDL fraction of cholesterol, our results stresed out that there was a statistically significant difference ($p < 0.05$) when HDL cholesterol values were compared between two groups of participants. It was observed that higher values were in the group of patents with the diagnosed RAO. The obtained results for triglycerides values showed no statistically significant difference ($p > 0.05$) when these values were compared between two groups of participants.

Table 2 shows minimal and maximal values for BMI and each lipid fraction in both groups. Our survey stressed out that regarding each parameter there was a wider interval range in the group with RAO. For BMI and triglycerides this range augmentation was 60.54% and 63.31%, respectively, while for LDL and HDL fractions of cholesterol it was 42.63% and 56.73%, respectively.

Table 2

Minimal and maximal values of body mass index (BMI) and lipid fractions

Parameters	Group with RAO			Group without RAO		
	Minimal values	Maximal values	Range interval	Minimal values	Maximal values	Range interval
BMI (kg/m^2)	16.50	40.10	23.60	20.90	35.60	14.70
LDL-C (mmol/L)	1.80	7.12	5.32	1.25	4.98	3.73
HDL-C (mmol/L)	0.68	2.31	1.63	0.75	1.79	1.04
Triglycerides (mmol/L)	0.40	7.21	6.81	0.79	4.96	4.17

RAO – retinal artery occlusion; BMI – body mass index; LDL-C – low density lipoproteins cholesterol; HDL-C – high density lipoproteins cholesterol

Discussion

Retinal artery occlusion if not diagnosed timely, could lead to loss of vision. Beside numerous factors that have studied regarding RAO, atherosclerotic plaques are one of them that could cause vasoobliteration [12]. Therefore, evaluation and role of risk factors responsible for atherosclerotic lesion formation are important in determing their significance in RAO etiology.

Several studies that were conducted more than 3 decades ago noticed that the majority of patients with atherosclerotic changes of retinal blood vessels had atherosclerotic changes on other arteries as well [13, 14]. It should be pointed out that in these studies serum lipids were not analyzed.

Recent epidemiological studies demonstrated that the diameter of retinal arteriolar caliber is associated with elevated blood pressure and obesity and can be valuable in predicting incidence of diabetes and coronary heart disease [15]. Therefore, beside evaluation of risk factors for RAO, such entity is a valuable parameter of other risk factors that are responsible for cardiovascular diseases.

This study suggests that the group of patients with RAO had no significantly higher values of BMI and triglycerides as compared to those without occlusion. However, the range interval between minimal and maximal values was wider in patients with RAO, stressing out that such state can be diagnosed both in people that are categorized as underweight with BMI lower than 17 kg/m^2, as well in those that are obese with BMI over 40 kg/m^2. A wider range of values interval, that is more than 50%, in the group I of participants implicates heterogeneity of this population and with other findings stresses out that occlusion of retinal artery is not closely influenced by BMI and triglycerides.

Further, the group I of participants had significantly higher values of LDL cholesterol and HDL cholesterol than those without occlusive condition. For patients from the group I minimal values as well as maximal values regarding LDL cholesterol were higher than for the participants from the group II, while for HDL cholesterol only maximal values were higher. These findings clearly indicate that LDL cholesterol fraction is associated with occlusive disease of retinal artery. Such observations are in accordance with other studies [5]. This fact is demonstrated in our study also by a lower widening of range interval between minimal and maximal values (below 50%), pointing out less heterogeneity contrary to BMI, and even, HDL cholesterol findings. It is important to notice that even there is higher protective role of HDL cholesterol, speaking in terms of its higher values in the group I of participants, it is LDL cholesterol that is more atherogenic in the processes of occlusion.

Conclusion

This study demonstrated that certain factors such as BMI and triglycerides have less important role in atherogenic pathogenesis of retinal artery occlusion, while LDL cholesterol is the lipid fraction that is shown to be most potent in such etiological processes.

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Mehanička ventilacija kod bolesnika sa najtežim oblicima gripa A H1N1

Mechanical ventilation in patients with most severe forms of influenza A H1N1

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Apstrakt

Uvod/Cilj. Pandemija gripa izazvanog virusom A H1N1 zapažena je po naglom širenju, ali i po posledicama kao što je teška akutna respiratorna slabost koja zahteva mehaničku ventilaciju (MV) i intenzivno lečenje (IL). Cilj rada je bio da se ustanovi značaj primene MV i prisustva komorbiditeta na ishod bolesti kod obolelih sa teškim oblikom influence izazvane virusom A H1N1. **Metode.** U studiju bilo je uključeno pet bolesnika sa akutnom respiratornom insuficijencijom prouzrokovanom gripom A H1N1 koja je zahtevala MV. Tok i ishod lečenja posmatrani su u odnosu na uzrast i pol obolelih, prateća oboljenja, vreme pojave gripa, vreme prijema u odeljenje intenzivne terapije, vreme početka endotrahealne intubacije i MV, trajanje MV i pojavu sekundarnih infekcija. **Rezultati.** Tri ispitanika bila su na MV 39, 43, odnosno 20 dana i svi su preživeli. Umrla su dva ispitanika kod kojih je trajanje MV bilo značajno kraće (14 i 12 dana). Smrtni ishod objašnjen je fudroajantnim tokom bolesti i pratećim oboljenjima. Neočekivano, dužina MV pozitivno je korelisala sa preživljavanjem, iako se kod dva bolesnika koja su najduže bila na MV (43 i 39 dana), kao komplikacija razvila sekundarna bakterijska pneumonija. **Zaključak.** Intenzivno lečenje bolesnika sa respiratornom slabošću izazvanom virusom gripa A H1N1 zahteva MV koja se mora izvoditi shodno preporukama svetskih i evropskih foruma. Tome ide u prilog i neočekivano zapažanje da dužina trajanja MV negativno koreliše sa smrtnim ishodom. Intenzivno lečenje ovih bolesnika, posebno MV, zbog toga što može biti dugotrajno, zahteva specijalne anesteziološke timove, posebna, izolovana odeljenja za intenzivnu terapiju i visok stepen zaštite da bi se, kao u našoj studiji, potpuno izbeglo prenošenje infekcije na medicinsko osoblje.

Ključne reči:
virusne bolesti; grip A virus, podtip H1N1; disanje, mehaničko; lečenje, ishod.

Abstract

Background/Aim. Pandemic of A H1N1 influenza is noted for its rapid spreading and life-threatening consequences like acute respiratory distress syndrome (ARDS) which requires mechanical ventilation (MV) and intensive therapy (IT). The aim of the study was to determine the significance of mechanical ventilation application in the presence of comorbidities on the outcome of the disease and patients with severe forms of acute influenza caused by A H1N1 virus. **Methods.** Five patients with acute respiratory failure caused by A H1N1 influeza that required MV were included in the study. Course and outcome of the treatment were monitored in relation to age and sex of the patients, concomitant diseases, time of influenza beginning, a time of admittance in an intensive care unit, a time of an endotracheal intubation and MV beginning, MV duration and occurrence of secondary infections. **Results.** Three patients were on a very prolonged MV (39, 43 and 20 days, respectively) and they all survived. Two patients with a significantly shorter duration of MV (14 and 12 days, respectively) died because of a very severe clinical course and concomitant diseases. Unexpectedly, we found a positive correlation between duration of MV and survival although two patients, who were on MV for the longest period of time (43 and 39 days, respectively), developed, as a complication, secondary bacterial pneumonia. **Conclusion.** Intensive therapy of patients with ARDS due to A H1N1 influenza virus requires MV which should be carried out according to guidelines of international expert forums. That is in accordance with our unexpected observation on negative correlation between duration of MV and fatal outcome. Intensive treatment of these patients, specially MV, can be very prolonged and, therefore, requires specialized teams of anesthesiologists, separate, isolated intensive therapy units and high level of medical staff protection, as was the case in this study, so no member of medical staff was infected.

Key words:
virus diseases; influenza A virus, H1N2 subtype; high-frequency ventilation; treatment outcome.

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Uvod

Pandemija gripa uzrokovana virusom A H1N1 („svinjski grip") izazvala je brojne polemike među zdravstvenim stručnjacima kako u pogledu njene prevencije, tako i u pogledu lečenja i naglog širenja. U aprilu 2009, Ministarstvo zdravlja Meksika izvestilo je o porastu broja bolesnika sa teškom pneumonijom među mladima [1]. Novi oblik gripa identifikovan je i veoma brzo dobio pandemijski karakter [2]. Ova pandemija počela je na severnoj hemisferi tokom ranog proleća i za nekoliko nedelja smanjila intenzitet širenja [3], da bi se potom proširila na južnu hemisferu (Australija i Novi Zeland) sa skoro osam puta većim brojem bolesnika nego u SAD-u [4]. Prema jednom od poslednjih izveštaja Svetske zdravstvene organizacije (*World Heath Organization* – WHO), tokom 2009. godine (zaključno sa 7. februarom 2010. godine), novi oblik gripa A (H1N1) proširio se na više od 212 zemalja širom sveta, sa najmanje 15 292 smrtna ishoda [5]. Primećeno je da infekcija novim virusom influence (H1N1) ima progresivan tok i brzo zahvata donje respiratorne puteve. Često se razvijaju upale pluća, a kod težih oblika javlja se teška akutna respiratorna infekcija (*Severe acute respiratory infection* – SARI) [6]. Obično je izaziva akutni respiratorni distres sindrom (ARDS). Ovaj sindrom predstavlja najteži blik respiratorne slabosti koji se manifestuje brzim nastankom, rendgenološki uočljivim bilateralnim plućnim infiltratima (snežna mećava) i slabom oksigenacijom arterijske krvi (odnos parcijalnog pritiska kiseonika u arterijskoj krvi – PaO_2 i inspiratorne frakcije kiseonika – FiO_2, manji od 200). Tim bolesnicima neophodna je respiratorna podrška, odnosno primena mehaničke ventilacije (MV) u odeljenjima intenzivne terapije. Sa registrovanjem prvih slučajeva obolevanja od novog oblika gripa u Srbiji, sanitetska služba Vojske Srbije brzo je reagovala tako da je u Klinici za infektivne i tropske bolesti Vojnomedicinske akademije (VMA) u Beogradu formirano Odeljenje za intenzivnu terapiju (OIT), opremljeno ventilatorima, različitim sistemima za monitoring i ostalom opremom namenjenom za intenzivno lečenje bolesnika sa najtežim oblicima gripa. U OIT, pored infektologa, 24 h dnevno dežurala je anesteziološka ekipa (anesteziolog, anestetičar). Angažovana je epidemiološka služba i Odeljenje za kontrolu bolničkih infekcija VMA i stvoreni su preduslovi za sprečavanje intrahospitalnog širenja virusne infekcije i zaštite osoblja, shodno novim preporukama [6].

Cilj rada je bio da se ustanovi značaj primene MV i prisustva komorbiditeta na ishod bolesti kod obolelih sa teškim oblikom influence izazvane virusom A H1N1.

Metode

U prospektivnoj kliničkoj studiji ispitano je 5 bolesnika sa akutnom respiratornom slabošću uzrokovanom novim oblikom gripa koja je zahtevala MV. Ispitanici su lečeni u VMA, Beograd od 10. novembra 2009. do 12. marta 2010. godine. Kriterijumi za uključenje u studiju bili su: akutno febrilno stanje (> 38 °C), simptomi bolesti koji su vezani za grip (kašalj, mialgija, mučnina i povraćanje); akutna respiratorna slabost (tahipneja sa respiratornom frekvencijom > 30/minuti; dispneja; cijanoza; korišćenje pomoćne disajne muskulature); razvoj ARDS (nagli nastanak, bilateralni plućni inflitrati, $PaO_2/FiO_2 < 200$). Ovim bolesnicima uzimani su uzorci krvi za virusološku analizu (radi potvrde dijagnoze infekcije virusom H1N1) i odmah su smeštani u OIT u Klinici za infektivne i tropske bolesti. Potvrda infekcije virusom H1N1 izvođena je uobičajenim serološkim probama. Bolesnici sa znacima SARI su oksigenirani (inhalacija kiseonika putem maske za lice), a kod progresije respiratorne slabosti oni su endotrahealno intubirani i započeta je MV (ventilator Savina, Dreger, Nemačka). Prilikom intubacije i manipulacije bolesnicima poštovane su preporuke epidemiološke službe o zaštiti medicinskog osoblja prilikom rada sa zaraženima virusom gripa A H1N1 [7]. Primenjivana je ventilacija (*Intermitent Positive Pressure Ventilation* – IPPV) modom uz početni pritisak (*Positive End-Expiratory Pressure* – PEEP) od 5 cm H_2O koji je sukcesivno povećavan u zavisnosti od pogoršanja parametara oksigenacije (PaO_2), sa respiratornim volumenom od 6–8 mL/kg idealne telesne mase i vršnim pritiskom do 30 cm H_2O [8]. Kod svih bolesnika, pored perifernih venskih kanila, plasiran je centralni venski kateter (CVK) i arterijska linija za direktno merenje krvnog pritiska i uzimanja uzoraka arterijske krvi za gasne analize. Vršen je kontinuirani, 24-časovni monitoring vitalnih funkcija: EKG, krvni pritisak, pulsna oksimetrija, *end-tidal* CO_2, temperatura (GE AS/5 Monitori). Na svakih 60 minuta meren je centralni venski pritisak (CVP). Postavljeni su nazogastrična sonda i urinarni kateter uz satno merenje gastrične sukcije (do početka enteralne ishrane) i satne diureze. Uzorci arterijske krvi za gasne analize uzimani su i evidentirani tri puta dnevno (na 8 h). Radiografija grudnog koša vršena je svakog dana MV portabilnim rendgen aparatom. Laboratorijske analize (krvna slika, Astra 8) uzimane su svakodnevno. Prema razvoju kliničke slike, a najmanje dva puta nedeljno, uzimani su uzorci venske krvi iz CVK i nezavisne periferne vene na bakteriološke analize (hemokulture), dok je kod pojave sumnje na sekundarnu bakterijsku pneumoniju [9] vršena bronhoalveolarna lavaža (BAL) i uzimani su uzorci na bakteriološku analizu, uz hemokulture. Sekundarna bakterijska pneumonija dijagnostikovana je kao pojava visoke temperature (> 38,0 °C) uz groznicu, pojačan purulentni sputum, radiografskom potvrdom, uz pozitivne bakteriološke analize traheobronhijalnih aspirata.

Odluka o prijemu bolesnika u OIT donosila se na osnovu potvrđene dijagnoze gripa A H1N1, teškog opšteg stanja bolesnika, respiratorne slabosti – tahipneje (> 25 udaha/minuti), cijanoze, dispneje, pada saturacije tkiva kiseonikom ($SO_2 < 90\%$), hemodinamske nestabilnosti (tahikardija, bradikardija, hipotenzija). Kod ispitanika su praćeni demografski podaci (uzrast, pol), prateća oboljenja, vreme oboljevanja od gripa virusom A H1N1, vreme prijema u OIT, vreme endotrahealne intubacije i započinjanja MV, trajanje MV, pogoršanje zdravstvenog stanja (primenom *Sequential Organ Failure Assessment* – SOFA skoring sistem) [10], pojava sekundarnih infekcija, ishod lečenja, vreme otpusta iz OIT i vreme otpusta iz bolnice.

Rezultati

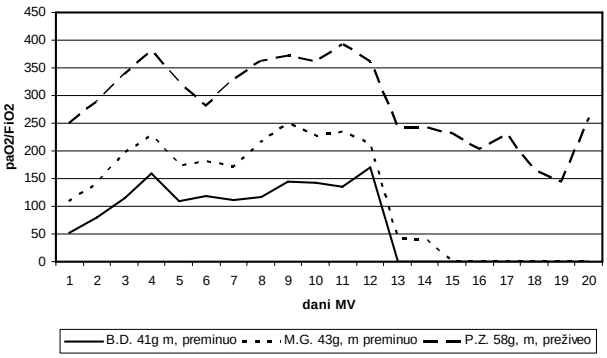
Od 10.11.2009. do 21.02.2010. godine u OIT Klinike za infektivne i tropske bolesti Vojnomedicinske akademije u Beogradu mehanički je ventilisano pet bolesnika sa teškim oblikom gripa izazvanog virusom influence A H1N1 i manifestnim ARDS.

U tabeli 1 prikazani su demografski podaci ispitanika, a u tabeli 2 prikazane su vrednosti telesne temperature, broj leukocita i neutrofila.

Dužina lečenja u OIT, trajanje MV i ishod lečenja dati su u tabeli 3.

Prema trajanju MV ispitanici su bili podeljeni u dve grupe: 1. MV kraća ili jednaka 20 dana i 2. MV duža od 20 dana (tabela 3).

Vrednosti oksigenacije (PaO_2/FiO_2) u prvoj grupi ispitanika date su na slici 1.



Sl. 1 – Vrednosti oksigenacije (PaO_2/FiO_2) u prvoj grupi ispitanika (MV ≤ 20 dana)
PaO_2 – parcijalni pritisak kiseonika u arterijskoj krvi; FiO_2 – inspiratorna frakcija kiseonika; MV – mehanička ventilacija

Tabela 1
Prikaz bolesnika prema polu, starosti, pratećim oboljenjima i ishodu lečenja

Inicijali bolesnika	Pol (m/ž)	Starost (god)	Komorbiditet	Ishod lečenja
Š. I.	m	39	Apendektomija pre šest godina	Preživeo
M.G.	m	43	Negira	Umro
P. Z.	m	58	Kardiomiopatija hron. kompenzovana; psihoza	Preživeo
B. D.	m	41	Infarkt miokarda pre 6 godina; hipertenzija; gojaznost	Umro
S. Lj.	ž	56	Cerebrovaskularni insult pre 4 g; psihoorganski sindrom	Preživela

Tabela 2
Zbirna tabela vrednosti temperature, leukocita i neutrofila kod ispitanika

Inicijali bolesnika	Telesna temperatura (0^C)	Leukociti ($\times 10^9$/L)	Neutrofili (%)
S. Lj.	37,3 ± 0,45	11,46 ± 4,53	80,52 ± 8,97
	36,2 – 38,1	4,3 – 22,7	50,9 – 94
	37,3	10,7	82,1
B. D.	37,7 ± 0,48	12,2 ± 4,7	80,6 ± 14,5
	37,9 – 39,3	3,56 – 18,7	49,8 – 91,6
	38,6	12,5	87,05
P. Z.	36,9 ± 0,47	10,4 ± 2,02	69,4 ± 8,57
	36,6 – 38,1	7,65 – 15,2	55,3 – 85,1
	36,9	10	69,25
Š. I.	37,3 ± 0,82	12,2 ± 2,96	82,9 ± 7,56
	36,5 – 39,5	6,57 – 23,4	65,6 – 94
	37,7	12	9
M. G.	39,3 ± 0,39	14,7 ± 2,14	86,6 ± 4,56
	38,9 – 40	9,59 – 17,4	77,9 – 96,8
	39,2	15,1	86,45

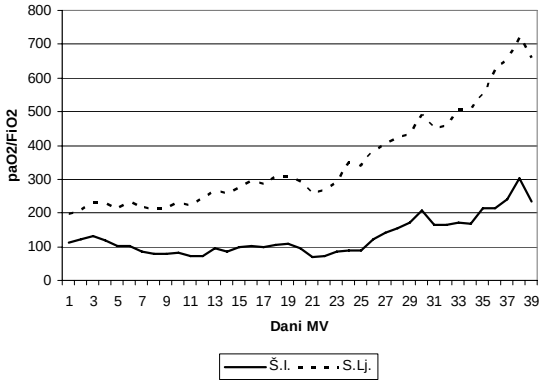
Svi parametri su dati u formi: prosečna vrednost ± standardna devijacija; minimalna vrednost – maksimalna vrednost; medijana

Tabela 3
Prikaz bolesnika prema dužini lečenja u Odeljenju intenzivne terapije (OIT), trajanju mehaničke ventilacije (MV) i ishodu lečenja

Inicijali bolesnika	Dužina lečenja u OIT (dani)	Trajanje MV (dani)	Ishod lečenja
Š. I.	64	39†	Preživeo
M. G.	15	14*	Preminuo
P. Z.	32	20*	Preživeo
B. D.	12	12*	Preminuo
S. Lj.	68	43†	Preživela

*** – 1. grupa ispitanika (MV ≤ 20 dana); † – 2. grupa ispitanika (MV > 20 dana)**

Vrednosti oksigenacije (PaO_2/FiO_2) u drugoj grupi ispitanika date su na slici 2.



Sl. 2 – Vrednosti oksigenacije (PaO_2/FiO_2) u drugoj grupi ispitanika (MV > 20 dana); oba ispitanika preživela
PaO_2 – parcijalni pritisak kiseonika u arterijskoj krvi; FiO_2 – inspiratorna frakcija kiseonika; MV – mehanička ventilacija

Učestalost komplikacija kod ispitanika prikazana je u tabeli 4.

Vrednosti SOFA skora prikazane su kod svih ispitanika na slici 3a prikazani su bolesnici sa trajanjem MV > 20 dana, dok su vrednosti ispitanika sa trajanjem MV ≤ 20 dana prikazane na slici 3b.

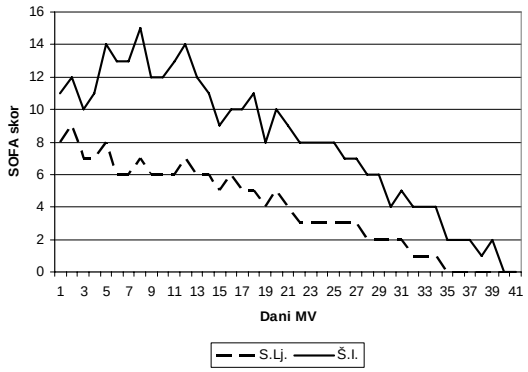
postoji uverenje da se radi o starijim bolesnicima, sa značajnim komorbiditetima. Međutim, u našoj grupi ispitanika radilo se o bolesnicima srednje starosti (od 39 do 58 godina). Teška prateća oboljenja imala su tri ispitanika (kardiomiopatija, preležan infarkt miokarda i cerebrovaskularni insult), od kojih su preživela dva, a preminuo je samo ispitanik sa preležanim infarktom miokarda (tabela 1).

Grip izazvan virusom A H1N1 kod ispitanika imao je tipičan, influenci sličan oblik (*Influenza like infection* – ILI) sa visokom temperaturom u početku (> 38 ºC), porastom broja leukocita (tabela 2), kašljem, slabošću i bolovima u mišićima, mučninom i povraćanjem, a potom naglim pogoršanjem stanja posle 4–5 dana i razvojem teške respiratorne infekcije (SARI). Ova respiratorna infekcija napredovala je do akutnog oštećenja pluća (*acute lung injury* – ALI), definisanog kao $PaO_2/FiO_2 < 300$ i akutnog respiratornog distres sindroma (ARDS), definisanog kao $PaO_2/FiO_2 < 200$, što se klinički maifestovalo tahipnejom (> 30 udisaja/minut), poremećajem svesti (somnolencija do gubika svesti) i padom saturacije krvi kiseonikom (< 90%). Slične nalaze opisali su i drugi autori [11].

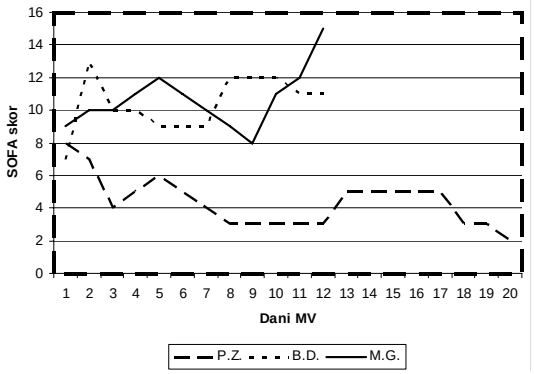
Vezano za MV, odmah po prijavljivanju prvog slučaja gripa izazvanog virusom A H1N1 u VMA Beograd oformljena je radna grupa infektologa i anesteziologa koja je učestvovala u pripremama za MV najtežih slučajeva. U Klinici

Tabela 4
Učestalost komplikacija kod ispitanika na mehaničkoj ventilaciji (MV)

Inicijali bolesnika	Trajanje MV (dani)	Sekundarna bakterijska pneumonija	Akutna bubrežna slabost	Ishod lečenja
Š. I.	39	+	–	Preživeo
M. G.	14	–	–	Preminuo
P. Z.	20	–	–	Preživeo
B. D.	12	–	+	Preminuo
S. Lj.	43	+	–	Preživela



Sl. 3a – *Sequential Organ Failure Assessment* (SOFA) skor kod ispitanika sa mehaničkom ventilacijom (MV) > 20 dana



Sl. 3b – *Sequential Organ Failure Assessment* (SOFA) skor kod ispitanika sa mehaničkom ventilacijom (MV) ≤ 20 dana

Diskusija

U prikazanoj grupi ispitanika (n = 5) jedna bolesnica bila je ženskog, a četiri bolesnika muškog pola. Prema dosadašnjem iskustvu u lečenju bolesnika sa posledicama influence u smislu respiratornih komplikacija i potrebe za MV, za infektivne i tropske bolesti formirano je OIT sa tri sobe i mogućnošću istovremenog lečenja do pet najtežih bolesnika, nabavljeni su novi ventilatori (Savina, Dreger, Nemačka), postavljeni monitoring sistemi (GE, AS 5) i ostala oprema. Bolesnici sa kliničkom slikom A H1N1 gripa lečeni su u izolatoru Klinike za infektivne i tropske bolesti VMA, a od-

mah po hospitalizaciji prvog bolesnika sa teškim oblikom gripa (14.11.2009. organizovano je 24-ovno stručno dežurstvo anesteziološke ekipe (anesteziolog specijalista, anesteziolog na specijalizaciji i respiratorni tehničar-anestetičar) koji su lečili bolesnike na MV od 17.11.2009. do 12.03.2010. godine (približno četiri meseca). Pre početka ove vanredne aktivnosti, kolegijum Klinike za anesteziologiju i intenzivnu terapiju više puta se sastajao, upoznao kolektiv i doneo smernice za način lečenja bolesnika sa teškim oblikom gripa, kao i za zašititu osoblja. Prilikom planiranja intenzivnog lečenja ovih bolesnika poštovane su savremene preporuke, posebno za izvodjenje MV: odluku o započinjanju MV donosi načelnik službe ili glavni dežurni anesteziolog; bolesnika endotrahealno intubira najiskusniji anesteziolog uz poštovanje mera zaštite od infekcije; MV se započinje pritiskom kontrolisanom ventilacijom, uz PEEP od 8–10 cmH_2O, respiratorni volumen 6 mL/kg idealne tm; održavanje „*driving*“ pritiska 14–18 cmH_2O i vršnim pritiskom do 30 cmH_2O. Kontinuirano su uzimani uzorci arterijske krvi za analizu i u slučaju pogoršanja hipoksemije, povećavane su vrednosti PEEP, primenjivani su miorelaksanti (mišićnom relaksacijom se smanjuje „sudaranje“ bolesnika sa ventilatorom i poboljšava MV), bolesnici su okretani na bok na svaka dva sata i primenjivan „rekrutman“ manevar (povremeno povećavanje i zadržavanje visokog pritiska u disajnim putevima i *Airway Pressure Realising Ventilation* – APRV). Stav naše Klinike (koji je u saglasnosti sa modernim preporukama za lečenje ARDS kod ovih bolesnika) jeste da se bolesnici kod kojih se primenjuje MV za lečenje drže na „suvoj strani“, odnosno da se izbegava njihovo prepunjavanje tečnostima, kako bi se izbegla transudacija tečnosti na alveolokapilarnoj membrani. Na sat vremena meren je CVP, a svakog jutra tzv. bilans tečnosti (odnos primljene i izgubljene tečnosti za 24 h) [6]. Na osnovu iznetih podataka može se zaključiti da je kod ispitanika MV izvođena istim ventilatorima, lečenje su izvodili različiti medicinski timovi, ali pod jednom komandom i po istoj medicinskoj doktrini koja je proveravana u svakodnevnim vizitama koje je vršio načelnik službe, tako da se može reći da je intenzivno lečenje, a pogotovo MV kod ispitanika izvođena na uniforman način.

U tabeli 3 prikazani su podaci o dužini lečenja ispitanika u OIT (od 12–64 dana) i trajanju MV (od 12–43 dana). Radi boljeg grafičkog prikaza rezultata ispitanici su podeljeni u dve grupe: grupa sa trajanjem MV < 20 dana (tri ispitanika) i grupa sa trajanjem MV > 20 dana (dva ispitanika, MV 39/43 dana). Kod ispitanika sa MV > 20 dana zapaženi su pojava sekundarnih bakterijskih pneumonija (rekurentna visoka febrilnost > 39ºC – kod bolesnika Š.I. 14–15. i 21–22. dana MV, a kod bolesnice S.Lj. između 31–39. dana MV) što je očekivano s obzirom na dužinu trajanja MV (tabela 4), ali ova komplikacija rešena je primenom antibiotske terapije i nije uticala na letalitet. Mada je naša grupa ispitanika mala, pa nismo određivali statističku značajnost, ipak je zanimljivo da su ispitanici koji su preminuli bili značajno kraće vreme na MV (do 15 dana), a preživeli su ispitanici koji su bili na dugotrajnoj MV (od 20 do 43 dana). U tabeli 1 i na slici 4 uočava se da su preminuli ispitanici M.G. (MV 14 dana) i B.D. (MV 12 dana), a ostali su preživeli. Sa stanovišta iskusnog kliničara intenziviste, dugotrajna MV je povezana sa brojnim komplikacijama (VILI, VAP i druge sekundarne infekcije) koje dodatno ugrožavaju život kritično obolelog i samim tim je za očekivati povećanu stopu smrtnosti baš u toj kategoriji bolesnika. Objašnjenje za ovakav ishod lečenja naših ispitanika možda leži u fudroajantnom toku osnovne bolesti (ARDS izazvan virusom gripa A H1N1), tako da se uzrok letaliteta može tražiti u samom karakteru oboljenja, a ne u pratećim komplikacijama MV. Vrednosti SOFA skora kod ispitanika (slika 3a i 3b) bili su značajno veće kod ispitanika koji su umrli (SOFA između 8 i 12) nego kod preživelih. Ispitanici druge grupe (slika 3b) imali su u početku visoke vrednosti SOFA skora, ali sa tendencijom snižavanja tokom dugotrajne MV i intenzivnog lečenja.

Što se tiče preminulih, obojica su bili muškarci, starosti 41 i 43 godine, s tim što je prvi preležao infarkt miokarda 6 godina ranije i bio umereno gojazan, dok je drugi bio dobrog zdravstvenog stanja pre obolevanja.

Kod ispitanika (43 g.), koji je bio dobrog zdravstvenog stanja pre obolevanja, bolest je počela 08.11.2009. godine visokom temperaturom (do 39 ºC) uz suvi kašalj i grebanje u grlu. Lečen je ambulantno (dobijao azitromicin) do hospitalizacije u Vojnu bolnicu Niš (12–14.11.2009) gde je uočena smanjena transparencija pluća obostrano, te je u terapiju uključen oseltamavir (Tamiflu®) i cefalosporin (Ceftriakson®), a potom je premešten u VMA 14.11.2009. Pri prijemu bio je svestan, afebrilan, eupnoičan. Drugog dana (15.11.2009) došlo je do naglog pogoršanja opšteg stanja sa tahipnejom, dispnejom, smanjenom saturacijom (59% i pored oksigenoterapije), pogoršanjem radiografskog nalaza na plućima (difuzni bilateralni infiltrati), te je započeta MV sa IPPV modom, PEEP od 10–12 cmH_2O, ali uz stalno lošu oksigenaciju krvi (PaO_2/FiO_2 između 50–100), i povećanje PEEP na 16–18 cmH_2O (PaO_2/FiO_2 se blago povećavao, ali se zadržavao na vrednosti od 100) (slika 3b), uz visoku febrilnost 39–40 ºC). Primenjivana je analgosedacija remifentanilom i midazolamom i mišićna relaksacija povremeno, kao i „rekrutman“ manevar. Osim antivirotika bolesnik je dobijao i cefalosporine, blokatore protonske pumpe, hranjen je enteralno (putem nazogastrične sonde). Međutim mere MV i intenzivnog lečenja, uopšte, nisu pokazale skoro nikakve rezultate, te je letalni ishod nastupio 28.11.2009. godine. Uzrokom smrtnog ishoda može se smatrati jedino osnovna bolest (grip izazvan virusom A H1N1) sa teškim oblikom ARDS, rezistentnim na sve pokušaje lečenja.

Drugi preminuli, (41g.) primljen je u OIT 11.12.2009. godine (bolest počela 6 dana ranije sa visokom temperaturom, lečen ambulantno) svestan, malaksao, visokofebrilan (> 39 ºC), dispnoičan, brzo se zamarao, a kada je govorio, bio je tahikardičan (95–110/minuti), sa saturacijom ispod 90% i pored primene oksigenoterapije, tako da je doneta odluka o endotrahealnoj intubaciji i započinjanju MV. Dijagnostikovan je ARDS sa obostranim pneumoničnim žarištima, uz difuzne mrljaste senke na oba plućna krila. Zbog izražene i progresivne hipoksemije (slika 3b, gde se kod ovog ispitanika uočavaju vrednosti PaO_2/FiO_2 od 100 do 150), povećale su se vrednosti PEEP, pa je primenjivana analgosedacija re-

mifentanilom i midazolam i mišična relaksacija povremeno. Od početka MV bolesnik je bio hipotenzivan i tahikardičan, pa je pored inicijalne popune cirkulatornog volumena (prva tri dana MV, bilans tečnosti plus 1 750 mL ukupno) i održavanja CVP između 10–13 cmH_2O, bila neophodna i primena vazoaktivnih medikamenata (fenilefrin i dopamin). Od trećeg dana intenzivnog lečenja razvijala se akutna bubrežna slabost, pa je konsultovan nefrolog i svakodnevno vršena hemodijaliza sa ultrafiltracijom. Kardiolog je konstatovao da se kod bolesnika radi i o hroničnoj dilatativnoj kardiomiopatiji sa biventrikularnim blokom, te je uključena i antikoagulantna i antiagregacijska terapija, uz antiaritmike. Pored oseltamivira (Tamiflu®), bolesnik je dobio i antibiotsku terapiju (cefalosporini 3. generacije, azitromicin, ciprofloksacin) i antimikotike. Od ostalih lekova primenjivani su blokatori protonske pumpe, bronhodilatatori i diuretici. Pored preduzetih mera lečenja, 12. dana kod bolesnika je došlo do srčanog zastoja, tipa ventrikularne fibrilacije (dva puta uzastopno uspešno defibriliran), potom je došlo ponovo do asistolije i nastupio je letalni ishod. Uz postojeću respiratornu slabost (ARDS), kod bolesnika se razvila srčana i bubrežna slabost, tako da se sindrom multiorganske disfunkcije (MODS) može smatrati uzrokom lošeg ishoda lečenja.

Sagledavajući tok bolesti oba preminula, možemo zaključiti da je prvi bolesnik (43g) doživeo smrtni ishod kao direktnu posledicu gripa A H1N1, dok je kod drugog (41g), smrt nastupila kao posledica MODS izazvanog osnovnim oboljenjem (grip A H1N1), odnosno da grip nije bio direktan uzrok smrti, već je izazvao pogoršanje zdravstvenog stanja bolesnika, sa oboljenjem kardiovaskularnog sistema. Slične rezultate dobili su i drugi autori [12–17]. Na kraju potrebno je istaći da nijedan medicinski radnik koji je učestvovao u intenzivnom lečenju i MV ispitanika nije oboleo od gripa izazvanog virusom A H1N1.

Zaključak

Grip izazvan virusom H1N1 može imati težak, pa čak i dramatičan tok sa respiratornom slabošću koja ugrožava život obolelog. Intenzivno lečenje bolesnika sa respiratornom slabošću izazvanom virusom gripa zahteva MV koja se mora izvoditi shodno preporukama svetskih i evropskih foruma. Intenzivno lečenje ovih bolesnika, posebno MV, može biti dugotrajno i stoga zahteva specijalne anesteziološke timove, posebna, izolovana odeljenja za intenzivnu terapiju i visok stepen zaštite medicinskog osoblja.

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Neurofiziološka evaluacija bolesnika sa degenerativnim oboljenjima cervikalne kičme

Neurophysiological evaluation of patients with degenerative diseases of the cervical spine

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Apstrakt

Uvod/Cilj. Dijagnostički protokol bolesnika sa degenerativnim oboljenjima cervikalne kičme zahteva, pored neuroradioloških metoda morfološke vizuelizacije (magnetna rezonancija cervikalnog mijelona), dodatnu funkcionalnu procenu nizom neurofizioloških metoda (somatosenzitivni, motorni evocirani potencijali i elektromioneurografija) u cilju evaluacije mogućnosti supkliničkog zahvatanja dugih puteva spinalne medule. Imajući u vidu raznovrsnost kliničkih ishoda ovakva složena evaluacija obezbeđuje prognozu napredovanja bolesti. **Metode.** Ispitan je ukupno 21 bolesnik (48,24 ± 11,01 god) sa kliničkom prezentacijom cervikalne spondilatropatije, bez pouzdanih neuroradioloških znakova mijelopatije. Pored konvencionalnih neurofizioloških testova (somatosenzorni evocirani potencijal – SSEP, motorni evocirani potencijal – MEP, elektromioneurografija – EMNeG) kod svakog bolesnika vršena je evaluacija centralnog vremena motornog provođenja (CVMP) u zavisnosti od položaja glave (dinamički testovi). **Rezultati.** Abnromalnosti perifernog motornog neurona kod ovih bolesnika utvrđene su primenom konvencionalne EMNeG kod 2/3 bolesnika, što je slično analizi korenskog vremena provođenja. Međutim, u cilju detekcije supkliničkih oblika cervikalnih spondilotskih mijelopatija, produženje CVMP konvencionalnom metodom utvrđeno je kod 29% bolesnika, dok je primenom dinamičkih testova učestalost ovih abnormalnosti povećana na 43%. Abnormanosti pokazatelja SSEP sa *n. medianus* za istu grupu ispitanike ispoljila su se kod 38% bolesnika sa cervikalnom spondilozom. **Zaključak.** Primena proširenog protokola neurofizioloških testova funkcije centralnih i perifernih motornih neurona, uključujući dinamička testiranja zavisna od položaja, neposredno utiču na utvrđivanje supkliničkih oblika bolesti već u najranijim stadijumima. Pored konvencionalnih neurofizioloških testova u protokol ispitivanja supkliničke cervikalne spondilotske mijelopatije, optimalno je uvrstiti i dinamičke testove transkranijumske magnetne stimulacije, kao i merenje provodljivosti u proksimalnim (korenskim) segmentima perifernih motoneurona.

Ključne reči:
spondiloza; vrat; kičmena moždina, bolesti; dijagnoza, diferencijalna; evocirani potencijali; elektromiografija; magnetna rezonanca, snimanje.

Abstract

Bacground/Aim. Diagnostic protocol for patients with degenerative diseases of the cervical spine demands, in parallel with neuroimaging methods, functional evaluation through neurophysiological methods (somatosensitive and motor evoked potentials and electromyoneurography) aiming to evaluate possible subclinical affection of spinal medula resulting in neurological signs of long tract abnormalities. Considering diversities of clinical outcomes for these patients, complex diagnostic evaluation provides a prognosis of the disease progression. **Methods.** The study included 21 patients (48.24 ± 11.01 years of age) with clinical presentation of cervical spondylarthropathy, without neuroradiological signs of myelopathy. For each patient, in addition to conventional neurophysiological tests (somatisensory evoked potentials – SSEP, motor evoked potentials – MEP, electromyoneurography – EMG, nerve conduction studies), we calculated central motor conduction time ($CMCT^F$), as well the same parameter in relation to a different position of the head (maximal anteflexion and retroflexion), so-called dynamic tests. **Results.** Abnormalities of the peripheral motor neurone by conventional EMNeG was established in 2/3 of the patients, correponding to the

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findings of root condution time. Prolonged conventional $CVMP^F$ were found in 29% of the patients, comparing to 43% $CVMP^F$ abnormalities found with the dynamic tests. In addition, the SSEP findings were abnormal in 38% of the patients with degenerative diseases of the cervical spine. **Conclusion.** An extended neurophysiological protocol of testing corticospinal functions, including dynamic tests of central and periheral motor neurons are relevant for detection of subclinical forms of cervical spondylothic myelopathy, even at early stages. In addition to the conventional neurophysiological tests, we found usefull to include the dynamic motor tests and root conduction time measurement in diagnostic evaluation.

Key words:
spondylosis; neck; spinal cord diseases; diagnosis, differental; evoked potentials; electromyography; magnetic resonance imaging.

Uvod

Cervikalna spondiloza (CS) predstavlja skupni termin kojim su obuhvaćena degenerativna oboljenja vratne kičme visoke učestalosti, pre svega, kod starije populacije. U kliničkom pogledu, reč je o nekoliko sindroma sa uzajamnim preklapanjem koji se odnose na bolna stanja predela vrata i ramenog obruča, simptome i/ili znakove cervikalnih radikulopatija (CR) ili u najozbiljnijoj formi cervikalnih spondilotskih mijelopatija (CSM), po pravilu uzrokovane ekstraduralnom kompresijom degenerisanih koštanih i/ili kartilaginoznih elemenata [1]. Studije sprovedene u Severnoj Americi upućuju da je CMS najučestaliji oblik oboljenja spinalne medule kod osoba starijih od 55 godina života [2], čemu u prilog govore i podaci prospektivne studije u Velikoj Britaniji gde je više od 23% bolesnika sa para- ili tetraparezom hospitalizovanih u ustanovi tercijarnog ranga imalo CSM [3].

Međutim, uprkos visokoj učestalosti CS, neretko se kod bolesnika opažaju uporedna ispoljavanja CR i CSM [4], otežavajući precizno i pouzdano definisanje prirodnog toka bolesti svakog sindroma ponaosob. Stoga, prvo određenje koje je neophodno u donošenju relevantne terapijske odluke jeste diferenciranje doprinosa svakog pojedinačnog entiteta u okviru CS. Nadalje, u slučaju CSM, tok bolesti se smatra veoma raznovrsnim, u rasponu od tipično sporo progresivnog do veoma dugih perioda stagnacije napredovanja [5], iz čega je razumno pretpostaviti da ovakve nedoumice otvaraju pitanje koncepta lečenja, odnosno selekcije optimalnih kandidata za hirurški tretman. Pojedine studije u kojima su praćeni ishodi hirurškog tretmana kao isključivi povoljni prediktor procenile su trajanje simptoma, tako da su bolesnici operisani u roku od jedne godine po ispoljavanju tegoba pokazivali značajno bolji oporavak [6]. Savremeni konsenzusi o indikacijama za operativno lečenje, ipak, u najvećoj meri, oslanjaju se na kombinovane nalaze morfoloških promena, u vidu izmenjenog intenziteta signala u T2W sekvenci magnetne rezonance cervikalnog mijelona [7], uporedo sa funkcionalnim promenama prisutnim u analizama neurofizioloških parametara somatosenzitivnih (SSEP) i motornih evociranih potencijala (MEP) i elektromiografiji, odnosno studijama provodljivosti motornih i senzitivnih perifernih nerava (EMNeG) [8]. Međutim, doprinos svake od nabrojanih neurofizioloških metoda i dalje je predmet razmatranja. U ovom istraživanju ocenili smo nalaze navedenih tehnika (MEP, SSEP i ENeG), uključujući i po prvi put definisane dinamičke studije provodljivosti duž centralnih motornih puteva kod bolesnika sa CS referisanim pod sumnjom na mogućnost supkliničke mijelopatije, bez pouzdanih morfoloških korelata na magnetnoj rezonanciji (MR) cervikalne kičme.

Metode

Istraživanje je obuhvatilo 21 bolesnika, starosti 48,24 ± 11,01 god, (33–70 godina), od čega 10 žena, koji su pod kliničko-radiološkom slikom cervikalne spondiloze i/ili cervikalne radikulopatije upućivani na dodatnu neurofiziološku evaluaciju moguće supkliničke forme CMS, u periodu 2005–2010. god. u Funkcijsku neurološku dijagnostiku Vojnomedicinske akademije u Beogradu.

Subjektivne tegobe kod bolesnika trajale su između 3 i 12 meseci. Uzorak je obuhvatao isključivo bolesnike bez neuroloških znakova afekcije dugih puteva spinalne medule.

Magnetna rezonancija (MR) cervikalnog mijelona (MRI-C) rađena je na uređajima od 1,0 do 1,5 T, uz standardne pulsne sekvence: T1-*weighted* (T1W) i T2 -*weighted* (T2W) sekvence u aksijalnoj i sagitalnoj ravni, i opciono T2W GRE (*gradient recalled echo*). U pogledu evaluacije neuroradioloških nalaza MRI-C, prihvaćena je podela u skladu sa već publikovanim istraživanjima, prema kojoj postoje četiri stadijuma u skladu sa stepenom kompresije cervikalnog mijelona od degenerativnih osteokartilaginoznih elemenata [9]. S obzirom na to da je ovo istraživanje imalo za cilj testiranje bolesnika sa eventualnim supkliničkim manifestacijama CSM, uključeni su samo bolesnici sa stadijumom I (CS sa ili bez kontakta sa cervikalnom medulom, ali bez deformiteta medule) i stadijumom II (blago utiskivanje ili zaravnjenje cervikalne medule, ali uz anteroposteriorni prečnik koji nije manji od 2/3 originalnog). U oba stadijuma ne beleže se hiperintenziteti signala u T2W-sekvenci u aksijalnoj ravni.

Standardizovani EMNeG pregled sastojao se od detekcione elektromiografije (selekcija mišića odgovarala je kliničkoj prezentaciji) i studija provodljivosti motornih i senzitivnih nerava na rukama (najmanje dva) od strane lekara sa odgovarajućom supspecijalističkom edukacijom, a u cilju uniformne interpretacije nalaza. Neurofiziološka dijagnoza CR bila je potvrđena u slučaju prisustva abnormalne spontane aktivnosti (denervacionih potencijala) u ispitivanim mišićima i/ili potencijala motorne jedinice produženog trajanja, visokih amplituda i polifaznog oblika („neurogene“ karakteristike) u najmanje tri mišića, inervisana iz istog miotoma, ali u isto vreme sa različitom perifernom inervacijom.

Ispitivani su primenom SSEP standardizovane metode, stimulacijom desnog *n. medianus*-a u predelu ručnog zgloba

pomoću cefaličke referentne elektrode na poziciji Fz. Frekvencija stimulacije perifernog nerva iznosila je 3 Hz, uz trajanje pojedinačnog stimulusa pravougaonog oblika od 0,2 msec. Intenzitet stimulacije bio je prilagođavan na vrednost neposredno iznad praga motornog odgovora, što je za posledicu davalo slab mišićni trzaj u predelu tenara. Površinske Ag-AgCl disk elektrode prečnika 0,7 cm pozicionirane su u predelu ipsilateralne natključne jame (Erbova tačka), na posteriornoj strani vrata u projekcijama trnastih nastavaka 2. i 7. vratnog pršljena, kao i kontralateralno nad skalpom u poziciji parijetalne tačke C3', koja reprezentuje projekciju primarnog somatosenzitivnog korteksa leve velikomoždane hemisfere.

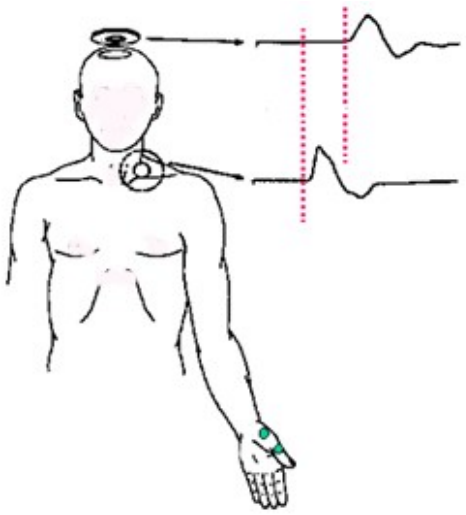
Elektrodna impedanca održavana je konstantno na vrednostima nižim od 3 kΩ. Niz od 512 ponavljanih odgovora bio je usrednjavan i skladišten na disku računara u cilju naknadne evaluacije (*off-line*) latencije i amplitude pojedinačnih komponenti odgovora. Vremenska baza iznosila je 100 msec. Raspon filtera podešen je na vrednosti između 32 Hz (-3 dB) i 1 600 Hz (-6 dB). Registrovana su najmanje dva ponavljana zapisa u cilju potvrđivanja reproducibilnosti, te olakšanog prepoznavanja pojedinih komponenti odgovora, pre svega u slučajevima patološki izmenjenih talasnih formi. Amplitude N9 i spinalnih N13 komponenti merene su između inicijalne pozitivnosti i naknadne negativnosti. Amplitude ključnih kortikalnih komponenti merene su između vrha inicijalne kortikalne negativnosti (N19) i sledeće pozitivnosti (P25) u kontralateralnoj parijetalnoj derivaciji.

Transkranijumska magnetna stimulacija bila je primenjena u skladu sa preporukama o bezbednoj primeni [10, 11], dok su svi bolesnici ispitivani na rizik od izazivanja neželjenih dejstava primenom upitnika prevedenog na srpski jezik [12].

Ispitanici su bili smešteni u komfornu stolicu/ležaj posebno projektovan za ovu namenu, sa podesivim naslonom za glavu i naslonima za ruke, u cilju potpune relaksacije tokom čitavog registrovanja. Ispitivanja su bila sprovođena u sobi izolovanoj od zvuka, poluzatamnjenoj u odnosu na dnevnu svetlost. Na mišićni trbuh ciljnog mišića APB, bila je postavljena površinska Ag-AgCl elektroda promera 9 mm (aktivna elektroda), dok je referentna bila postavljana na koštanu prominenciju prve metakarpalne kosti palca, središta elektroda udaljenih međusobno 20–30 mm. Signal EMG je pojačavan i filtriran (0,02–2 kHz, MS 91 Medelec, UK).

Stimulacija pojedinačnim magnetnim pulsevima sprovođena je kružnim kalemom velikog prečnika (90 mm) postavljenim iznad verteksa (u slučaju kortikalne stimulacije), odnosno iznad spinoznog nastavka sedmog vratnog pršljena (u slučaju cervikalne – spinalne stimulacije, uz intenzitete koji su iznosili kortikalno 80–100% maksimalne izlazne snage stimulatora odnosno, 60% za spinalnu stimulaciju. Ciljni mišić sve vreme ispitivanja održavan je u stanju lake voljne preinervacije (oko 10% maksimalne voljne kontrakcije). U svrhe merenja, kao rezultat beležena je najkraća latencija u četiri ponovljene stimulacije (slika 1).

Centralno vreme motornog provođenja (CVMP – *central motor conduction time*) predstavlja vrednost dobijenu oduzimanjem minimalne latencije kortikalnog odgovora od minimalne latencije spinalno izazvanog MEP.



Sl. 1 – Položaji stimulativnog kalema pri kortikalnoj i spinalnoj stimulaciji u cilju procene centralnog vremena motornog provođenja

$CVMP^M$ (ms) = Kortikalni MEP (ms) – Spinalni MEP (ms)

Međutim, magnetna stimulacija na spinalnom nivou ne vrši podražaj samih α-motoneurona prednjih rogova spinalne medule, već neuralnih elemenata spinalnih korena u predelu njihovog izlaska iz intravertebralnih otvora na udaljenosti između 2 i 4 cm od tela neurona [13]. Dakle, minimalna latencija MEP dobijenog pri spinalnoj stimulaciji uključuje vreme CVMP, ali, pored toga, i još najmanje jedan period sinaptičkog kašnjenja na spinalnom nivou, kao i vreme provodljivosti u proksimalnom segmentu korena.

Stoga, u primeni je i druga formula za izračunavanje realnog $CVMP^F$, pri čemu se od minimalne latencije kortikalnog izazvanog MEP, oduzima tzv. periferno vreme motornog provođenja koja se izražava formulom: $CVMP^F$ (ms) = kortikalni MEP (ms) – (lat. F-talasa. + lat. M-odg. – 1) / 2.

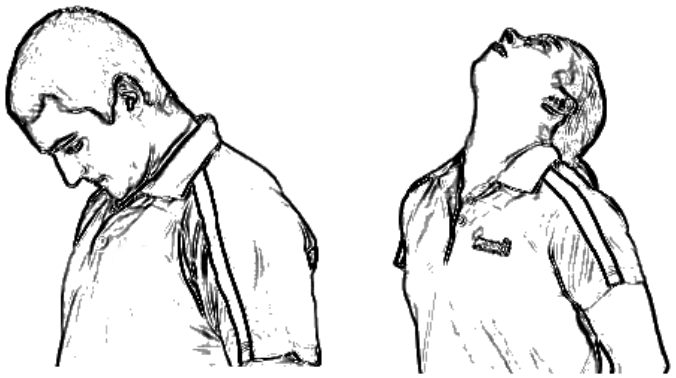
Periferno vreme motornog provođenja predstavlja vreme provođenja od spinalnog α-motoneurona i obuhvata zbir minimalnih latencija F-talasa i M odgovora, od čega se oduzima 1 ms, kao pretpostavljeno vreme sinaptičkog kašnjenja, na nivou spinalne medule, a potom se sve deli sa dva [14].

Pored uobičajene metode računanja CVMP sa položajem glave u središnjem položaju, kortikalna stimulacija vršena je i u položajima maksimalne antefleksije i retrofleksije, sa očekivanjem da će ovakvi dinamički testovi voditi ka provociranju izrazitijih abnormalnosti, ukoliko se iste ne ustanove na standardni način (slika 2).

Rezultati

U pogledu EMNeG ispitivanja, pozitivan nalaz, sugestivan za CR, registrovan je kod 14/21 ispitanih bolesnika sa CR (67%).

Pri analizi pokazatelja evociranih potencijala (SSEP i MEP), koji su se odnosili na latencije (merene u ms) i amplitude (merene u μV) primenjivani su restriktivni kriterijumi koji zahtevaju da patološki nalaz prevazilazi srednju vrednost u normativnoj grupi uvećanu za 3 standardne devijacije [15].



Sl. 2 – Položaji maksimalne antefleksije i retrofleksije u kojima su vršena merenja centralnog vremena motornog provođenja

Normativni podaci za MEP iz m.APB definisani su na populaciji od 18 neurološki zdravih ispitanika, starosti 45,91 ± 14,55 godina, ravnomerne polne zastupljenosti (tabela 1).

bilo jednostrano ili obostrano. Prikazani procenat abnormalnosti podudaran je učešću cervikalnih radikulopatija koje su definisane uz pomoć EMNeG pregleda, premda se u analizi ne odnosi nužno na iste bolesnike (slika 3).

Tabela 1

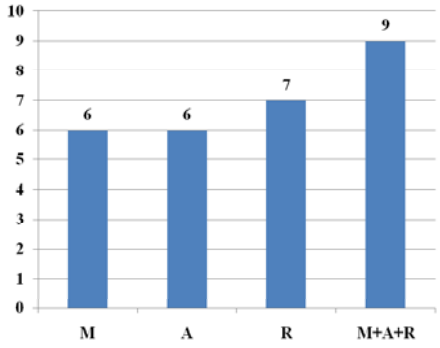
Pregled normativnih vrednosti ispitivanih parametara motornih evociranih potencijala (MEP) i nalaza u grupi ispitivanih bolesnika sa cervikalnom spondilozom (CS)

Neurofiziološki pokazatelji MEP	Normativni podaci (ms)	Maksimalna odstup. od norm. vrednosti (ms) $\bar{x} \pm 3SD$	Bolesnici sa CS (ms)	Normativi razlike strana (ms)	Razlika strana kod CS (ms)
Latencija nakon kortikalne stimulacije (ms) – medijalno	20,3 ± 1,9	–	21,71 ± 1,49	–	0,96 ± 0,66
Latencija nakon kortikalne stimulacije (ms) – antefleksija			21,78 ± 1,47		0,52 ± 0,56
Latencija nakon kortikalne stimulacije (ms) – retrofleksija			21,73 ± 1,44		0,75 ± 0,78
Latencija nakon spinalne stimulacije (ms)	–	15,40	14,37 ± 1,23	–	0,52 ± 0,46
$CVMP^M$ / medijalno (ms)	–	7,70	7,33 ± 1,16	1,00	0,87 ± 0,44
$CVMP^M$ / antefleksija (ms)			7,20 ± 1,04		0,98 ± 0,81
$CVMP^M$ / retrofleksija (ms)			7,13 ± 1,02		1,06 ± 0,62
$CVMP^F$ / medijalno (ms)	–	6,30	4,94 ± 1,57	0,80	1,02 ± 0,59
$CVMP^F$ / antefleksija (ms)			4,69 ± 1,34		0,54 ± 0,54
$CVMP^F$ / retrofleksija (ms)			4,65 ± 1,29		0,78 ± 0,65
Ukupno vreme perifernog provođenja (ms)	15,5 ± 1,51	–	16,6 ± 0,97	–	0,45 ± 0,46
Korensko vreme provođenja (ms)	0,88 ± 0,39	2,05	2,15 ± 0,63	–	0,41 ± 0,31

CVMP – centralno vreme motornog provođenja

Analizom abnormalnosti koje su ustanovljene pri testiranju integriteta kortikospinalnih puteva utvrđeno je postojanje relevantnog usporenja $CVMP^F$ kod 6 od 21 (29%) bolesnika sa CS, ukoliko je glava ispitanika bila u središnjem položaju (M – medijalni položaj); istovetna učestalost abnormalnosti (29%) postignuta je i u položaju maksimalne antefleksije (A), dok je nešto više odstupanja (33%) zabeleženo pri položaju maksimalne retrofleksije (R). Međutim, ukoliko su se sve abnormalnosti $CVMP^F$ sabirale, 9 od 21 bolesnika sa CS (43%) imali su abnormalni nalaz.

Uz rezultate koji se odnose na provođenje duž centralnog motornog neurona ($CVMP^F$), potrebno je prikazati i korensku brzinu provođenja u proksimalnim segmentima perifernih motornih neurona, budući da vrednosti proizilaze iz zajedničkih kalkulacija. U ispitanom uzorku 14 bolesnika (67%) imalo je produženje korenskog vremena provođenja



Sl. 3 – Ukupan broj bolesnika sa produženjem centralnog vremena motornog provođenja, izmerenim u središnjem položaju (M), u položaju maksimalne antefleksije (A), retrofleksije (R) ili kao zbir abnormalnosti u svim od navedenih položaja (M+A+R); brojevi na ordinati odgovaraju broju bolesnika sa abnormalnim nalazom

U analizi SSEP sa nivoa *n. medianus* normativni podaci prikupljeni su kod 32 neurološki zdrava ispitanika, starosti 37,42 ± 11,89 godina, ravnomerne polne zastupljenosti (tabela 2).

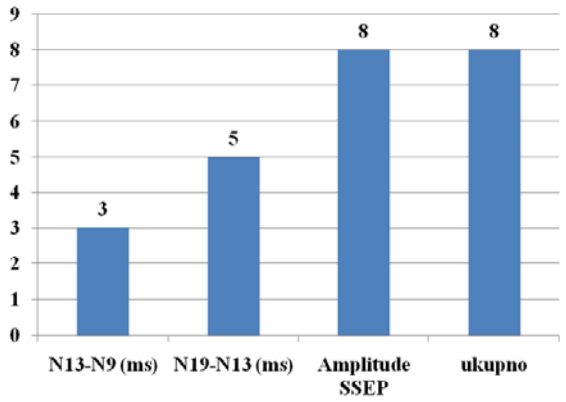
Postojanje CR, sa druge strane, otkriveno je uporedo kod oko 2/3 bolesnika, bilo na osnovu konvencionalnih EMeG nalaza, ili uz pomoć tzv. korenskog vremena provođenja, neurofiziološkog pokazatelja izvedenog kombinacijom električne stimulacije perifernih nerava i magnetne stimulacije u nivou cervikalnog segmenta spinalne medule.

Tabela 2

Pregled normativnih vrednosti ispitivanih parametara somatosenzitivnih evociranih potencijala (SSEP) i nalaza dobijenih u grupi bolesnika sa cervikalnom spondilozom (CS)

Neurofiziološki pokazatelji SSEP	Normativni podaci	Maksimalna odstupanja od norm. vrednosti (ms) $\bar{x} \pm SD$	Bolesnici sa CS	Normativi razlike strana	Razlika strana kod CS
Apsolutne latencije izazvanih odgovora (ms)					
N9 komponenta	9,11 ± 0,43	9,97	10,16 ± 0,67	—	—
N13 komponenta	13,27 ± 0,69	14,65	14,17 ± 0,81	—	—
N19 komponenta	19,87 ± 0,86	21,59	19,66 ± 1,36	—	—
Intertalasne latencije (ms)					
N13-N9	3,70 ± 0,53	4,76	4,04 ± 0,61	1,40	0,49 ± 0,46
N19-N13	5,78 ± 0,61	7,00	8,77 ± 3,90	1,30	0,71 ± 0,83
N19-N9	9,30 ± 0,66	10,62	9,48 ± 1,29	1,30	0,59 ± 0,65
Amplitude negativnog dela talasa (μV)					
N9 komponenta	4,80 ± 1,71	1	3,45 ± 2,14	50%	50 ± 23%
N13 komponenta	2,30 ± 0,91	0,50	1,81 ± 1,03	48%	43 ± 26%
N19 komponenta	3,20 ± 1,14	0,80	3,24 ± 2,51	47%	31 ± 25%

Analiza abnormalnosti u ovoj kategoriji neurofizioloških pokazatelja (slika 4) pokazala je postojanje produženja intertalasne latencije N13-N9 kod 3 od 21 bolesnika (14%), produženja intertalasne latencije N19-N13 kod 5 bolesnika (24%), razlike strana za amplitude izazvanih odgovora N9 i N13 kod 8 bolesnika (38%), ili ukoliko se sabiralo prisustvo bilo koje od navedenih abrnormalnosti na ovom uzorku bolesnika iznosilo je, takođe, 8 od 21 bolesnika sa CS (38%).



Sl. 4 – Ukupan broj bolesnika sa različitim somatosenzornim evociranim potencijalima (SSEP) sa nivoa *n. medianus*; vrednosti amplituda SSEP komponenti ispod donje granice normativa (amplitude SSEP); produženje intertalasnih latencija (N19-N13 i N13-N9) ili kao zbir svih abnormalnosti SSEP (ukupno)

Diskusija

Rezultati ove studije govore u prilog postojanju supkliničkih oblika CSM kod približno 40% bolesnika sa CS, bez kliničkih znakova oštećenja dugih puteva spinalne medule i potvrde u skladu sa neuroradiološkim kriterijumima CSM [7, 9].

Patofiziološki procesi koji leže u osnovi ovog poremećaja obuhvataju dve vrste mehaničkih faktora (statičke i dinamičke) kao i ishemiju kičmene moždine [16]. Statički faktori odnose se na osteofite, degenerativne kifoze i subluksacije, konstitucionalna suženja spinalnog kanala kao i hipertrofiju, odnosno zadebljanja *ligg. flava* [17]. Međutim, posebnu pažnju neophodno je posvetiti i dinamičkim mehaničkim faktorima, što i predstavlja neposredni doprinos ovog istraživanja. Naime, u slučajevima već postojeće ili nagoveštene statičke kompresije, pri mehaničkoj fleksiji vrata dolazi do „izduženja“ cervikalnog segmenta mijelona, sa mogućnošću dodatnog pritiska od strane ventralnih osteofita, dok za vreme ekstenzije vrata hipertrofisane i kalcifikovane *ligg. flava* mogu „potiskivati“ kičmenu moždinu koja dalje biva stešnjena između njih i ventralnih osteofita. Ovakve ponavljane epizode, najčešće hiperekstenzije, imaju za posledicu prolazne akutne kompresije spinalne medule, oponašajući u „malom“ događaje kod akutne povrede kičmene moždine. Ovakvi događaji, najčešće i leže u osnovi kliničkih pogoršanja kakva se često viđaju kod bolesnika sa CSM [18]. Naposletku, kao patofiziološki faktor beleži se i ishemija na nivou mikrocirkulacije, verovatna posledica smanjenog protoka kroz pijalne pleksuse, ali i verovatne venske kongestije i kompresije velikih krvnih sudova, kao prednje spinalne arterije [19].

Kako je već ranije navedeno, prema sadašnjim stavovima dijagnoza CSM može se postaviti isključivo ukoliko bolesnik ima simptome i/ili radiološke znakove kompresije kičmene moždine [7], uprkos činjenici da podudarnosti u ove dve osovine nalaza, neretko nisu idealne [20]. U isto vreme MRI cervikalnog segmenta izvesno predstavlja proceduru izbora u početnoj proceni bolesnika sa CSM, s obzirom na to da pored egzaktnog merenja stepena stenoze spinalnog kanala, omogućuje identifikaciju drugih oboljenja kičmene

moždine (npr. tumori, infarkti, subakutna kombinovana degeneracija), koja dolaze u obzir kao diferencijalne dijagnoze [20]. Uprkos navedenom, u realnim kliničkim situacijama MRI veoma retko egzistira samostalno, budući da ova senzitivna metoda morfološke vizuelizacije neuralnih struktura često otkriva i patološke promene koje nisu u vezi sa simptomima kod bolesnika ili čak kod asimptomatskih bolesnika (lažno pozitivni nalazi), tako da izveštaj Teresija i sar. [21] ukazuje da 57% bolesnika starijih od 65 godina ima bubrenje diska (*disc bulging*), a da više od četvrtine osoba u ovoj starosnoj grupi pokazuje na MRI snimcima znakove kompresije kičmene moždine.

Nadalje, prema rezultatima prethodnih studija spinalni nivoi pojačanog intenziteta signala u T2 sekvenci na MRI pregledu nisu odgovarali najznačajnijim nivoima medularne kompresije na funkcionalnim testovima evociranim potencijalima [9], što potvrđuje, pored mehaničkih faktora, pretpostavljeni doprinos patofizioloških faktora poput edema, glioze, ishemije i poremećaja mikrocirkulacije [22]. Međutim, dosadašnja primena svih navedenih patofizioloških mehanizama najmanje je primenjivala mogućnost dinamičke mehaničke kompresije, tako da je, prema našim saznanjima, svega jednom do danas potvrđena u okviru neuroradioloških studija [23], a nikada nije evaluirana za neurofiziološke testove.

U definisanju značenja tehnika evociranih potencijala, pri evaluaciji ovih bolesnika, situacija je (pod)jednako kompleksna. U nastojanju da se objasne patofiziološki mehanizmi pretpostavljena je veća vulnerabilnost struktura kortikospinalnog trakta, nasuprot sistema dorzalnih kolumni [24], s obzirom na to da se kompresivni efekat ranije i većinom ispoljava anteriorno usled hernijacije cervikalnog diska.

Sa nivoa *n. medianus* i *n. tibialis* SSEP u upotrebi namenjeni su evaluaciji ovog kliničkog problema već oko 30 godina. Opštim konsenzusom smatra se da pojedine komponente na cervikalnom spinogramu, kao N13, odražavaju segmentnu disfunkciju kičmene moždine [25], ali uporedo sa nedovoljnom lokalizacionom preciznošću [26] anatomska pozicija sistema dorzalnih kolumni, kako je napred navedeno, ne odgovara potrebama što ranije identifikacije funkcionalnih abnormalnosti provođenja duž dugih puteva. Istine radi, nedavno je publikovana i jedna neurofiziološka studija u kojoj je evaluacijom latencija pojavljivanja izazvanih odgovora postignuta izvanredna senzitivnost koja se nasuprot MRI nalazima kreće do 98%, ali uz relativno oskudne kliničke podatke o toku i trajanju bolesti, čime je interpretacija ove publikacije ograničene vrednosti [27].

Opšte shvatanje je da su motorni evocirani potencijali, odnosno izvedeni parametar CVMP, senzitivniji u poređenju sa pokazateljima SSEP [28], te da čak obezbeđuju mogućnost supkliničke detekcije CSM [29, 30].

Više je razloga uz pomoć kojih se mogu objasniti relativne prednosti MEP. Pre svega, CVMP odražava abnormalnosti kortikospinalnih vlakana sa najbržim provođenjem, a njegove abnormalnosti predstavljaju neposrednu disfunkciju piramidnog trakta usled, smatralo se, desinhronizacije signala koji putuju nishodno, njihove eventualne vremenske disperzije, postojanja konduktivnog bloka ili čak i aksonske degeneracije [31]. Istraživanja u kojima je primenjivano direktno registrovanje signala iz epiduralnog prostora pružile su novi uvid u verovatni mehanizam produženja CVMP, pridajući relativno mali značaj usporenju provođenja duž kortikospinalnih projekcija, a verovatnije proređenu vremensku sumaciju salve multiplih descedentnih signala, čime spinalni alfa-motorni neuroni imaju duže vreme pražnjenja, stvarajući produženje CVMP [32].

Od značaja je, takođe, komentarisati izbor ciljnih mišića za testiranje MEP kod naše grupe ispitanika, tim pre što klinička slika spastičkog tipa CSM vodi pre svega ka afekciji donjih ekstremiteta, odnosno poremećajima hoda. Razlog tome, smatra se, leži u somatotopskoj organizaciji kortikospinalnih vlakana u cervikalnoj meduli, za gornje i donje ekstremitete, pri čemu su poslednja smeštena više lateralno, pa, stoga, bivaju pre komprimovana [29]. Ipak, kako u studijama tako i u kliničkoj rutini, izbor mišića šake opravdava se velikom intrinzičkom varijabilnosti MEP u mišićima donjih ekstremiteta [33], odnosno najvećom gustinom kortikomotoneuronalnih projekcija za mišiće šake [34].

Međutim, uprkos generalnoj prednosti testiranja kortikospinalnih puteva, posebno u slučajevima tipičnih spastičkih mijelopatija, pojedine kliničke prezentacije CSM podrazumevaju predominantno senzornu simptomatologiju, bilo da je reč o striktno lokalizovanim segmentnim lezijama unutar sive mase, kao u slučajevima siringomijelija, ili tzv. dinamičke kompresije kičmene moždine u posterolateralnim delovima od strane hipertofisanih *ligg. flava*, što je i pokazano u studiji sa epiduralnim registrovanjem bolesnika sa CSM, ali urednim CVMP, gde je testiranje somatosenzitivnih projekcija potvrdilo funkcionalna oštećenja [35].

Zaključak

Izloženi rezultati ove studije upućuju na posebnu pažnju u evaluaciji bolesnika sa degenerativnim oboljenjima cervikalne kičme, naglašavajući suštinsku vrednost funkcionalnih testova koji mogu da anticipiraju jasne morfološke promene kakve se beleže neuroradiološkim tehnikama ispitivanja. Izbor neurofizioloških tehnika neophodno treba da sledi spektar simptoma i znakova prisutnih kod bolesnika, uz insistiranje na individualnom pristupu. Primena višestrukih modaliteta evociranih potencijala sa namenom testiranja integriteta dugih somatosenzitivnih i kortikospinalnih puteva uvećava verovatnoću rane detekcije mijelopatskih oštećenja kod bolesnika sa suspektnom CSM.

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Clinical manifestations, therapy and outcome of pandemic influenza A (H1N1) 2009 in hospitalized patients

Kliničko ispoljavanje, terapija i ishod pandemijskog gripa A (H1N1) 2009 kod hospitalizovanih bolesnika

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Abstract

Background/Aim. Increasing number of epidemiological and clinical studies to date showed that the pandemic influenza A (H1N1) 2009, by its characteristics, significantly differs from infection caused by seasonal influenza. Therefore, the information about clinical spectrum of manifestations, risk factors for severe form of the disease, treatment and outcome in patients with novel flu are still collected. **Methods.** A total of 98 patients (mean age 32 ± 15 years, range 14–88 years) with the signs and simptoms of novel influenza were treated in the Clinic for Infectious and Tropical Diseases, Military Medical Academy. There were 74 (75.5%) patients with suspected influenza A (H1N1) 2009, 10 (10.2%) with the likelihood and 14 (14.3%) with the confirmed influenza. In all the patients we registered the basic demographic data, risk factors for severe disease, symptoms and signs of influenza, laboratory tests and chest radiography. We analyzed antiviral therapy use and disease outcome (survived, died). **Results.** The average time from the beginning of influenza A (H1N1) to the admission in hospital was 3 days (0–16 days) and from the moment of hospitalization to the Intensive Care Unit (ICU) admission was 2 days (0–5 days). There were 49 (50.0%) patients, 20–29 years of age and 5 (5.1%) patients older than 65. A total of 21 (21.4%) patients were with underlying disease, 18 (18.4%) were obese, 19 (19.4%) were cigarette smokers. All of the patients had fever, 81 (82.6%) cough, while dyspnea and diarrhea were registered in ¼ of the patients. In more than 75% of the patients laboratory tests were within normal limits. The real-time polymerase chain reaction (PCR) test for identification of influenza A (H1N1) 2009 was positive in 14 (77.8%), while pneumonia was verified in 30 (30.7%) of the patients. Six (6.1%) patients, mean age of 45 ± 14 years (31–59 years) were admitted to the ICU, of whom five (5.1%) had Adult Respiratory Distress Syndrome (ARDS). Risk factors were registered more frequently in the patients with acute respiratory failure (14.2% *vs* 4.9%, $p < 0.05$). A total of 67 (68.4%) patients received oseltamivir, 89 (90.1%) was applied to antibiotics and 64 (65.3%) were treated with a combined therapy. Antiviral therapy was applied to 43 (43.3%) patients in the first 48 hours from the onset of the disease, of whom only one (3.4%) developed ARDS. Fatal outcome was noted in 2.0% of the patients (2 of 98 patients) and in 33.3% of the patients treated in the ICU. **Conclusion.** Novel influenza A (H1N1) is most commonly manifested as a mild acute respiratory disease, which usually affects young healthy adults. A small number of the patients develop severe illness with acute respiratory failure and death. Patients seem to have benefit from antiviral therapy especially in first 48 hours.

Key words:
influenza A virus, H1N1 subtype; disease transmission, infections; disease progression; drug therapy; mortality.

Apstrakt

Uvod/Cilj. Više epidemioloških i kliničkih studija do sada pokazalo je da se pandemijska influenca A (H1N1) 2009 po svojim karakteristikama značajno razlikuje od infekcije izazvane virusom sezonske influence. Zato se i dalje prikupljaju informacije o kliničkom spektru ispoljavanja, faktorima rizika od težih oblika bolesti, terapiji i ishodu kod obolelih od novog gripa. **Metode.** U Klinici za infektivne i tropske bolesti Vojnomedicinske akademije lečeno je 98 bolesnika sa novim gripom, prosečne starosti 32 ± 15 godina (14–88 godina). Broj bolesnika sa sumnjom na grip A (H1N1) 2009 bio je 74

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(75,5%), sa verovatnim gripom 10 (10,2%), a sa potvrđenim gripom 14 (14,3%). Kod svih bolesnika registrovani su osnovni demografski podaci, faktori rizika od težeg oblika bolesti, simptomi i znaci gripa, laboratorijski nalazi i radiografija grudnog koša. Analizirana je primenjena antivirusna terapija i ishod bolesti (preživeli, umrli). **Rezultati.** Prosečno vreme od početka gripa A (H1N1) 2009 do prijema u bolnicu bilo je 3 dana (0–16 dana), a do prijema u jedinicu intenzivne nege (JIN) 2 dana (0–5 dana). U životnom dobu od 20–29 godina bilo je 49 (50,0%) bolesnika, a ≥ 65 godina 5 (5,1%) bolesnika. Osnovne bolesti imao je 21 (21,4%) bolesnik, gojaznih je bilo 18 (18,4%), pušača cigareta 19 (19,4%). Povišenu telesnu temperaturu imalo je svih 98 bolesnika, kašalj 81 (82,6%), dispneju i dijarealni sindrom ¼ bolesnika. Više od 75% bolesnika imalo je laboratorijske nalaze u granicama normale. *Real-time polymerase chain reaction* (PCR) test za identifikaciju virusa influence A (H1N1) 2009 bio je pozitivan kod 14 (77,8%) bolesnika. Pneumonija bila je verifikovana kod 30 (30,7%) bolesnika. U JIN bilo je primljeno 6 (6,1%) bolesnika, prosečne starosti 45 ± 14 godina (31–59 godina), od kojih je akutni respiratorni distres sindrom (ARDS) imalo 5 (5,1%). Faktori rizika registrovani su češće kod bolesnika sa akutnom respiratornom insuficijencijom (14,2% prema 4,9%, $p < 0,05$). Oseltamivir je dobijalo 67 (68,4%), antibiotike 89 (90,1%), a kombinovanu terapiju 64 (65,3%) bolesnika sa novim gripom. U prvih 48 sati od početka gripa oseltamivir bio je primenjen kod 43 (43,3%) bolesnika, od kojih je samo jedan (3,4%) razvio ARDS. Smrtni ishod zabeležen je kod 2,0% bolesnika (2 od 98 bolesnika), odnosno kod 33,3% bolesnika lečenih u JIN. **Zaključak.** Novi grip ispoljava se uglavnom kao blaga akutna respiratorna bolest, od koje najčešće obolevaju mlađe odrasle osobe. Mali broj bolesnika razvija teške forme bolesti. Antivirusna terapija može biti od velike koristi, posebno kada se sa njenom primenom otpočne u prvih 48 sati od početka bolesti.

Ključne reči:
grip A virus, podtip H1N1; bolest, prenošenje; bolest, progresija; lečenje lekovima; mortalitet.

Introduction

The first two cases of swine flu in humans, caused by a pandemic strain of influenza A (H1N1), originating from pigs were registered in the territory of the United States in April 2009. [1, 2]. In the same period epidemic occurrence of acute respiratory illness caused by new flu virus was recorded in Mexico [3]. In just two months the virus spreaded to every continent and most countries in the world, so that the World Health Organization declared the first pandemic of the 21st century on 11th June 2009. [4–10]. In these circumstances it was the matter of time when the new strain of influenza A (H1N1) virus would occur in Serbia. One of the events in 2009 which was considered as the event of high risk for virus entry into Serbia was the Universiade in Belgrade held in July 1–14, 2009. Since the Military Medical Academy (MMA) was responsible for health care status in the participants in the Universiade, the first cases of new influenza patients were treated in the Clinic for Infectious and Tropical Diseases of MMA, just during the event. Despite the occurrence of sporadic cases of the disease during July, the epidemic occurrence of pandemic flu in Serbia began in November 2009.

Unique genetic and antigenic properties of new influenza virus A (H1N1) resulted in a high incidence of infection in the U.S. and other countries. It is estimated that during the pandemic of new influenza A (H1N1), in a period from April 2009 to April 2010, across the U.S. between 43 and 89 million people were infected with the virus, resulting in approximately 274,000 hospitalizations and 12,470 deaths associated with the novel flu virus [11–15]. Information about the clinical spectrum of manifestations, risk factors for the severity of disease, treatment and outcome in patients with influenza A (H1N1) are still being collected, although a few clinical studies were published on this issue in the past year [13–26]. Some of these studies indicate that the most serious form of swine flu, which are accompanied by severe hypoxemia, multiple organ failure, septic shock, prolonged mechanical ventilation and death are often recorded in young, previously healthy adults [18–26].

The aim of this study was to investigate clinical symptoms, risk factors for severe forms of influenza, treatment and outcome in patients with novel influenza A (H1N1) hospitalized in the Clinic for Infectious and Tropical Diseases MMA.

Methods

During a pandemic influenza A (H1N1) 1,288 patients with symptoms and signs of flu-like illness were treated in the Clinic for Infectious and Tropical Diseases, MMA. Out of that number, 98 (7.6%) hospitalized patients were included in this study. There were 68 (69%) men and 30 (31%) women. A total of 52 (53.1%) were the members of the Serbian Army and 46 (46.9%) had health insurance by other institution. Six (6.1%) patients were participants in the Universiade in July 2009, they were sporadic, imported cases of swine flu, while 92 (93.9%) were the patients hospitalized during the period from November 5th 2009 to January 20th 2010, when novel flu assumed a character of an epidemic in Serbia. The average age of the hospitalized patients was 32 ± 15 years (14–88 years). In the first group it was 22 ± 2 years (20–24 years), and the second 33 ± 16 years (14–88 years), which was a statistically significant difference ($p < 0.05$).

The criteria for hospitalization of patients with clinical signs of flu-like illness were: body temperature ≥ 38.0°C, findings of pulmonary infiltrates on chest radiography, hypoxemia, acute lung injury ($pO_2/FiO_2 < 300$), acute respiratory failure (ARF), hemodynamic instability and dysfunction of other organs, myositis and encephalitis, as well as the existence of predisposing chronic diseases and comorbid conditions (risk factors for severe forms of influenza), such as asthma, chronic obstructive pulmonary disease (COPD), diabetes, chronic cardiovas-

cular disease, chronic kidney disease, epilepsy, neoplasms, immunosuppressive therapy, extreme obesity, second and third trimester of pregnancy and the age over 65 years.

In all of the patients, in addition to the basic demographic data, we registered the presence of predisposing diseases and conditions for more severe disease symptoms and signs of influenza. Laboratory tests were performed (complete blood count, C-reactive protein, urea, creatinine, transaminases, creatine kinase, lactate dehydrogenase, and, if necessary, gas analysis and other laboratory findings). In addition, all the patients on admission underwent chest radiography at the Institute of Radiology, MMA. We used the real-time polymerase chain reaction (PCR) to identify the virus A (H1N1) 2009 from nasopharyngeal swabs of the hospitalized patients. The test was performed in a reference laboratory in the Institute of Immunology and Virology "Torlak". Detection of antibodies against influenza A viruses in paired sera was performed by a complement fixation reaction (CFT), which like other necessary microbiological analyses was performed in the Institute of Microbiology, MMA. The diagnosis of viral or bacterial pneumonia was based on physical findings in the lungs, laboratory findings and radiographic infiltrates in the lung parenchyma. The diagnosis of acute respiratory distress syndrome (ARDS) was based on clinical findings of the acute respiratory infection (ARI), massive bilateral pneumonia on chest radiography, the absence of heart failure and the relationship of partial pressure of oxygen (pO_2) and a fraction of oxygen in inspired air (FiO_2).

Dyspnea and the presence of infiltrates in the lung parenchyma were the key criteria for the introduction of antiviral therapy, but we respected the recommendations of the Center for Disease Control (CDC) and some authorities for treatment of seasonal and pandemic influenza [27–29]. Antibiotic and antiviral therapies were analyzed in all the patients, as well as the response to the therapy and the final outcome (survived/died).

Body Mass Index (BMI – weight in kilograms divided by body surface area in m^2), was determined to assess the degree of obesity in the patients. The patients with BMI > 30 kg/m^2 were classified as obese, while those with BMI > 40 kg/m^2 were classified as extremely obese. Smoking cigarettes was registered among other potential risk factors for severe forms of influenza.

The Intermediate Care Unit in the Clinic for Infectious and Tropical Diseases, MMA, was adapted to the Intensive Care Unit (ICU) during preparation for pandemic of swine flu including a daily anesthesiologist duty, to establish an effective communication between a specialist in infectious diseases and an anesthesiologist and to separate patients with influenza requiring mechanical ventilation from seriously ill in the ICU.

The results were presented as numbers, percentages and mean ± SD. The χ^2 test to assess the significance in differences between the groups was used. Probability level of $p < 0.05$ was considered statistically significant.

Results

The average time from the occuring the first symptoms of novel influenza A (H1N1) to hospitalization in our series of patients was 3 days (0–16 days). Average time from the beginning of flu to hospitalization of patients with acute respiratory failure (ARF) was 5 days (1–7 days), while average time from hospital admission to admission in the ICU was 2 days (0–5 days). In 28 (28.6%) patients, average age of 21 ± 6 years (16–37 years) the main criterion for admission was fever (≥ 38.0°C). A total of 15 (15.3%) patients were over 50, and only 5 (5.1%) over 65. It was shown that 50% of all the hospitalized patients were 20 to 29. The number of these patients as compared to the number of the patients in other age groups was significantly higher ($p < 0.01$) (Table 1).

Table 1

Age of 98 hospitalized patients with novel influenza A (H1N1)

Age (years)	% of patients
10–19	12
20–29	50*
30–39	14
40–49	8
50–59	8
≥ 60	7

***p* < 0.01 as compared to other age groups**

Totally 21 (21.4%) of the patients were with predisposing chronic diseases for the development of severe clinical symptoms of influenza A (H1N1), of whom five patients had ≥ 2 risk factors. Chronic cardiovascular diseases were noticed in 8 (8.2%) of the patients, diabetes mellitus in 6 (6.1%), asthma and COPD in 5 (5.1%) and a long-term immunosuppressive therapy in 4 (4.1%) of the patients. Among the hospitalized patients there was one (1.0%) pregnant woman in the second trimester of pregnancy. In addition, among the hospitalized patients 18 (18.4%) were obese, and 2 (2.0%) extremely obese. A total of 19 (19.4%) patients were cigarette smokers.

Figure 1 shows that the majority of patients demonstrated clinical symptoms and signs of general infectious syndrome, characteristic for influenza. All of 98 patients had

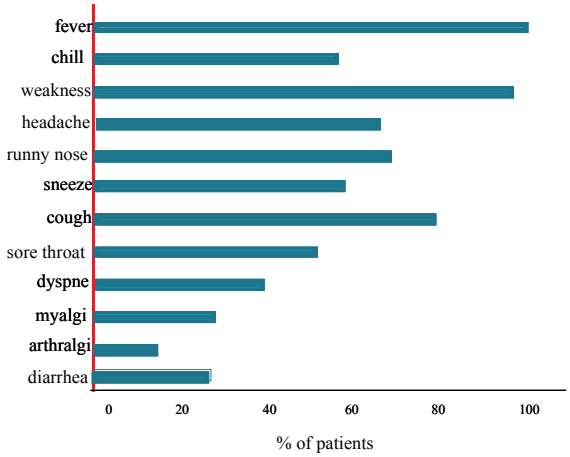

Fig. 1 – The signs and symptoms of novel influenza A (H1N1) in 98 hospitalized patients

fever, fatigue was registered in 94 (95.9%), chills in 60 (61.2%) and headache in 65 (66.3%) of the patients. Myalgia, arthralgia, and symptoms of gastrointestinal tract were recorded in less than ¼ of the patients. Most patients manifested more or less pronounced symptoms and signs of the respiratory tract, and cough was registered in 81 (82.6%), sore throat, runny nose and sneezing in about 60% of the patients, while dyspnea in ¼ of the patients.

Most patients (> 75%) with new influenza A (H1N1) in our series had laboratory findings within the limits of normal. As shown in Figure 2 anemia and leukopenia were registered in 15 (15.3%), while leukocytosis was noted only in 7 (7.1%) of the patients, and thrombocytopenia in 17 (17.3%) of the patients. Monocytosis was found in a total of 20 (20.4%) of the patients. Elevated serum enzymes were found in less than ¼ of the patients, LDH in 23 (23.5%), ALT in 12 (12.2%), GGT in 7 (7.1%) and CK in 20 (20, 4%) of the patients.

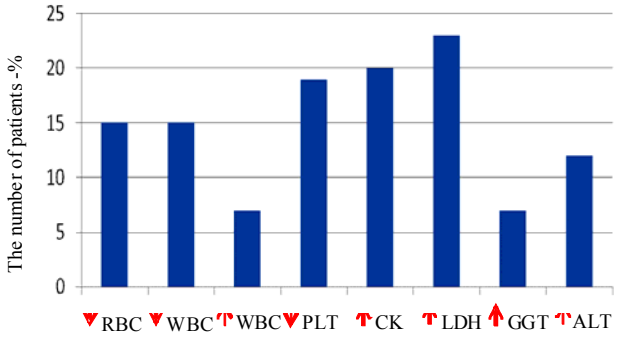

Fig. 2 – The laboratory findings in 98 hospitalized patients with novel influenza A (H1N1)

RBC – red blood cells; WBC – white blood cells; PLT – platelets; CK – creatine kinase; LDH – lactic acid dehydrogenase; GGT – gamma-glutamate transpherase; ALT –alkaline phosphatase

14 (14.3%) with confirmed influenza. All of them were treated for novel pandemic influenza.

In 50 (51.0%) patients novel flu manifested as acute upper respiratory tract infections (rhinitis, pharyngitis, laryngitis), in 18 (18.3%) patients as acute bronchitis, and 30 (30.7 %) patients had radiologically verified pneumonia (Figure 3). Among the patients with risk factors for severe influenza pneumonia was registered in 8 (38.1%) of 21 patients, and among those without risk factors in 22 (28.6%) of 77 patients which was not a statistically significant difference.

Unilateral pneumonia was registered in 15 (15.3%) of the patients, bilateral pulmonary infiltrates in 10 (10.2%) of the patients, and ARDS in 5 (5.1%) of the patients with novel influenza. Acute respiratory failure had a total of 7 (7.1%) patients, six of them admitted to the ICU. The average age of patients with pneumonia was 28 ± 19 years (14–59 years).

Six (6.1%) patients with clinical signs of swine flu and ARI, mean age 45 ± 14 years (31–59 years) were admitted to the ICU. Five of them with clinical signs of ARDS were treated with invasive mechanical ventilation, while one patient met criteria for acute lung injury and was treated with noninvasive mechanical ventilation. Among the patients with ARF, risk factors for developing severe forms of influenza had 14.2% (3 of 21) of the patients, and no risk factors was confirmed in 4.9% (3 of 77) of the patients. This difference was statistically significant ($p < 0.05$). Concerning the occurrence of ARDS in these two groups, the ratio was even more pronounced (14.2% *vs* 2.6%, $p < 0.01$). Sepsis was registered in two (2.0%), and multiorgan dysfunction in one (1.0%) of the patients. In these patients, *Staphylococcus aureus*, *Acinetobacter* spp and *Pseudomonas aeruginosa* were isolated from blood cultures.

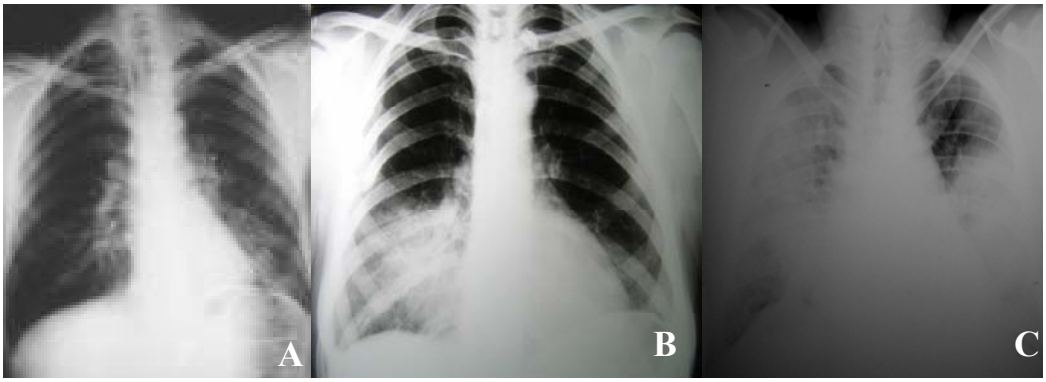

Fig. 3 – Radiographic findings in three patients with novel influenza A (H1N1)

A – viral pneumonia; B – Bacterial pneumonia; C – Adult Respiratory Distress Syndrome (ARDS)

The real-time PCR test for identification of influenza A (H1N1) was performed in only 18 patients due to technical reasons. It was positive in 14 (77.8%) of the patients, while the complement fixation tests (CFT) for the detection of antibodies against influenza A viruses was done in 19 patients, but quadruple increase in titer was registered in 10 (52.6%) of them. There were 74 (75.5%) patients with suspected novel influenza A (H1N1), 10 (10.2%) with a likelihood and

Antiviral therapy, oseltamivir 150 mg per day orally, was prescribed to 67 (68.4%) of the patients, of whom 64 (65.3%) received antibiotic therapy at the same time, and 3 (3.1%) patients were treated only with oseltamivir. In the group of patients treated with a combination of therapies 31 (31.6%) patients received oseltamivir and azithromycin, and 33 (33.7%) oseltamivir, azithromycin and ceftriaxone.

Antiviral therapy was prescribed in all 67 patients after admission to the clinic, and the average time from the onset of symptoms to the initiation of the therapy was 2.6 days (0–12 days). The application of oseltamivir in the first 48 hours after the beginning of novel flu was started in 29 (43.3%) patients, among whom only one (3.4%) developed ARDS. Oseltamivir was given to 38 (56.7%) patients 48 hours after the onset of flu, of whom 4 (10.5%) had ARDS. The appearance of ARDS among the patients who received oseltamivir after 48 hours from the start of flu was three times higher, compared to the first group, but the difference was not statistically significant.

Antibiotic therapy (ceftriaxone 2 g daily, intravenously, and azithromycin 500 mg daily, orally) was administered to 89 (90.1%) of the patients with novel influenza. Only antibiotics (without antiviral drugs) were administered to 25 (25.5%) of the patients, azithromycin to 20 (20.4%), ceftriaxone to one (1.0%), and azithromycin combined with ceftriaxone to 4 (4.1%) the patients.

Six (6.1%) of the patients were treated only with symptomatic therapy.

Fatal outcome was noted in 2 (2.0%) of 98 patients (33.3% of patients treated in the ICU). Risk factors for severe forms of influenza had an impact on the outcome of the disease, which can be illustrated by the example of two patients at the age of 41 years. The first patient who died had arterial hypertension, was extremly obese and havy smoke, while another one, who survived, had no risk factors. In the first patient antiviral therapy was included on the sixth day, and in another ones on the seventh day from the start of flu. Before the start of the therapy initial ARDS in both patients had alredy been regisered.

Discussion

The study presented a series of 98 patients with novel influenza A (H1N1) who were hospitalized in the Clinic for Infectious and Tropical Diseases, MMA during a 10-week period of an epidemic of influenza in Serbia. The number of male patients was twice as high as the number of women, probably because over 50% of the patients were from the ranks of the Serbian Army. Cui et al. [18] registered a similar ratio of genders in patients with influenza A (H1N1) and pneumonia, but the cause of that relationship was not considered. The clinical features of imported influenza A (H1N1) to the Universiade 2009 participants involved in the study did not differ from the clinical picture in patients during a pandemic, although there was a significant difference in age between the two groups.

The average age of the patients in our study was 32 years, in contrast to 21 years in 272 patients studied by Jain et al. [17], and 27 years in 1,088 patients studied Louie et al. [26] This difference was probably because the aforementioned authors included in their research the youngest population of pediatric patients, while the youngest patient in our study was 14 years old. The average age of patients with influenza A (H1N1) treated in the ICU was higher in our than in several other studies. In the study of Jain et al. [17] it was 29 years, in the study of Kumar et al. [23] (215 critically ill patients) 32 years, and in the study of Davies et al. [25], who presented 68 critically ill patients with novel flu it was 34 years. In two other studies the average age of critically ill patients with novel flu was similar to that in this study, so that in the study of Cui et al. [18] it was 41 years, and in the study of Domínguez-Cherita et al. [22] it was 44 years. According to the available data it cannot be concluded precisely if the difference in age among the patients treated in ICU in these studies could have an impact on the outcome.

The average time from the beginning of the first flu symptoms to hospitalization of our patients was not significantly different in comparison to some other studies. For example, in the study of Jain et al. [17] it was 3 days (0–18 days), and in the study of Kumar et al. [23] it was 4 days (0–22 days). In our study, the average time between hospital admission and admission to the ICU was 2 days, whereas in the study of Kumar et al. [23] and Domínguez-Cherita et al. [22] it was only one day. The conclusion of these authors was that the critical illness caused by influenza A (H1N1) occurs rapidly after admission to hospital, often in young adults and is accompanied by severe ARDS, refractory hypoxemia, shock and high mortality rate. Reasons for the difference in time before admission to the ICU, or to the development of critical illness, cannot be considered correctly because of the lack of information about it, so it remains to be investigated.

Epidemiological characteristics of novel influenza related to hospitalization, severity of disease and mortality rate have been intensively investigated since the start of a pandemic, and so far the results have been very interesting. According to the obtained data, epidemiological profile of novel flu is different from diseases caused by seasonal influenza virus. Pandemic influenza A (H1N1) most commonly affects younger persons and generally causes mild illness, while the most severe form of seasonal influenza usually affects people under the age of 2 years and older than 65 and patients with predisposing diseases or conditions for the development of severe forms of influenza. It is known that in the peak period of disease, hospitalizations are commonly necessary among people over 65 in seasonal influenza and that more than 90% of deaths from seasonal influenza are registered in elderly patients. On the other hand, when it comes to novel influenza, young adults, pregnant women and people with chronic disease pandemic virus infected are at higher risk of hospitalization and the development of severe forms of illness or death [26, 27, 30–40].

In our study 50% of the hospitalized patients were in the third decade of life, and only 5% of them had more than 65 years. The difference in affected population could be explained by the fact that young people were more often exposed to novel influenza virus A (H1N1), and that younger febrile persons were more often tested for influenza virus A (H1N1) than the elderly who often had no fever, and that persons under 60 were susceptible to infection with influenza virus A (H1N1), as indicated by the results of several serological studies [30, 41–44].

According to the literature, between 44% and 84% of adult hospitalized patients with seasonal influenza have an underlying disease, and similar results were obtained in the case of patients with novel influenza [15–31]. Perez-Padilla et al. [35] showed 18 patients with pneumonia of which 50% had an underlying disease, while the study of Cui et al. [18] recorded an underlying disease in 34% of 68 patients. In the study of Louie et al. [26] risk factors for developing complications associated with influenza had 68% of patients, in the study of Lee et al. [29] 79%, and in the study of Jain et al. [17] 82% of the patients. In contrast, in our study predisposing diseases for the development of severe forms of influenza had only 21% of the patients, although the number of patients with risk factors was higher when taking into account a pregnant woman, obese patients and smokers. A small number of patients with primary disease may be interpreted by their demographics and the fact that they were members of the army, who are usually healthy young people. In patients with seasonal influenza asthma and COPD are the most common underlying diseases, which coincides with data from some studies on patients with novel influenza [13–20].

The main comorbidities in critically ill patients with influenza A (H1N1) in the United States and Mexico were chronic lung disease, obesity, hypertension, diabetes and smoking cigarettes, while in our study there were mostly cardiovascular diseases and diabetes [15, 17, 19, 22, 26]. According to the results of some studies obesity, pregnancy and COPD were associated with the development of severe forms of pneumonia caused by influenza A virus (H1N1), often with ARDS, but age, high APACHE II and SOFA scores and deferred antiviral therapy with higher morbidity and mortality [19–26].

Physiological changes and immune "deviation" from cell to humoral immunity that occurs during pregnancy are hypothetical preconditions for an increased vulnerability of pregnant women. Pregnant women were at higher risk of morbidity and mortality during novel influenza, similar to the earlier period of seasonal and pandemic influenza [39–51]. Denholm et al. [14] in their study of 112 cases of influenza A (H1N1), among who were 15 pregnant women, claimed that pregnant women were at high risk of developing severe and fatal form of the disease, which required urgent application of antiviral therapy. The percentage of hospitalizations of pregnant women suffering from novel flu in our study was small, as compared to other studies that ranged up to 10% [17, 39–51]. Those differences in the number of hospitalized pregnant women between this and other studies can be explained by the fact that the majority of our patients belonged to a group of previously healthy, young male with military health insurance.

According to the available literature data the number of hospitalized obese patients with influenza A (H1N1) was higher than in our group. For example, Jain et al. [17] reported that 45% of hospitalized patients were obese, and half of them extremely obese, while the number of obese in the study of Domínguez-Cherita et al. [22] was 36%. Cui et al. [18] took the example of 32% of obese patients in their study and showed that obesity as a risk factor was associated with higher mortality rate from influenza A (H1N1). Similarly Lee et al. [19] presented a series of 47 fatal cases of influenza A (H1N1), among them 58% of obese patients. Obese patients often have other comorbidities that are associated with increased risk of developing complications of influenza, and even death. For example, one of the deceased patients in our study, in addition to extreme obesity also had hypertension and was a smoker.

Hospitalized patients of seasonal and pandemic influenza A (H1N1) have a similar clinical presentation, whether it is a mild or severe disease [27–36]. However, unlike seasonal influenza, where gastrointestinal symptoms are described mainly in children in less than 5%, in our and other studies in patients with novel flu, gastrointestinal symptoms were more common, both in children and adults. Cui et al. [18] showed that 52% of patients with pneumonia and novel influenza had a reduced number of CD4 + cells and that lymphopenia, which was not improving for five days from the onset of treatment was a factor associated with death. We did not discuss the relationship of certain blood parameters with patient outcome, but we noticed that the number of patients with leukopenia and thrombocytopenia was similar to that of other authors [17].

The most severely ill patients and those who died had the highest values of lactate dehydrogenase and creatine kinase, but their prognostic value was not interpreted [22–26]. In seasonal influenza, during the peak period up to 90% of the total number of death were registered among persons older than 65, while the highest mortality in patients with novel flu was recorded in the age of 20 to 49 years [27–36]. Increased mortality in younger patients as compared to those over 59 years when it comes to a novel influenza could be explained by the presence of cross protective antibodies to infuenza A (H1N1), which can be found in older patients because they were exposed to different strains of A (H1N1) during 1950 [30, 41–44].

In seasonal influenza, bacterial superinfections are registered in 6–24% of the patients, which are mostly caused by *Staphylococcus aureus*. In previous pandemics of influenza the majority of deaths were associated with bacterial pneumonia. According to the Center for Disease Control 29% of 77 patients who died from novel influenza had bacterial infection, and in 10 of them *Streptococcus pneumoniae* was confirmed [27–31, 52–55]. Lee et al. [19] described 28% of bacterial superinfections among a series of 47 fatal cases of influenza A (H1N1). Louie et al. [26] registered a secondary bacterial infection in only 4% of the patients with novel flu, while we noticed a positive blood culture in three patients treated in the ICU. A small number of bacterial infections in our study was associated with a small number of patients treated in the ICU and the application of antibiotics before obtaining samples for culture.

Novel flu was expresed in a severe form such as pneumonia, ARF and ARDS, in about ⅓ of the patients, which resulted in admission to the ICU of 6% of the patients, similar to the study of Domínguez-Cherita et al. [22]. In a slightly more than ⅓ of the patients we registered the

risk factors for developing severe forms of influenza, but they did not have a significant impact on the development of pneumonia. This is consistent with the experience of other authors, according to whom a severe form of new influenza primarily affects young and previously healthy people [17–19]. One of the conclusions of the Jain et al. [17] was that pandemic strain of influenza virus A (H1N1) causes severe disease accompanied by pneumonia, ARDS and death in a significant number of previously healthy young people. In this prospective study, pneumonia was registered in 40.2% of the patients, usually in the form of bilateral infiltrates (26.5% of patients), whereas in our study, pneumonia occurred in less than ⅓ of patients, usually in the form of unilateral infiltrates. Among hospitalized patients with influenza A (H1N1) presented by Louie et al. [26] as many as 66% had pneumonia and 31% were admitted to ICU. Zhao et al. [28] presented 68 patients with pneumonia and confirmed influenza A (H1N1), of which 44% were admitted to ICU. Many of these patients had been previously healthy and only few over 65 years.

A number of authors suggested that clinical course of swine flu can be very severe, especially in patients with comorbidities and may be accompanied by high mortality. The experience gained during a pandemic showed that novel influenza can go into ARDS with refractory hypoxemia in healthy young person for a few hours and may result in rapid death. The first publications on patients with severe influenza A (H1N1) and ARDS showed variable mortality of 15%–40% [21–26]. That may be due to different populations of patients included in the study, the different characteristics of ARDS, and various human and material resources in the ICU in individual countries. The highest rate of mortality (41.4%) was described in Mexico, the first one to be affected by pandemic influenza [22]. Davies et al. [26] showed 68 cases of new influenza with severe ARDS that were treated with extracorporeal membrane oxygenation with mortality rate of 21% [26].

Cui et al. [18] presented 68 patients with confirmed influenza A (H1N1), of which 44% admitted to ICU with a mortality of 14.7%. According to the study of Jain et al. [17] mortality was noted in 28.4% of 67 patients treated in ICU. Denholm et al. [14] pointed out 26.8% of 112 patients with novel influenza admitted to ICU and mortality of 10%. Kumar et al. [23] showed that total mortality among critically ill patients on the day 28 was 14.3%, and on the day 90 17.3%, which was significantly lower than in other studies. In our study, novel flu resulted in death in about ⅓ of the patients admitted to ICU and in only 2% of all hospitalized patients.

Influenza A (H1N1) is almost always sensitive to neuraminidase inhibitors, oseltamivir and zanamivir. In this context, antiviral therapy should be given in all hospitalized patients with influenza A (H1N1), in pregnant and all immunocompromised outpatients [55–62]. The study of Belongia et al. [15] published in 2010 in favor of these views and suggested that the risk of serious complications of influenza A (H1N1) was not greater than the risk for recent seasonal influenza. There is a consensus on the highest benefit of antiviral therapy if the treatment starts early, in the first 48 hours after the onset of novel influenza. However, antiviral drugs should not be withheld in any other patient in whom it has been more than 48 hours after the onset of a novel flu [56–61]. Prospective studies, in which the oseltamivir therapy was conducted in hospitalized patients with influenza, showed a significant reduction in mortality, even when the treatment started within 48 hours after the onset [61, 62].

The results of the majority of previous studies indicate that delayed antiviral therapy may have impact on the increased severity of disease and mortality in patients with influenza A (H1N1). Lee et al. [19] showed that the time from the onset of influenza A (H1N1) to the hospitalization was longer for non-survivors than for survivors (3 *vs* 2 days, $p < 0.05$), like the time for begining oseltamivir therapy (6.5 *vs* 3 days, $p < 0.01$). The patients with fatal outcome in this study rarely received oseltamivir in the first two days of hospitalization in contrasts to survivors (61% *vs* 96%, $p < 0.01$). The results of our study also suggest that antiviral therapy in patients with novel flu could be useful, especially when started early in the disease. We administered oseltamivir in 68.4% of the patients, of whom nearly 43% received the drug in the first 48 hours after the onset of the illness. The appearance of ARDS in the patients who recived oseltamivir in the first 48 hours from the onset of the illness was three times higher as compared to those who recived the therapy after 48 hours. However, the number of patients with ARDS in our country was small to make a reliable conclusions. Jain et al. [17] applied antiviral therapy in 75% of hospitalized patients after the average time from the beginning of flu and the therapy of 3 days (0–29 days). However, in the first 48 hours of the onset of novel influenza antiviral therapy was applied an only 39% of patients. Patients admitted to ICU and those with fatal outcome, compared to patients with less severe form of flu rarely received antiviral therapy during the first 48 hours after the onset of stroke (23% *vs* 86%). The average time from the start of flu to the introduction of antiviral therapy in the deceased patients was 8 days (3–20 days), in patients admitted to the ICU 6 days (0–24 days), which is longer than in our study [17]. We prescribed oseltamivir in almost all of the patients immediately after the reception, which might be attributed to the small number of admission to the ICU in our study. In the study of Louie et al. [26] mortality was 10.8%, although 79% of patients received antiviral therapy. The most common cause of death in this study was viral pneumonia and ARDS [26]. These results can probably be caused by a delayed antiviral therapy.

Some studies showed that bacterial pneumonia was associated with influenza A (H1N1) in 30% of cases admitted to the ICU, which required early antibiotic therapy in combination with antiviral therapy [52]. In this regard, in most studies, including our, antibiotic therapy was administered in almost all hospitalized patients [17]. For example, Jain et al. [17] applied antiviral therapy in 73% and antibiotic therapy in 97% of patients with pneumonia. In this study, all patients with lethal outcome were treated with antibiotics, while antiviral therapy recived 90% of the patients. According to some authors the use of antibiotics in patients

with influenza A (H1N1) and pneumonia is necessary because of the lack of reliable diagnostic methods for bacterial pneumonia [17, 30–32]. However, this view is difficult to support, taking into account the availability of high quality and rapid laboratory-microbiological analysis (C-reactive protein, procalcitonin, detection of bacterial antigens, etc.). However, we also applied antibiotic therapy in 90% of the patients with influenza A (H1N1) and in all of those with pneumonia.

Conclusion

Pandemic influenza A (H1N1) is mainly manifested as a mild acute respiratory disease, which usually affects young adults. A small number of patients develop severe forms of the disease and the development of ARDS occurs more frequently in patients with risk factors. Application of oseltamivir can be very useful, especially when treatment is started within the first 48 hours after onset.

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O P Š T I P R E G L E D

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Povrede grudne aorte i njenih grana

Injuries of the thoracic aorta and its branches

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Ključne reči:
aorta, torakalna; povrede; dijagnoza, diferencijalna; hirurgija, kardiovaskularna, procedure; mortalitet.

Key words:
aorta, thoracic; wounds and injuries; diagnosis, differential; cardiovascular surgical procedures; mortality.

Uvod

Povreda grudne aorte i velikih krvnih sudova u grudnom košu relativno je retka, ali zbog često fatalnog ishoda, ima veliki medicinski i socijalni značaj. Penetrantne povrede grudne aorte, još uvek se znatno češće dijagnostikuju na obdukcionom, nego na operacionom stolu zbog iskrvarenja. To se posebno odnosi na povrede nastale u ratnim uslovima kada je broj *post mortem* dijagnostikovanih slučajeva dva i po puta veći od onih koji su dijagnostikovani klinički [1].

Zbog saobraćajnog traumatizma u velikom porastu su i tupe povrede grudne aorte. Godišnje u SAD 7 500–8 000 osoba, starih između 20 i 30 godina, doživi ovakvu povredu. Od toga, na mestu nesreće umre 80% povređenih, a samo 20% inicijalno preživi. Od tog broja 30% umire u narednih 6 sati, 40% tokom prvog dana, 72% tokom prve nedelje, a više od 90% tokom prvih 10 nedelja. Manje od 10% povređenih preživi ovaj period, kada dolazi do formiranja pseudoaneurizme, što predstavlja relativnu stabilizaciju stanja [2, 3].

Od svih supraaortnih grana povredama je najčešće izložena arterija anonima. Istovremeno, ove povrede su najteže. Sve do samog kraja prošlog veka, bilo je malo autora koji su opisali više od jedne povrede ove arterije. Tokom Vijetnamskog rata zabeležene su samo tri hirurški zbrinute povrede arterije anonime, što je svega 0,3% od ukupno 1 000 operisanih arterijskih povreda [4]. Od ukupno 144 ratne povrede krvnih sudova iz jugoslovenskog građanskog rata lečene u Klinici za vaskularnu i endovaskularnu hirurgiju Kliničkog centra Srbije, nije bilo slučajeva povrede arterije anonime [5]. Razlog je već opisano iskrvarenje koje je pratilo penetrantne povrede grudnog koša. Poslednjih dvadeset godina u mirnodopskim uslovima, zbog bržeg transporta, bolje dijagnostike i većeg učešća tupe trauma, čija je prognoza bolja, povrede arterije anonime sreću se i češće [6, 7].

Penetrantne povrede grudne aorte i supraaortičnih grana inicijalno imaju dva ishoda. Ako postoji komunikacija sa spoljašnjom sredinom, a to je najčešće penetracija zida grudnog koša, veoma brzo dolazi do iskrvarenja, srčanog zastoja i smrtnog ishoda. Samo mali broj laceracionо-transekcionih povreda grudne aorte i velikih krvnih sudova grudnog koša, stiže do hirurga. U pitanju su manje laceracione povrede, gde je krvarenje relativno sporo, što stvara uslove za nastanak tromba. Tromb zajedno sa krvlju koja je izlivena u perikard, odnosno medijastinum ili hemitoraks, ponekad može da napravi privremenu hemostazu tamponadom. Čak 90% ovakvih bolesnika inicijalno preživi [8]. Zato, neophodno je da se u ovakvim slučajevima deluje izuzetno brzo. Sugeriše se sledeća taktika: 1) ako od mesta nastanka povrede do ustanove u kojoj se ovakva povreda može zbrinuti ima manje od 12 minuta, indikovan je hitan transport; 2) ako je to vreme duže od 15 minuta, smatra se da ima smisla nadoknadom tečnosti pokušati korekciju hipotenzije, pa onda započeti sa transportom [9]. Neki autori sugerišu primenu „antišok pantalona“ (*Military Antyshock Trausers* – MAST) koje, teoretski, imaju dva efekta [10]. Prvi je translokacija venske krvi iz infra- u spradijafragmalni deo tela, što u preseku kod odrasle osobe iznosi 1,5 litara. Drugi je redukcija priliva arterijske krvi u donje ekstremitete povećavanjem perifernog otpora. Time se privremeno povećava arterijski pritisak i olakšava centralizacija protoka (slika 1).

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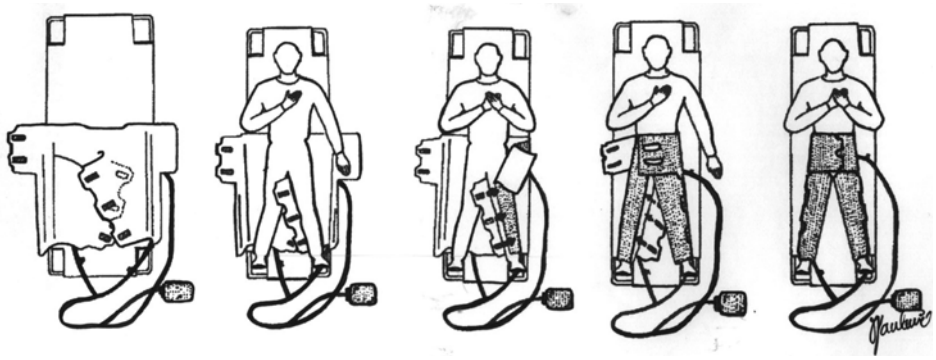
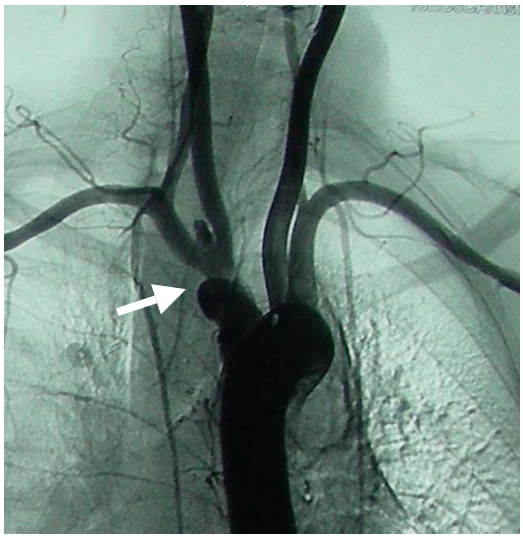


Sl. 1 – ′Antišok pantalone′

Etiopatogeneza

Povrede grudne aorte i supraaortičnih grana nastaju tokom njene tupe ili penetrantne traume, odnosno nekih medicinskih postupaka. Patoanatomski, u pitanju su laceracija, transekcija, kontuzija, pseudoaneurizma i arteriovenska fistula.

Za razliku od znatno češćih penetrantnih povreda koje se sreću kod 80% povređenih i koje, uglavnom, zahvataju distalni deo arterije anonime, tupe povrede sreću se kod 20% povređenih i, najčešće, zahvataju proksimalni deo arterije anonime. Postoje dva mehanizma kojima se tumači nastanak tupe povrede arterije anonime. Prvi započinje spoljašnjom kompresijom na sternum usled čega dolazi do pomeranja srca ulevo, sa istovremenim maksimalnim istezanjem arterije anonime. Drugi mehanizam uzrokuje deceleracija usled koje istovremeno započinju hiperekstenzija vrata i rotacija glave ulevo, što je praćeno longitudinalnim pritiskom na anonimu. U situaciji kada je aortni luk fiksiran, a arterija anonima mobilna, njeno ishodište u oba slučaja trpi veliku tenziju, pa nakon velikog istezanja nastaje avulzija na njenom ishodištu iz aortnog luka. Upravo to uzorkuje masivno krvarenje i otežava zbrinjavanje (slika 2) [6].



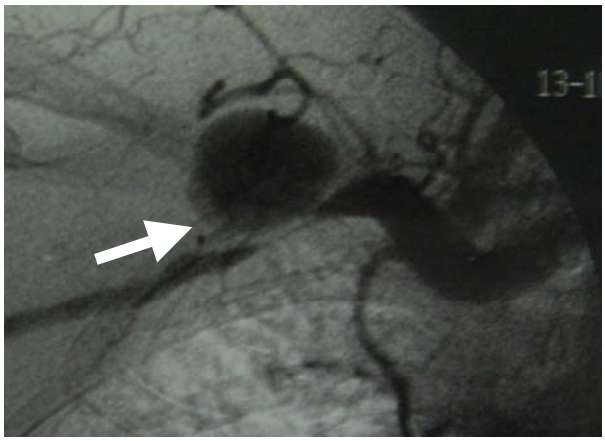
Sl. 2 – Avulziona povreda arterije anonime (strelica) nastala u okviru tupe povrede grudnog koša tokom saobraćajne nesreće (bolesnica je uspešno operisana u Klinici za vaskularnu i endovaskularnu hirurgiju Kliničkog centra Srbije)

Od kako je Korte 1879. godine prvi objavio, publikovano je više od 100 slučajeva fistule između traheje i arterije anonime koje nastaju u vezi sa traheostomijom [11]. Incidencija ove opasne komplikacije je 0,1–1,0%. Razloga za njen nastanak ima više [12]. Prvi je nisko urađena traheostoma. Naime, arterija anonima obično ukršta traheju u nivou 9. trahealne hrskavice, ali to može varirati od 6. do 13. nivoa hrskavice. Stoga, svaka traheostoma urađena ispod 4. nivoa hrskavice može dovesti do pojave fistule sa arterijom anonimom. Drugi razlog je prenaduvan balon za fiksiranje kanile, što dovodi do cepanja mukoze traheje. Treći razlog su anomalije aortnog luka za koje se obično ne zna, pre izvođenja trahesotomije. Ipak, s obzirom na to da preko 70% fistula između arterije anonime i traheje nastaje nakon tri nedelje od postavljanja kanile, verovatno je infekcija najznačajniji razlog za njihov nastanak. S obzirom na masivno krvarenje koje u ovakvim slučajevima nastaje, privremena hemostaza je od izuzetnog značaja. Ona se može izvesti na dva načina [13]. Prvi je maksimalno naduvavanje balona kojim je fiksirana kanila u traheji. Na ovaj način se arterija anonima pritiska uz zid grudnog koša i krvarenje iz nje smanjuje. Drugi manevar se primenjuje nakon vađenja kanile, što je izuzetno delikatan momenat. Kroz traheostomni otvor treba uvesti kažiprst i njime arteriju anonimu pritisnuti uz sternum.

Jatrogene povrede nekih od takozvanih velikih intratorakalnih krvnih sudova, mogu nastati i tokom drugih medicinskih procedura. Jedna od najčešćih je postavljanje centralnog venskog katetera u desnu unutrašnju jugularnu ili potključnu venu. Pri tom su povredama posebno podložni arterija anonima i potključna arterija (slika 3) [14, 15].

Tupe povrede grudne aorte najčešće zahvataju aortni istmus, što je posledica načina nastanka [3, 8, 16–19]. Njihov nastanak tumači se na dva načina. Prvi podrazumeva takozvanu deceleracionu povredu. Deceleracija može biti vertikalna (pad sa visine), ili, češće, horizontalna, koja najčešće nastaje tokom saobraćajnog traumatizma. Za vreme deceleracione lezije, srce, ascedentna aorta i aortni luk nastavljaju da se kreću napred, dok je kretanje descedentne aorte limitirano njihovim zadnjim pripojima (ligamentum arteriozum i dijafragmalni hijatus) [3, 8, 16–19]. Drugi razlog je slabost aortnog zida u predelu istmusa. Još šesdesetih godina, eksperimentalno dokazano je da, ako se izoluje od adventicije, istmični deo grudne aorte poseduje samo dve trećine snage ascedentne aorte [8]. Prema drugoj hipotezi, glavnu ulogu u tupoj traumi aorte ima direktan pritisak na manubrijum, prvo rebro i srednji deo klavikule koji se povlače

nadole i pozadi uzrokujući kompresiju istmičnog dela aorte [19]. Usled tupe povrede na grudnoj aorti mogu nastati: intimalna hemoragija, laceracija intime, laceracija medije, kompletna laceracija, transekcija aorte i pseudoaneurizma [8]. Iako je jedna od incijalnih lezija, laceracija intime ne mora da bude bezazlena. Zbog konsekutivne diskecije može biti praćena razvojem „akutnog koarktacionog sindroma“ [20].



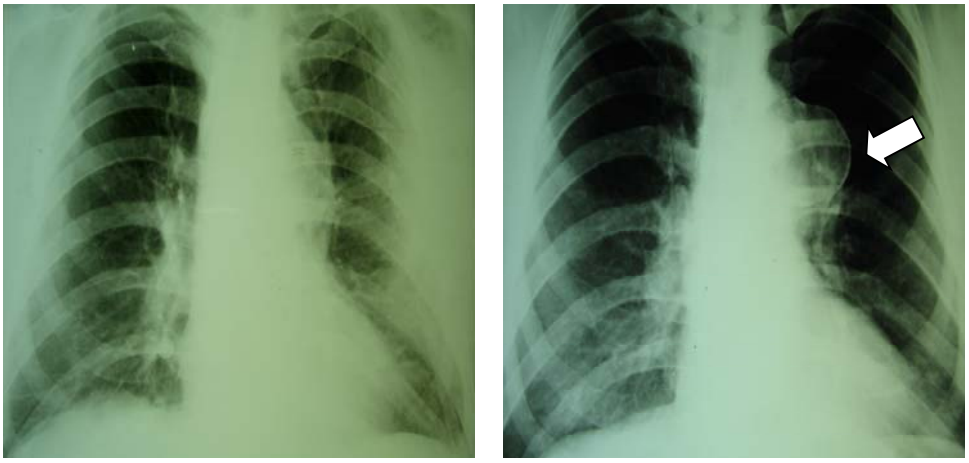
Sl. 3 – Jatrogene pseudoaneurizme desne potključne arterije nastale tokom kateterizacije desne potključne vene (bolesnici koji su uspešno operisani u Klinici za vaskularnu i endovaskularnu hirurgiju Kliničkog centra Srbije)

Sumnju na postojanje tupe povrede grudne aorte trebalo bi da izazovu: podaci o deceleracionoj povredi u uslovima velike brzine, serijski prelom rebara i/ili torakalni „kapak”, prelom prvog ili drugog rebra, prelom sternuma, gubitak pulseva, iznenadna pojava hipertenzije, interskapularni sistolni šum, krv u omotaču karotidne ili potključne arterije, iznenadna promuklost ili promena glasa i sindrom gornje šuplje vene [16–21].

Hipotenzija i šok su najupečatljiviji znaci povrede grudne aorte i velikih krvnih sudova u grudnom košu. Međutim, hipotenzija i stanje šoka nakon povrede toraksa ne moraju biti samo znak krvarenja. Diferencijalno-dijagnostički moraju se uzeti u obzir: srčana tamponada (na nju će, pored hipotenzije, uputiti nabrekle vratne vene, mukli srčani tonovi i povišen centralni venski pritisak), ventilni pneumotoraks (dispneja, nečujno disanje, cijanoza), odnosno sekcija kičmene moždine [21].

Dijagnoza

U slučaju povrede grudne aorte ilustrativan je i običan nativni snimak grudnog koša. Na njemu se mogu videti: medijastinalna senka šira od 8 cm, opstrukcija aortnog dugmeta, zatvoren aortopulmonalni prozor, devijacija traheje udesno, depresija glavnog levog bronha (slika 4) [22].

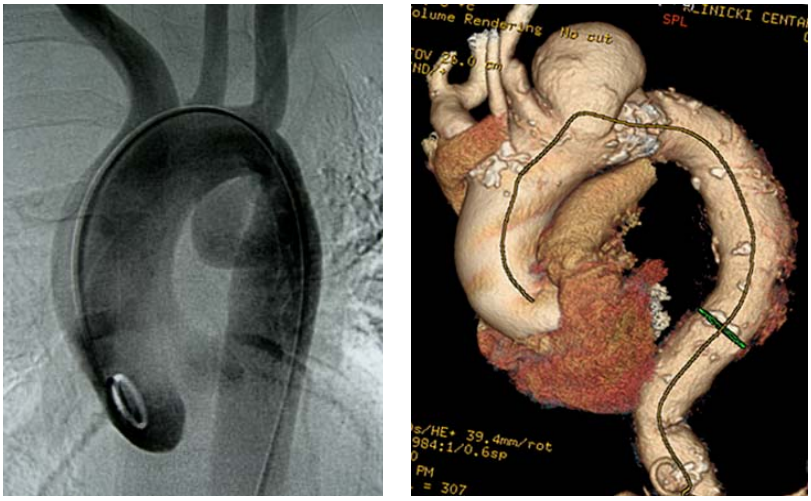


Sl. 4 – Levo – proširen medijastinum kod bolesnika sa tupom povredom grudnog koša koji ukazuje na verovartnu povredu grudne aorte; Desno – strelica pokazuje kalcifikacije u zidu stare pseudoaneurizme [22]

U kliničkoj slici bolesnika sa povredom grudne aorte i supraaortnih grana dominira hipotenzija i hemoragijski šok. Povreda descedentne torakalne aorte može izazvati ishemiju kičmene moždine sa paraplegijom. Širenje disekcije uzrokovane traumom aorte, može izazvati ishemiju i u drugim organima. Zbog zahvatanja koronarnih arterija i korena aorte, retrogradna disekcija može uzrokovati ishemiju miokarda, pa čak i infarkt, odnosno akutnu aortnu insuficijenciju. Širenje disekcije u karotidne arterije dovodi do različitih neuroloških deficita uključujući i moždani udar. Ako disekcija zahvati visceralne grane abdominalne aorte, može nastati mezenterična ishemija, odnosno akutna bubrežna insuficijencija. Širenje disekcije u ilijačne i femoralne arterije uzrokuje ishemiju donjih ekstremiteta [21].

Za definitivnu dijagnozu tupe traume grudne aorte neophodno je učiniti ili angiografiju, ili multislajsnu kompjuterizovanu tomografiju. Pregled MSCT je superiorniji jer daje sve podatke neophodne za planiranje eventualne endovaskularne procedure (slika 5) [21, 22].

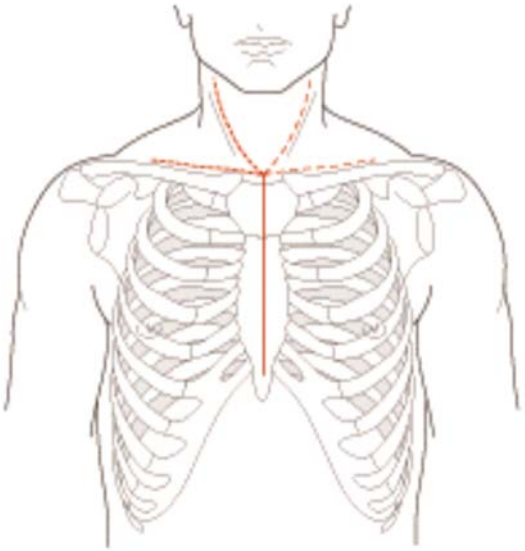
Ukoliko se na CT snimku bolesnika koji je imao povredu grudnog koša uoči medijastinalni hematom, bez obzira na njegovu veličinu i lokalizaciju neophodno je uraditi angiografiju ili MSCT pregled. Angiografski nalaz ekstravazacije kontrasta, stenoze, okluzije, pseudoaneurizme, arteriovenske fistule, sigurni su znaci povrede velikih intratorakalnih arterija. Ako je CT nalaz negativan, a pacijent hemodinamski stabilan nije neophodno raditi angiografiju.



Sl. 5 – Levo – angiografija; desno – MSCT postraumatske psudoaneurizme grudne aorte [22]

Lečenje povreda supraaortnih grana

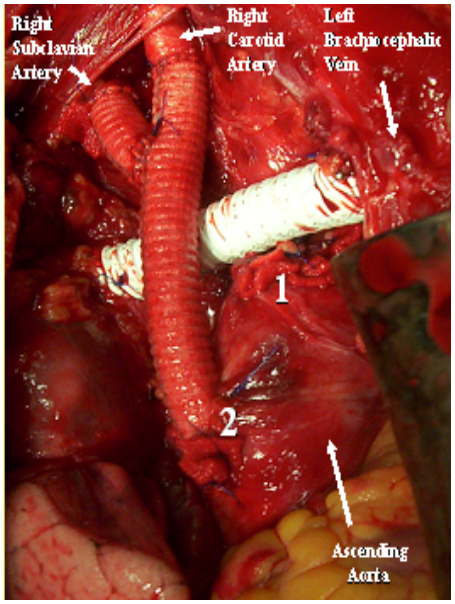
Hirurško lečenje povreda supraaortnih grana zahteva medijalnu sternotomiju uz dodatnu cervikotomiju, čiji pravac zavisi od toga koja je od grana povređena (slika 6).



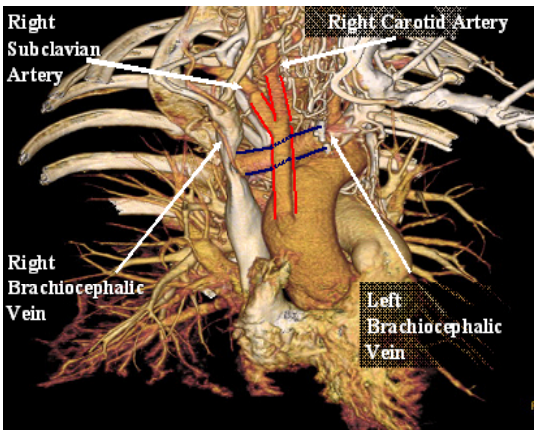
Sl. 6 – Pristup supraaortnim granama, medijalna sternotomija i jedna od vratnih ekstenzija (cervikotomija)

Nakon pristupa neophodno je što pre uspostaviti kontrolu krvarenja. Avulzione lezije zahtevaju parcijalno klemovanje aortnog luka da bi se kontrolisalo krvarenje i suturirao defekt na njemu. Nakon toga, klemuju se distalni krajevi povređenih arterija. Sama rekonstrukcija izvodi se vaskularnim graftom sa ascedente aorte koja se, takođe, parcijalno klemuje bez upotrebe ekstrakorporalne cirkulacije (slika 7 i 8) [6, 7, 14].

U slučaju fistule između arterije anonime i traheje, zbog velike opasnosti od infekcije i smrtonosnog sekundarnog krvarenja, ne preporučuje se rekonstrukcija arterije. Operativno lečenje podrazumeva resekciju dela arterije anonime koji je angažovan fistulom i najčešće inficiran, i slepo zatvaranje proksimalnog i distalnog kraja [12, 13]. Zbog retrogradnog pro-



Sl. 7 – Avulziona povreda arterije anonime, zbrinuta u Klinici za vaskularnu i endovaskularnu hirurgiju Kliničkog centra Srbije. Korišćen je darkonski "ručno" konstruisan graft "Y" oblika. Proksimalna anastomoza je na ascedentnoj aorti, a distalne na desnoj potključnoj i desnoj karotidnoj arteriji. PTFE graftom (bela boja) rekonstruisana je istovremeno povređena leva brahiocefalična vena



Sl. 8 – Kontrolni MSCT urađen nakon tri meseca pokazuje protočnost graftova

toka iz spoljašnje u unutrašnju desnu karotidnu arteriju, ovakvi bolesnici ne dobijaju cerebrovaskularni inzult, a bogata koleteralna cirkulacija ramenog pojasa, sprečava akutnu ishemiju ruke. Otvor na traheji zbrinjava se ekscizijom i suturom. Od 2001. godine primenjuje se i endovaskularni tretman ovih fistula, bilo da je reč o primeni embolizacije (manja opasnost od sekundarne infekcije) [23] ili endovaskularnog grafta (veća opasnost od sekundarne infekcije) [24].

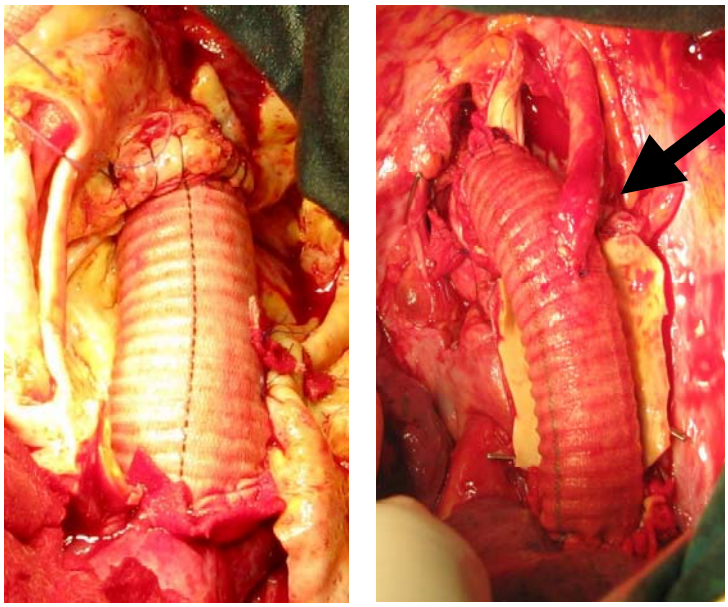
Lečenje povreda grudne aorte

Bez obzira na težinu kliničke slike koja prati takva stanja, gruzijski hirurg Dzanelidze, još 1922. godine, uspešno je suturirao penetranu povredu ascedentne aorte [9]. Ovo je i danas veliki anesteziološko-hirurški izazov, pa se u literaturi sreću samo pojedinačni slučajevi. Manje opsežne laceracije ascedentne aorte mogu se zbrinuti nakon parcijalnog klemovanja aorte direktnom suturom, odnosno *patch* plastikom, dok opsežnije laceracije i transekcije zahtevaju totalno klemovanje u uslovima ekstrakorporalne cirkulacije i interpoziciju vaskularnog grafta.

Tupe povrede grudne aorte danas se mogu lečiti otvoreno hirurški ili endovaskularno. Otvoreno hirurško lečenje zahteva torakotomiju koja se kod povreda istmičnog dela aorte izvodi kroz peti levi međurebarni prostor. Izuzetno je važna primena Carlens-ovog tubusa jer se eksuflacijom levog plućnog krila olakšava hirurški rad i smanjuje njegova intraoperativna trauma. Neki autori smatraju da je čak kod 20% povređenih reparacija povređene aorte moguća šavom ili terminoterminalnom anastomozom. Preduslov je da defekt na aorti ne bude duži od dva santimetra [25–28]. Kod većine povreda neophodna je interpozicija vaskularnog grafta [3, 16–22, 25–28]. Ako je lezijom zahvaćena leva potključna arterija, neophodna je i njena rekonstrukcija. To je važno, kako zbog vaskularizacije leve ruke, odnosno njenog učešća u vaskularizaciji mozga, tako i zbog učešća arterije supklavije u vaskularizaciji kičmene moždine (slika 9) [29].

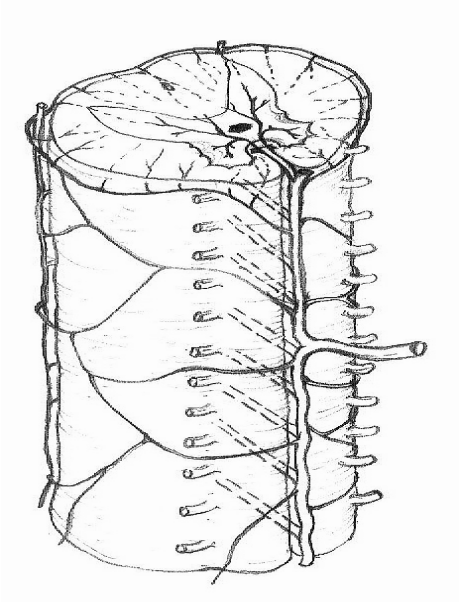
Zaštita kičmene moždine tokom lečenja povreda grudne aorte

Ključni problem koji se javlja pri zbrinjavanju povreda grudne aorte jeste ishemija kičmene moždine. Ona nastaje zbog intra- i postoperativne hipoperfuzije. Intraoperativna hipoperfuzija je rezultat prolongiranog klemovanja grudne aorte (duže od 30 minuta), a postoperativna, ako se poremeti protok kroz Admakijevićevu arteriju [2, 19, 30–32]. Razlog je izuzetno kompleksna vaskularizacija kičmene moždine. Ona potiče od dva sistema. Prvi čine spinalne, a drugi radikularne arterije [33, 34]. Neparna prednja i dve parne zadnje spinalne arterije nastaju od intrakranijalnog dela vertebralnih arterija. Pošto napuste lobanju spuštaju se odgovarajućom stranom kičmene moždine do njenog donjeg kraja. Prednja spinalna arterija je u torakalnom delu prekinuta. Na nivou svakog segmenta kičmene moždine prednje i zadnje spinalne arterije grade perimedularne anstomoze koje nisu dovoljno funkcionalne. Radukularnih arterija ima 31 par. Pošto uđu u kičmeni kanal, pored ostalog daju spinalne ogranke koji su anastomozirani sa prednjim i zadnjim spinalnim arterijama. Nemaju sve radikularne arterije isti značaj. Značajno je samo sedam do osam, a one su neravnomerno raspoređene. U vezi sa tim se na kičmenoj moždini razlikuju tri segmenta: gornji ili cervikotorakalni, srednji ili torakalni i donji ili lumbosakralni [33, 34]. Gornji ili cervikotorakalni segment, koji se proteže od prvog cervikalnog do četvrtog grudnog pršljena, najbolje je vaskularizovan jer se u njemu od pomenutih sedam-osam, nalazi pet značajnih radikularnih arterija. U srednjem ili torakalnom segmentu, koji se pruža od petog do osmog grudnog pršljena, nalazi se obično samo jedna značajna radikularna arterija i to ona u Th7 nivou. Isto važi i za lumbosakralni segment (Th9-L3) u kome se nalazi samo *a. radicularis magna* ili Adamkijevićeva arterija [35]. Prema najnovijim studijama ona je uglavnom neparna i kod 15% povređenih polazi u nivou Th V-VIII, kod 75% u nivou Th IX-XII, a kod 10% u nivou L I-II [36]. Vaskularizacija lumbosakralnog dela kičmene



Sl. 9 – Levo – vaskularni graft kojim je reparirana posttraumatska aneurizma grudne aorte; Desno – u ovom slučaju u vaskularni graft je implantirana leva potključna arterija (strelica) [22]

moždine je insuficijentna iz tri razloga. Prvi je diskontinuirana prednja spinalna arterija, drugi insuficijentnost perimedularnih anastomoza između prednjih i zadnjih spinalnih arterija, a treći nedovoljan broj adekvatnih radikularnih arterija i njihov neravnomeran raspored (slika 10).



Sl. 10 – Vaskularizacija kičmene moždine

Zbog toga, tokom operativnog zbrinjvanja povreda grudne aorte, kičmena moždina mora se zaštiti od ishemije. Ona se izvodi: uticanjem na spinalnu perfuziju, merama neuroprotekcije i kombinacijom ove dve metode. Može se govoriti o intra- i postoperativnoj perfuziji kičmene moždine. Intraoperativna perfuzija podrazumeva retrogradnu perfuziju, drenažu likvora i intratekalnu primenu vazodilatatora koji bolje deluju u laboratorijskim, nego u kliničkim uslovima, pa se retko primenjuju. Da bi se obezbedila trajna postoperativna perfuzija kičmene moždine mora se sačuvati ili, po potrebi, reimplantirati kritična interkostalna arterija. Kod istmičnih lezija to je potrebno veoma retko jer je najčešće ishodište Adamkijevićeve arterije postvaljeno znatno niže. Retrogradna perfuzija izvodi se levo-levim šantom (najčešća varijanta je *left heart bypass* zbog čega se kanilišu leva pretkomora i leva femoralna arterija), ili parcijalnim kardipulmonalnim bajpasom [37–44]. Najjednostavnija varijanta levo-levog šanta je heparinizirani Goot-ov šant koji omogućava pasivnu drenažu arterijske krvi distalno pod dejstvom gradijenta pritiska [37]. Ovaj pasivan protok ne obezbeđuje uvek adekvatnu retrogradnu perfuziju (neophodan je pritisak od minimalno 60 mmHg) [31, 32, 41], pa se u šant ′umeće′ biopumpa, čime se ostvaruje kontrolisan protok i bolja retrogradna perfuzija. Parcijalni kardiopulmonalni bajpas zahteva kanilisanje leve femoralne, ilijačne ili renalne vene, kao i leve femoralne arterije (što je jednostavije), punu heparinizaciju i primenu oksigenatora (povećava zastupljenost hemoragijskih komplikacija politraumatizovane osobe) [38, 42–45].

Drugi način da se nakon klemovanja torakalne aorte obezbedi perfuzija kičmene moždine, jeste drenaža likvora. Perfuzioni pritisak u kičmenoj moždini predstavlja razliku arterijskog i likvornog pritiska koji se povećava kao refleksna reakcija na proksimalnu hipertenziju uzrokovanu klemovanjem aorte, pa nastaje takozvani *spinal cord compratment syndrom* [46]. Ovo se sprečava drenažom likvora. Procedura započinje stavljanjem katetera u epiduralni prostor na L3 nivou tokom uvođenja bolesnika u anesteziju. Drenaža likvora započinje pre klemovanja aorte, a traje intraoperativno i naredna 72 sata posle operacije tako da likvorni pritisak bude manji od 10 mmHg [46]. Ukoliko u pomenutom periodu dođe do poremećaja drenaže likvora, po geometrijskoj progresiji raste verovatnoća razvoja paraplegije [47]. Da bi se obezbedila trajna postoperativna perfuzija kičmene moždine mora se reimplantirati kritična interkostalna arterija koja daje Adamkijevičevu arteriju. Ona se pre toga mora identifikovati, što se može izvesti digitalnom supstrakcionom spinalnom, CT ili NMR angiografijom [36, 48]. Prema aritmetičkoj progresiji povećava se verovatnoća razvoja paraplegije, ako se ne sačuvaju (reimplantiraju) 11. i 12. u odnosu na 8. interkostalnu arteriju [49].

Drugi način zaštite kičmene moždine, tokom klemovanja grudne aorte, jeste neuroprotekcija koja se može izvoditi hipotermijom i medikamentima koji su efikasniji u laboratorijskim, nego u kliničkim uslovima, pa se retko koriste. Mnogo je efikasnija epiduralna hipotermija. Izvodi se ubacivanjem rastvora ohlađenog na +4C koji sadrži Ringer laktat, 25 g manitola po litru i 1 g metilprednizolona po litru, kroz kateter u nivou ThX u epidiralni prostor. U nivou L3 nalazi se kateter kojim se pomenuta tečnost, kao i likvor, dreniraju, uz istovreno merenje likvornog pritiska koji mora biti manji od 10 mm Hg, i temperature koja mora biti 25–27^{o}C [50]. Kliničke studije pokazale su da se najbolja zaštita kičmene moždine nakon klemovanja toakalne aorte postiže takozvanom kombinovanom metodom [46, 47, 49, 50]. Ona podrazumeva drenažu likvora na prethodno opisan način, retrogradnu perfuziju u uslovima sekvencijalnosegmetnog klemovanja grudne aorte i očuvanje ili reimplantiranje kritičnih interkostalnih arterija. Suština sekvencijalnosegmetnog klemovanja grudne aorte je da se iz cirkulacije isključi njen, što je moguće, manji deo. Time se stvara bazen za retrogradnu perfuziju i smanjuje opasnost od deklamping šoka. Dakle, tokom kreiranja proksimalne anastomoze iz cirkulacije je isključen samo kratak segment grudne aorte i za to vreme se nesmetano odvija retrogradna perfuzija kičmene moždine i visceralnih organa. Ako je nivo distalne anastomoze iznad ishodišta kritične interkostalne arterije, a to je kod povreda grudne aorte najčešće, onda su svi problemi rešeni. U protivnom, sledi reimplantacija kritičnih interkostalnih arterija. Tokom ove procedure i dalje je očuvana retrogradna perfuzija visceralnih organa, a ishemija kičmene moždine traje samo 10–15 min što bi trebalo da uz drenažu likvora spreči paraplegiju.

Endovaskularno lečenje povreda grudne aorte

Ovu proceduru prvi je izveo ruski hirurg Volodos [51] 1988. godine. Na ovaj način se izbegava torakotomija, klemovanje grudne aorte i ekstrakorporalna cirkulacija, koji su kod određenih kategorija bolesnika veoma rizični [20, 22].

Iako je značajno unapredila lečenje aneurizmi grudne aorte, kao i sve ostale procedure i endovaskularna procedura (*endovascular aortic repair* – EVAR) ima svoje prednosti i

nedostatke; limite i komplikacije, a samim tim indikacije i kontraindikacije. Prvi limit je rastojanje između mesta lezije odnosno pseudoaneurizme i leve potključne arterije. Da bi se procedura mogla izvesti ono mora biti duže od 2 cm, inače će graft prekriti ishodište leve potključne arterije. Imajući u vidu njenu ulogu vezanu za vaskularizaciju mozga, kičmene moždine i ruke, pre endovaskularne intervencije ili neposredno posle nje, mora se učiniti transpozicija leve potključne u levu karotidnu arteriju, ili karotidosupklavijalni bajpas [20, 29, 52–54]. U slučaju da je lezija lokalizovana na aortnom luku, mora se učiniti njegov *debranching* sa kompleksnom anatomskom ili ekstraantomskom rekonstrukcijom. Sledeći limit je konfiguracija aortnog luka. Da bi se procedura mogla izvesti on ne sme biti oštar (takozvana „gotska" forma). Poslednji limit se odnosi na ilijačne i femoralne arterije. One moraju imati relativno pravilnu konfiguraciju i njihov prečnik mora biti veći od 8 mm [20, 29, 52–54].

Ako se tokom endovaskularne procedure prekrije ishodište kritične interkostalne artrerije, može nastati paraplegija. Zato je ona nepreporučljiva kod bolesnika sa lezijom ispod Th7 nivoa. Još veći problem predstavlja neadekvatno fiksiranje endovaskularnog grafta. Zbog toga postoji realna opsanost da on kolabira ili migrira kada je neophodna hitna hirurška reintervencija (slika 11) [20, 29, 52–54].

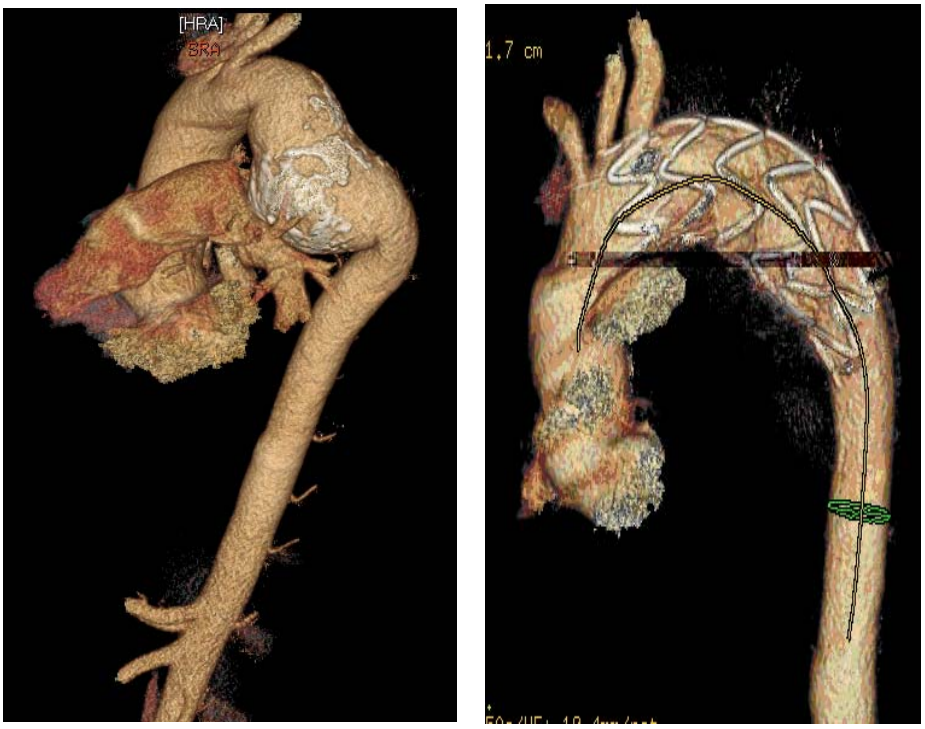
Rezultati lečenja povreda grudne aorte

Tabela 1 prikazuje rane rezultate različitih načina lečenja bolesnika sa tupom povredom grudne aorte u poslednjih 10 godina. Obuhvaćeno je preko hiljadu lečenih bolesnika [20].

Tabela 1
Mortalitet i paraplegija u zavisnosti od načina lečenja tupih povreda grudne aorte [20]

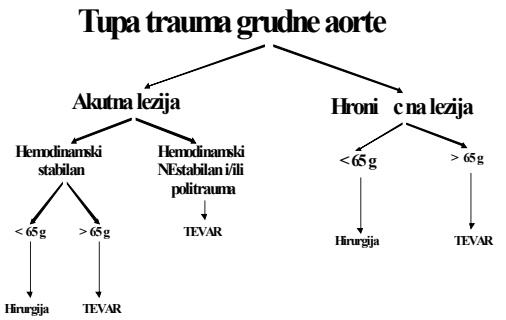
Procedura	Broj bolesnika	Mortalitet (%)	Paraplegija (%)
Clamp and Sew	393	19	6,4
Left Heart Bypass	192	13	2,4
Parcijalni kardiopulmonalni bajpas	202	11,4	2,1
Endovaskularna procedura	137	9,7	0,0

Otvoreno hirurško lečenje bez ikakve zaštite kičmene moždine (*clamp and sew* tehnika) bio je praćen najvišim mortalitetom i stopom postoperativne paraplegije. *Left heart bypass*, odnosno parcijalni kardiopulmonalni bajpas, daje bolje rezultate posebno kada je u pitanju postoperativna paraplegija. Evidentno je da je stopa mortaliteta najniža kod endovaskularno lečenih bolesnika. S druge strane, endovaskularne procedure imaju svoja već pomenuta anatomska ograničenja, kontraindikacije i nedostatke. Zato se postavlja pitanje: Šta je metod izbora kod bolesnika sa posttraumatskom aneurzimom grudne aorte? Mnogi, uključujući i nas, pridržavaju se sledećeg algoritma [55–57]: kod hemodinamski stabilnih bolesnika sa akutnom traumom grudne aorte, koji su mlađi od 65 godina, indikovan je otvoreni tretman; kod iste kategorije bolesnika starijih, od 65 godina, indikovan je endovaskularni tretman; kod bolesnika sa akutnom traumom koji su hemodinamski nestabilni ili imaju pridruženu politraumu, apsolutno je indikovan endovaskularni tretman; bolesnici sa hroničnom povredom grudne aorte mlađi od 65 godi-



Sl. 11 – MSCT angiografija posttraumatske anaurizme istmičnog dela grudne aorte pre (levo) i posle (desno) endovaskularnog lečenja

na indikovani su za otvorenu hirurgiju, dok je kod starijih od 65 indikovan endovaskularno lečenje (slika 12).



Sl. 12 – Terapeutski algoritam kod bolesnika sa tupom povredom grudne aorte

TEVAR – endovaskularni tretman grudne aorte

Značaj autotransfuzije kod povreda grudne aorte i supraaortnih grana

Danas se zbrinjavanje povreda grudne aorte i supraaortnih grana ne sme ni zamisliti bez intraoperativnog spašavanja krvi i autotransfuzije [58]. Na ovaj način rešavaju se tri veoma važna problema. Prvi predstavljaju ′hronične′ nestašice krvi koje su godinama unazad prisutne u našoj zemlji. Drugi je mogućnost da se bukvalno odmah počne sa operativnim zahvatom. To znači, pre nego što stigne krv i pre nego što se odredi krvna grupa, što je sve skupa, kod životno ugroženog bolesnika koji krvari, od presudnog značaja. Treći je značajno smanjenje opasnosti od sindroma masivne transfuzije koja je u ovakvim slučajevima neophodna. Naime, u intraoperativno spašenoj krvi, zbog mikrofiltriranje i činjenice da će se primeniti odmah, nema agregata koji će okludirati plućnu cirkulaciju i posle par dana dovesti do akutnog respiratornog distres sindroma (ARDS).

Zaključak

Uspešno lečenje povreda aorte u supraaortnih grana zahteva brz transport povređenog u ustanovu u kojoj se povreda može zbrinuti. Već tokom tog postupka mora se ′mobilisati′ vaskularni tim. Sa operacijom mora se početi bez odlaganja, što omogućava intraoperativno spašavanje krvi i autotransfuzija. Neophodno je što pre uspostaviti adekvatnu kontrolu krvarenja, a potom izvesti što jednostaviju rekonstruktivnu vaskularnu proceduru. Ovakvi bolesnici zahtevaju izuzetno složene anesteziološko-reanimatološke postupke kako tokom operacije, tako i u ranom postoperativnom periodu.

Napomena

Rad je prezentovan na Kursu kontinuirane edukacije "Ratne povrede grudnog koša" koji je održan u Vojnomedicinskoj akademiji, Beograd, 5.12.2009. godine.

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Health claims made on food

Zdravstvene izjave i prehrambeni proizvodi

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Ključne reči:
hrana; hrana, obeležavanje; potrošači, zdravstvene informacije; zdravstvo, unapređenje; zakonodavstvo.

Introduction

According to the World Health Organization (WHO), 75% of all deaths in the year 2030 will be caused by mass noncommunicable diseases (NCDs) [1]. Causes of NCDs are known and can be non-preventable (age and genetic heritage) and preventable or modifiable (unhealthy eating habits, insufficient physical activity, tobacco use) [2].

Social and economic burden of population caused by NCDs is enormous and growing, so WHO set a specific goal in 2005 – an additional 2% reduction in chronic disease death rates worldwide per year over the next 10 years [2]. The WHO's Action Plan [3] from 2008 promotes healthy eating habits enabling consumers to make informed choices.

Declarations of foodstuffs, promotional materials and advertising campaigns are considered as means of direct producer-consumer communication, making it vital for the information written on declarations (as well as on promotional materials and in advertising campaigns) to be scientifically-based and well-understood by the consumers. Advances in knowledge and understanding of the link between nutrition and health resulted in shift from nutrition claims to health claims written on food declarations. Health claims present health benefits for consuming certain foods by consumers. Public interest in health promotion is a driving force behind the use of health claims and an incentive for innovation in food industry and pharmaceutical industry. Therefore, a well-designed legal system for approval of the use of health claims should exist.

Codex Alimentarius, a joint body of the Food and Agriculture Organization of the United Nations (FAO UN) and WHO defined health claims in 1997 as "any representation that states, suggests, or implies that a relationship exists between a food or a constituent of that food and health" [4]. Codex Alimentarius implies that national regulations concerning health claims should be harmonized in order not to disrupt free trade system [4].

Current legislation concerning health claims in different countries

Japan

Country that has introduced to the world the concept of "functional food" and, parallel, the idea of health claims is Japan. The use of health claims in Japan is controlled by the Ministry of Health, Labour and Welfare (MHLW) [5].

In 2001, MHLW divided foods bearing health claims into 2 groups: foods with nutrient function claims (FNFC) and food for specified health uses (FOSHU). FNFC standards and specifications so far have included nutrient function claims for 17 ingredients (12 vitamins and 5 minerals). FOSHU refers to foods containing ingredient with functions for health and is officially approved to claim its physiological effects on the human body. FOSHU is intended to be consumed for the maintenance or promotion of health or special use by people who wish to control health conditions. In order to sell food as FOSHU, health claims written on it must be approved by the MHLW. Specific requirements for FOSHU declarations limit their sales out of Japan [6–8].

United States of America (USA)

The American Food and Drug Administration (FDA) defined health claim as "any claim made on the label or in labeling food, including dietary supplements, that expressly or by implication, including "third party" references, written statements (e.g., a brand name including a term such as "heart"), symbols (e.g. a heart symbol), or vignettes, characterizes the relationship of any substance to a disease or health-related condition" [9, 10]. There are three ways by which FDA exercises its oversight in determining which health claims may be used on a label or in labeling food or dietary supplements:

1. The 1990 Nutrition Labeling and Education Act (NLEA) provides for FDA to issue regulations author-

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izing health claims for foods and dietary supplements after FDA's careful review of the scientific evidence submitted by food producer in health claim petitions concerning link beetwen certain food component and health. Health claims authorized as described, have to comply with the NLEA (1990), Dietary Supplement Act (1992) and Dietary Supplement Health and Education Act (DSHEA, 1994). The most common NLEA authorized health claims are ones describing the link beetwen fruit, vegetables and cereals and coronary artery disease, as well as the ones linking saturated fatty acid content and cholesterol content with the risk of cardiovascular disease.

2. The 1997 Food and Drug Administration Modernization Act (FDAMA) provides for health claims based on an authoritative statement of a scientific body of the US government or the National Academy of Sciences. Such claims may be used after submission health claim notification to FDA.
3. The 2003 FDA Consumer Health Information for Better Nutrition Initiative provides for qualified health claims where the quality and strength of scientific evidence falls below that required for FDA to issue an authorizing regulation. Such health claims have to be qualified to assure accuracy and non-misleading presentation to consumers [10, 11].

According to the strenght of supporting evidence, FDA recognizes 4 categories of health claims: A (supported by strong scientific evidence), B (moderate scientific evidence level), C (low scientific evidence level) and D (the lowest scientific evidence level) [10, 12].

Use of health claims in advertising campaigns is controlled by the Federal Trade Commission (FTC) leading to conflicting situations when health claims not approved by the FDA are used in advertising [11, 13].

European Union

Health claims in the European Union (EU) are covered by the European Commission Regulation No 1924/2006 on nutrition and health claims made on foods [14] in which a health claim is defined as "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health". According to the authorisation protocol, health claims in EU are divided into "article 13 claims" and "article 14 claims" accordant with the Regulation 1924/2006. Health claims other than those referring to the reduction of disease risk and to children's development and health, describing or referring to the role of nutrient or other substance in growth, development and functions of the body or psychological and behavioural functions or slimming or weight control are considered "article 13 claims", as well as health claims based on newly developed scientific evidence which include a request for the protection of proprietary data. Reduction of disease risk claims and claims referring to children's development and health are "article 14 claims".

Health claims in use in the EU must be authorized by the European Food Safety Authority (EFSA). EFSA is supposed to publish a list of approved, well-defined health claims in January, 2010. Criteria for authorisation of health claims in Europe are defined in the Process for the Assessment of Scientific Support for Claims on Foods (PASSCLAIM) project [15]. The basic clause of PASSCLAIM is that the link beetwen food constituent and disease risk reduction is confirmed by studies on humans [15].

Health claims are allowed only on food with certain nutrient profiles. Nutrient profile includes saturated fatty acids, sodium, dietary fiber and unsaturated fatty acid content of food. Definition of nutrient profiles is supposed to prevent "masking" of undesired nutrient profile of certain food by health claims [16].

Republic of Serbia

National regulation concerning health claims is currently underway.

Note: In July 2010, after this manuscript had been accepted, national regulation of health claim use was adopted. Now, in December 2010, the implementation of the regulation provisions concerning health claims is still pending.

Despite the regulation differences, requirements and limitations for the use of health claims are similar. A health claim must not attribute to food the property of preventing, treating or curing a human disesase. Health claims should not be false, ambiguous or misleading, nor should it give rise to doubt about the safety and (or) the nutritional adequacy of other foods or a balanced and varied diet. It is not allowed for health claims to encourage or condone excess consumption of food, refer to changes in bodily functions which could give rise to or exploit fear in the consumer [14].

Health claims have to refer to food ready for consumption in accordance with the manufacturer's instructions and must relate to the quantity of a product that can reasonably be expected to be consumed provided that a significant quantity of the nutrient or other substance to which the claim relates will produce the nutritional or physiological effect claimed as established by generally accepted scientific evidence. Health benefit can be the result of the presence, absence or a reduced content in food or category of food of a nutrient or other substance in respect to which the claim is made [14].

Health claims that are not allowed are these suggesting that health could be affected by not consuming food bearing a health claim, making reference to the rate or amount of weight loss and referencing to recommendations of individual doctors or health professionals. Beverages containing more than 1.2% alcohol by volume shall not bear health claims [14].

The use of health claims in labeling, presentation and advertising is allowed if followed by statements indicating the importance of a varied and balanced diet and healthy lifestyle, the quantity of food and pattern of consumption required to obtain the claimed beneficial effect, a statement addressed to persons who should avoid using food (where appropriate) and an appropriate warning for products that are likely to present health risk if consumed to excess [14].

Limitations of free trade

Different health claim regulation frameworks present a limitation in free trade systems. The most common conflicting situation is importing foodstuffs bearing a health claim into a country with different (or non-existant) health claim regulation. As a result, international community strives to harmonize regulatory systems [13].

Examples of health claims compliant and non-compliant with the mentioned regulations (US, EU, Serbia) are given in Table 1.

Table 1

Health claims in EU, USA and Serbia

Relevant data on foodstuffs	EU* (example of an authorized health claim [26])	USA† (example of health claim in use in USA – not in compliance with the regulation [27])	Serbia‡ (example of health claim in use in Serbia – sample product taken from the market)
Food constituent	Mixture of long chain omega-3 polyunsaturated fatty acides	Water-soluble dietary fiber	Not defined
Health effect	Blood pressure reduction (3 g/day) and serum triglyceride level reduction (2–4 g/day)	Coronary artery disease risk reduction	Treatment of type 2 diabetes (according to the producer)
Health claim	On the label of a dietary supplement contraining mixture of long omega-3 polyunsaturated fatty acides: "helping the reduction of serum triglyceride levels and maintaing of normal blood pressure"	On breakfast cereal's label: "reduces cholesterol by 4% in 6 weeks"	On the label of herbal tea: "proven efficacy in the treatment of type 2 diabetes: "one package of this tea is enough to reduce blood sugar levels by 10–15%"

Note:

*On the basis of the data presented, the European Food Safety Authority (EFSA) concluded that a cause and effect relationship exists between the consumption of eicosapentaenoic and docosahexaenoic acid and blood pressure and serum triglyceride level reduction. Opinion based on relevant scientific data, including:

1. *Ayalew-Pervanchon A, Rousseau D, Moreau D, Assayag P, Weill P, Grynberg A.* Long-term effect of dietary {alpha}-linolenic acid or decosahexaenoic acid on incorporation of decosahexaenoic acid in membranes and its influence on rat heart *in vivo*. Am J Physiol Heart Circ Physiol 2007;293:H2296-304.
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4. *Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ*. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. J Hypertens 2002;20:1493-9.
5. *Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J*. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis 2006;189:19-30.

†Health claim linking water-soluble dietary fiber and coronary artery disease risk reduction is Nutrition Labeling and Education Act (NLEA) authorized. Food and Drug Administrations (FDA's) position was that the health claim in question attributed the property of drug to food and in May 2009, asked the producer to provide scentific proof for the alleged cholesterol level reduction of 4% in 6 weeks. In June 2009, producer submitted 4 articles about the claim in question. In an public letter, FDA announced that the results of 3 out of 4 submitted articles were inconclusive and called for the revision of all available scientific data on the subject and the revision of possible health claim wording in order to prevent the misleading of consumers. The case is still pending.

‡Health claim in question does not comply with either USA, EU or Japan regulations

Consumers and health claims

The basic purpose of health claims is consumers' benefit by providing information about heatlhy eating habits, but food industry often uses health claims for advertising purposes [13, 17]. A well educated and motivated consumer is able to make informed choices about his diet [12, 13].

Studies done both in the USA and the EU showed that taste and price dictate food choices and that health benefits and nutritive characteristics of food are not among consumers' priorities [18–20]. Consumers' attitudes are tightly related to their age, social status and education level. Various EU nations are concerened by different health issues, making it necessary for the development and marketing of new food products to be market-oriented [12, 13, 21].

The underlying principle of all regulatory frames is for health claims to be truthful, clear and understandable. In practice, this seems to be the most controversial and scientificaly challenging principle. Inadequate wording of health claims may mislead consumers. Word "may" causes consumers to doubt a health claim, while words such as "proven" or "proof" are percieved as assuring. An average consumer prefers desriptive adjectives and visual representations over numbers. According to the consumers' associations, nutrition claims are often percieved as health claims [22, 23]. The absence of health claims can decrease the use of foods with proven health benefits (fruits and vegetables) [13].

The European Consumers' Organisation – *Bureau Européen des Unions de Consommateurs* (BEUC) pointed out

that food labels already contain too much information, making it hard for consumers to prioritize and demotivates them [5, 13, 23–25]. In the USA, the majority of consumers are unable to make a distinction between different health claims categories (A, B, C, D), regardless health claims' wording, despite FDA efforts [27].

Conclusion

Food labeling is equally important for food producers and consumers. Health claims should be used cautiously, in order not to undermine the fact that diet as a whole, and not a specific food constituent, is the key to maintaining good health.

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Kongenitalne intestinalne limfangiektazije

Congenital intestinal lymphangiectasia

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Apstrakt

Uvod. Kongenitalne crevne limfangiektazije su oboljenje iz grupe enteropatija sa gubitkom proteina. Karakterišu se proširenjem limfnih sudova u zidu i mezenterijumu tankog creva. Klinički se manifestuju malapsorpcijom, malnutricijom, steatorejom, edemima i izlivima. Terapija uključuje dijetu i primenu lekova. **Prikaz bolesnika.** Muškarac, star 19 godina, primljen je zbog oticanja trbuha, proliva, malaksalosti i zamaranja. Fizikalni pregled ukazao je na zastoj u rastu i razvoju, ascites i limfedem leve podlaktice i šake. Laboratorijske analize pokazale su hiposideremijsku anemiju, limfopeniju, malapsorpciju, pozitivan zapaljenski sindrom i urinarnu infekciju. Dijagnostičkim procedurama dokazano je prisustvo limfangiektazija u celom tankom crevu. Bolesnik je lečen dijetom, somatotropinom i suportivnom terapijom. Primenjena terapija dovela je do značajnog kliničkog i laboratorijskog poboljšanja. **Zaključak.** Kongenitalne limfangiektazije su retko oboljenje koje se, uglavnom, dijagnostikuju u dečijem uzrastu. One mogu biti uzrok brojnih komplikacija koje se sprečavaju ranom dijagnostikom i primenom adekvatnog lečenja.

Ključne reči:
crevo, tanko, bolesti; limfangiektazija, intestinalna; anomalije; dijagnoza, diferencijalna; lečenje lekovima.

Abstract

Background. Congenital intestinal lymphangiectasia is a disease which leads to protein losing enteropathy. Tortous, dilated lymphatic vessels in the intestinal wall and mesenterium are typical features of the disease. Clinical manifestations include malabsorption, diarrhea, steatorrhea, edema and effusions. Specific diet and medication are required for disease control. **Case report.** A 19-year old male patient was hospitalized due to diarrhea, abdominal swelling, weariness and fatigue. Physical examination revealed growth impairment, ascites, and lymphedema of the right hand and forearm. Laboratory assessment indicated iron deficiency anaemia, lymphopenia, malabsorption, inflammatory syndrome, and urinary infection. Enteroscopy and video capsule endoscopy demonstrated dilated lymphatic vessels in the small intestine. The diagnosis was confirmed by intestinal biopsy. The patient was put on high-protein diet containing medium-chain fatty acids, somatotropin and suportive therapy. **Conclusion.** Congenital intestinal lymphangiectasia is a rare disease, usually diagnosed in childhood. Early recognition of the disease and adequate treatment can prevent development of various complications.

Key words:
ileal diseases; lymphangiectasis, intestinal; congenital abnormalities; diagnosis, differential; drug therapy.

Uvod

Intestinalne limfangiektazije (IL) su retko oboljenje koje su prvi opisali Waldmann i sar. [1] 1961. godine. Karakterišu se dilatacijom limfnih sudova u zidu i mezenterijumu tankog creva i sledstvenim gubitkom proteina, lipida i limfocita [2]. U odnosu na etiologiju mogu biti primarne i sekundarne. Primarne su kongenitalne, dok se sekundarne javljaju kao posledica opstrukcije limfotoka, usled nekog drugog oboljenja (konstriktivni perikarditis, retroperitonealni tumori, hronični pankreatitis, tuberkuloza i sl) [3, 4]. Dijagnoza se postavlja na osnovu kliničke slike enteropatije sa gubitkom proteina i karakterističnog endoskopskog i patohistološkog nalaza. U terapiji se primenjuju dijeta siromašna mastima, uz unos triglicerida srednje teškog lanca, (*medium chain triglicerides* – MCT) oktreotid, antiplazminska i suportivna terapija.

Prikaz bolesnika

Bolesnik, star 19 godina, primljen je na bolničko lečenje zbog oticanja trbuha, otoka leve šake i podlaktice, stolice koja je na masnu hranu postajala tečna i svetlija, malaksalosti i lakog zamaranja. Imao je tegobe već 16 godina, ali su se intenzivirale mesec dana pre prijema. Inače, bolesnik se od

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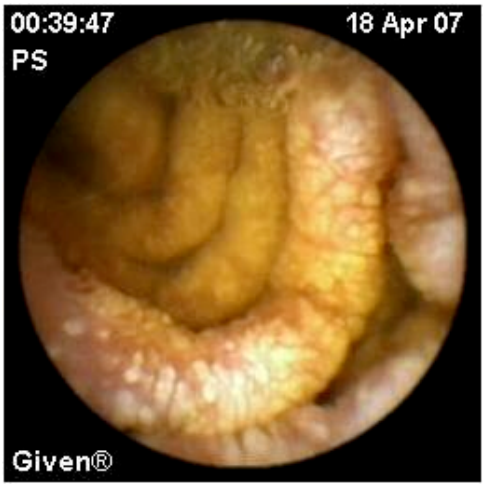
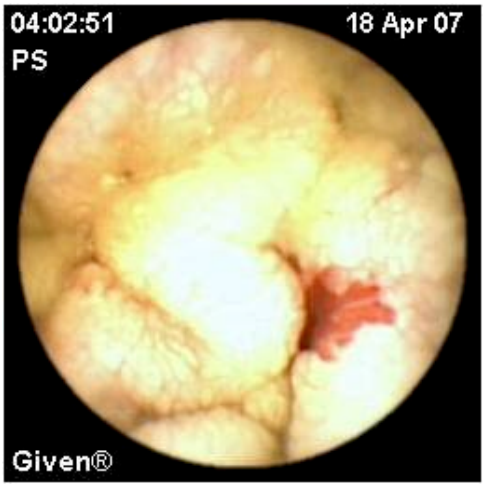
treće godine života lečio od kongenitalnih limfangiektazija i otoka leve podlaktice i šake. Lečen je dijetom koju je neredovno primenjivao, diureticima, evakuacionim punkcijama i povremeno kortikosteroidima. U više navrata bio je hospitalizovan zbog pogoršanja osnovne bolesti. U ličnoj anamnezi naveo je operaciju ingvinalne hernije u 8. godini. Negirao je bolesti od značaja za hereditet. Na fizikalnom pregledu konstatovan je niski rast, pothranjenost (visina 155 cm, telesna masa 47,2 kg), i zapremina testisa 8–10 mL, bledilo kože, redukovana aksilarna i pubična kosmatost. Fizikalni nalaz na plućima ukazao je na perkutornu tmulost i oslabljen disajni šum pri bazama, bilateralno. Abdomen je bio sa jasnim znacima slobodne tečnosti u trbušnoj duplji, a jetra i slezina nedostupne palpaciji. Ustanovljen je limfedem leve šake i podlaktice. Laboratorijski je ustanovljen pozitivan zapaljenski sindrom, hipohromna mikrocitna anemija, limfopenija, trombocitoza, hipoproteinemija, hipoalbuminemija i povišena aktivnost alkalne fosfataze u serumu. Elektroforezom proteina seruma detektovana je snižena albuminska i povišene α1 i α2 globulinske frakcije. Urinokulturom izolovane su *Klebsiella* i *Enterobacter* spp. Stolica je bila pozitivna na svarena mišićna vlakna, masti i skrob. Nalaz krvi na mikrofilarije bio je negativan. Ultrasonografski verifikovana je velika količina slobodne tečnosti u trbuhu, uz normalan nalaz na parenhimatoznim organima. Paracentezom dobijen je hilozan ascites sa proteinima 17 g/L, albuminima 9 g/L, (serum-ascites albuminski gradijent 11), holesterolom < 1,16 mmol/L i triglyceridima 2,85 mmol/L. Enteroskopijom u duodenumu i na eksplorisanom delu jejunuma, uočene su beličaste limfangiektazije koje su bioptirane. Endoskopska video kapsula ukazala je na prisustvo limfangiektazija u čitavom tankom crevu (slika 1), a na nekoliko mesta uočene su nekrvareće angio-

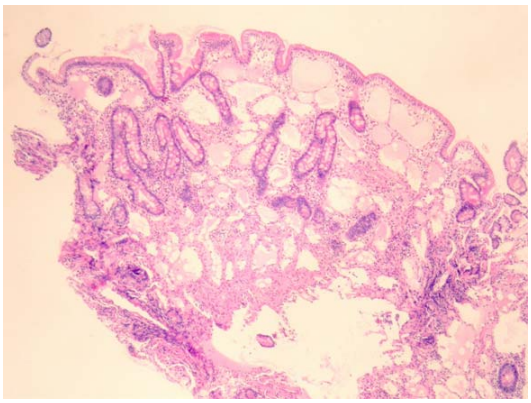


Sl. 1 – Endoskopska video kapsula prikazuje difuzne limfangiektazije tankog creva

displazije (slika 2). Patohistološki je potvrđena dijagnoza limfagiektazija. Detektovana je izražena i iregularna dilatacija limfatika, kao i skraćenje i distorzija vilusa i redukcija kripti (slika 3). Kolonoskopski, u cekumu, ascendensu i transverzumu viđene su manje limfangiektazije, kao i loptasta prominencija, promera oko 2 cm, glatke, intaktne površine,

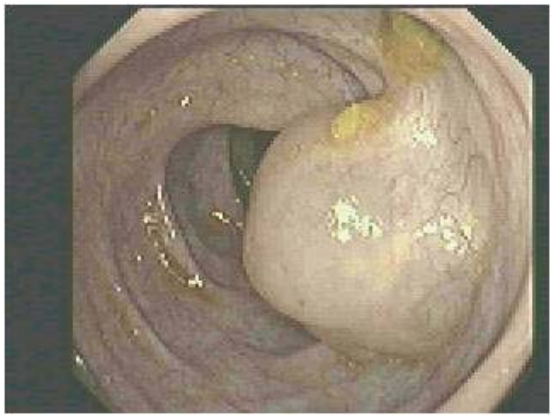


Sl. 2 – Endoskopska video kapsula prikazuje nekrvareću angiodisplaziju tankog creva i difuzne limfangiektazije

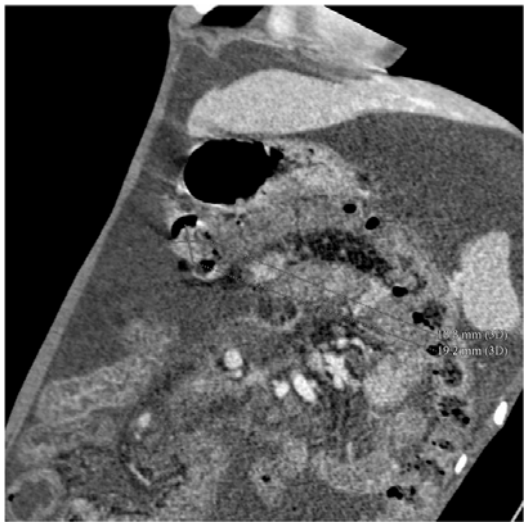


Sl. 3 – Patohistološki nalaz ukazuje na izraženu i iregularnu dilataciju limfatika, skraćenje i distorziju vilusa i redukciju kripti

mekše konzistencije u transverzalnom kolonu, koja nije bioptirana (slika 4). Multislajsni skener abdomena ukazao je na tumorsku formaciju u desnom delu transverzuma, promera 18,8 × 19,2 mm, koja je širokom bazom bila vezana za zid, hipervaskularizovana, zadržavala je kontrast u odgođenim skenovima, a odgovarala je limfangiomu (slika 5). Vijuge tankog creva bile su značajno zadebljalog zida (10 mm), sa prisutnim jezercima kontrasta u odloženoj fazi koji su odgovarali depoima limfe. Zbog zastoja u rastu i hipogonadizma urađene su hormonske analize koje su bile u referentnom opsegu, izuzev sniženog IGF-1 (*Insulin-like Growth Factor-1*) – 79 ng/mL i IGF-BP3 (*Insulin-like Growth Factor Binding Protein 3*) – 2 540 ng/mL. Testosteron bio je na donjoj granici referentnog intervala. Uporedni snimak obe šake ukazao je na nezatvorene epifizne pukotine uz levi karpus koji je bio neformiran. Koštana zrelost bila je ispod životnog doba. Nalaz ciljane radiografije turskog sedla bio je uredan. Bolesnik je lečen dijetom siromašnom mastima, sa unosom MCT i proteina (1,5 g/kg). Ordinirani su diuretici, antibiotici (ciprofloksacin), urađene su evakuacione abdominalne punkcije. Izvršena je supstitucija hormonom rasta (somatotropin) u dozi od 0,8 mg/dan *sc*. Supstituisani su liposolubilni vitamini, gvožđe i albumini. Na kontrolnom pregledu, nakon šest me-



Sl. 4 – Kolonoskopski prikazana loptasta submukozna lezija (limfangiom) u transverzalnom kolonu



Sl. 5 – Multislajsni skener abdomena ukazuje na limfangiom u transverzumu, promera 18,8 × 19,2 mm, koji je širokom bazom vezan za zid, hipervaskularizovan i zadržava kontrast i u odgođenim skenovima

seci bolesnik se subjektivno bolje osećao, porastao je ukupno 6 cm, korigovane su mu anemija, hipoproteinemija i hipoalbuminemija, redukovan ascites, ali je limfedem leve ruke i dalje perzistirao.

Diskusija

Kongenitalne IL su retko, urođeno oboljenje kod koga je prisutna dilatacija limfnih sudova tankog creva. Dilatacija limfatika može biti lokalizovana na laminu propriju ili zahvatiti submukozu, subserozu i mezenterijum tankog creva. Kod generalizovanih oblika zahvaćeni su svi slojevi [5]. U odnosu na distribuciju mogu biti: segmentalne, multifokalne i difuzne. Kod našeg bolesnika uočen je kongenitalni, difuzni tip limfangiektazija. Prevalencija kongenitalnih IL je nepoznata. Podjednako zahvata muškarce i žene. Najčešće se dijagnostikuje kod dece, pre treće godine života, ali su opisani slučajevi i kod mlađih odraslih osoba [6]. Etiologija kongenitalnih IL je nepoznata. Pretpostavlja se da je uzrok mutacija gena involviranih u limfangiogenezu: PROX1 (*prospero-related homeobox-transcriptional factor*) i VEGFR3 (*vascular endothelial growth factor receptor 3*) [7]. Zbog gubitka albumina i smanjenja onkotskog pritiska, u kliničkoj slici dominiraju umereni ili izraženi edemi, koji su najčešće lokalizovani na donjim ekstremitetima, kao i hilozni izlivi (ascites, pleuralne efuzije i dr). Sa IL su udruženi i limfedemi koji mogu zahvatiti donje i gornje ekstremitete [2]. Kod našeg bolesnika bio je prisutan refrakteran limfedem leve podlaktice i šake od rane mladosti. Većina bolesnika ima srednje teške prolive, steatoreju i druge znakove malapsorptivnog sindroma. Kod obolele dece javlja se zastoj u rastu. Laboratorijski su prisutni hipoproteinemija, hipoalbuminemija, hipogamaglobulinemija i limfopenija. Pored povišene koncentracije masti u stolici, povišen je i klirens alfa-1 antitripsina u 24-časovnoj stolici [8]. Enteroskopija sa patohistološkom analizom uzoraka tankog creva predstavlja 'zlatni standard' za dijagnostiku crevnih limfangiektazija. Makroskopski se detektuju beličasta zamućenja sluznice sa elevacijom submukoze i prosijavanjem dilatiranih limfnih kanalića [9, 10]. Histološki se vidi dilatacija limfnih prostora mukoze i submukoze. Sluznica tankog creva može se vizualizovati i video kapsulom [10–13]. Kod našeg bolesnika dijagnoza je potvrđena enteroskopijom i biopsijom tankog creva, a difuzni karakter promena potvrđen je video kapsulom. Kolonoskopija ima značaja u otkrivanju pratećih promena (limfangiomi kolona) ili uzroka sekundarnih limfangiektazija (Kronova bolest, Wippleova bolest, tuberkuloza creva, sklerodermija creva i dr) [4]. Limfangiografija, ultrasonografija i kompjuterizovana tomografija (KT) imaju veliki značaj u otkrivanju uzroka sekundarnih limfangiektazija, kao i u otkrivanju komplikacija.

U terapiji je najznačajnije pridržavanje odgovarajućeg dijetetskog režima koji se sastoji u restrikciji unosa masti, umesto kojih je dozvoljeno unošenje MCT [14–16]. Za razliku od dugolančanih triglicerida, MCT se direktno apsorbuju u portni sistem, te zaobilaze limfatični sistem i time sprečavaju rupturu limfnih kapilara. U više studija opisano je smanjenje intestinalnog gubitka albumina, pod uticajem oktreotida, kao splanhičnog vazokonstriktora [17–19]. Kod našeg bolesnika primena oktreotida nije dolazila u obzir, u ovoj fazi lečenja, zbog zastoja u rastu. Planirano je da se nakon zatvaranja epifiznih pukotina na supstituciju somatotropinom, izvrši supstitucija testosteronom, a tek potom terapija oktreotidom. Inače, naš bolesnik je dobro podneo terapiju somatotropinom, nije bilo nikakvih neželjenih efekata. Antiplazminska terapija, primenom traneksamične kiseline, smanjuje fibrinolizu i permeabilnost limfatika za proteine kod intestinalnih i torakalnih limfagiektazija [20]. Kod sekundarnih IL primenjuje se operativno ili medikamentno lečenje osnovnog uzroka. Supstitucija rastvorima albumina, liposolubilnim vitaminima i preparatima kalcijuma jeste važna, naročito u težim slučajevima [18].

Iako je kod prikazanog bolesnika bolest dijagnostikovana u detinjstvu, ovo predstvalja klinički značajan prikaz. Iako zakasnela, adekvatna terapija dovela je kako do poboljšanja opšteg stanja, tako i, makar delimičnog, rešavanja ozbiljnih komplikacija (zastoj u rastu i razvoju). Takođe, od značaja je i rezultat eksploracije celog digestivnog tubusa, kojim je verifikovana difuzna distribucija promena koja se u toj meri retko sreće.

Zaključak

Kongenitalne limfangiektazije su retko oboljenje koje se, uglavnom, dijagnostikuju u dečijem uzrastu. One mogu biti uzrok brojnih komplikacija koje se sprečavaju ranom dijagnostikom i primenom adekvatnog lečenja.

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P R I K A Z S L U Č A J A

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Primarni karcinoid jajnika

Primary carcinoid of the ovary

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Apstrakt

Uvod. Karcinoidni tumori su neuroendokrine neoplazme najčešće lokalizovane u gastrointestinalnom traktu i bronhopulmonalnom sistemu. Cilj ovog rada je bio da prikaže bolesnicu sa primarnim karcionoidnim tumorom jajnika kao jednom od ređih formi ove neoplazme. **Prikaz bolesnika.** Bolesnica, stara 49 godina, primljena je u bolnicu sa simptomima bola u trbuhu dijarejom i sumnjom na neuroendokrinu neoplazmu. Naime, četiri meseca pre prijema, bolesnici je urađena totalna klasična histerektomija sa obostranom adneksetomijom zbog tumora levog jajnika za koji je patohistološkom analizom utvrđeno da se radi o karcinoidu. Na prijemu, bile su prisutne umereno povišene vrednosti tumorskog markera CA 125 i visoke vrednosti 5-hidroksiindolsirćetne kiseline (5-HIAA). Skener abdomena ukazivao je na suspektan rest tumor u maloj karlici. Po završenoj obradi bolesnice urađena je relaparotomija i ustanovljeno prisustvo retroperitonealne fibroze. Šest meseci posle intervencije vrednosti 5-HIAA i CA 125 bile su normalne, a nuklearna magnetna rezonanca (NMR) abdomena i male karlice nije pokazivala znake tumorskog recidiva. **Zaključak.** Karcinoidi predstavljaju retku formu neoplazme ovarijuma (zastupljeni su u manje od 0,1% malignih tumora jajnika). Hirurški tretman i dalje praćenje su terapija izbora, pri čemu je važno imati u vidu mogućnost njihove pojave na neuobičajenim lokalizacijama, što je neophodno radi pravovremene dijagnostike i lečenja.

Ključne reči:
jajnik, neoplazme; karcinoid; histerektomija; tumorski markeri, biološki; tomografija; reoperacija.

Abstract

Background. Carcinoid tumors are distinct neuroendocrine neoplasms commonly located within the gastrointestinal tract and bronchopulmonary system. The aim of this case report was to present a patient with carcinoid tumor of the ovary as a less common form of this neoplasm. **Case report.** A 49 year old woman was admitted to the hospital with symptoms of diarrhea and abdominal pain and suspicion of neuroendocrine neoplasm, 4 month after bilateral salpingo-oophorectomy and total hysterectomy for ovarian tumor. Pathological diagnosis was typical for carcinoid tumor. At admission the patient had slightly eleveated levels of tumor marker CA 125 and highly elevated levels of 5- HIAA. Abdominal CT showed suspicious rest tumor in the pelvis. Relaparotomy was done and retroperitoneal fibrosis was found. Six months after the intervention the levels of 5-HIAA and CA 125 were normal, and NMR of the abdomen showed no signs of rest tumor. **Conclusion.** Carcinoid tumor of the ovary is rare form of ovarian tumors and less than 0.1% had malignant potential. Surgical therapy associated with a long-term follow-up was the treatment of choice. Consideration of unusual sites of carcinoid tumors facilitates appropriate diagnosis and treatment.

Key words:
ovarian neoplasms; carcinoid tumor; hysterectomy; tumor markers, biological; tomography; reoperation.

Uvod

Karcinoidi predstavljaju neuroendokrine neoplazme sa specifičnim histološkim, biološkim i kliničkim karakteristikama. Iako su najčešće lokalizovani u gastrointestinalnom i bronhopulmonalnom sistemu, značajan broj ovih tumora može se javiti i na manje uobičajenim anatomskim lokalizacijama što za posledicu može imati prilično dug period u kome tumor ostaje neprepoznat, sve do momenta pojave metastaza, odnosno ispoljavanja sekretorne aktivnosti [1]. Ovo za posledicu ima nespecifičnu kliničku prezentaciju koja može voditi neadekvatnom, neefikasnom i odloženom lečenju bolesnice [2]. Karci-

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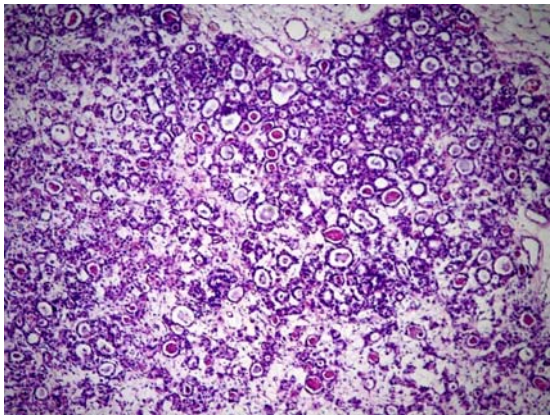
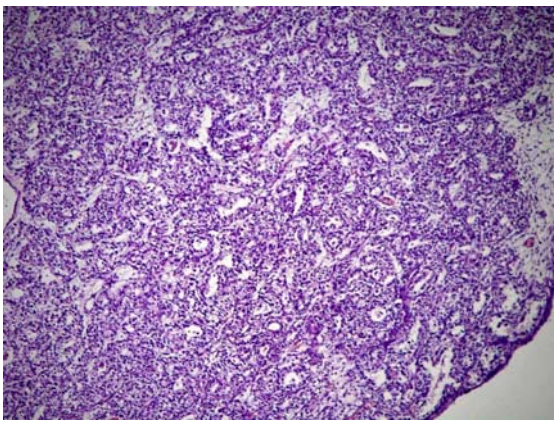
noidni tumori najčešće predstavljaju dijagnostički problem usled nejasne, odnosno nespecifične simptomatologije. Njihova sposobnost sekrecije hormona i biogenih amina ispoljava se u formi karcinoidnog sindroma [3]. Primarni karcionidni tumori jajnika su vrlo retki i čine manje od 1% svih karcionidnih tumora i manje od 0,1% malignih tumora jajnika [4].

Prikaz bolesnika

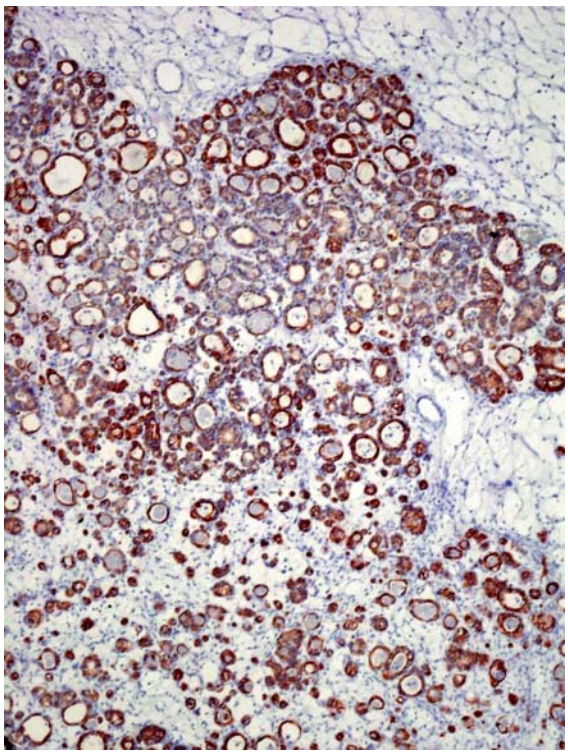
Bolesnica, stara 49 godina, primljena je u Institut za endokrinologiju i bolesti metabolizma Kliničkog centra Srbije u Beogradu sa dijarejom i bolovima u abdomenu kao dominantnim simptomima, i zbog sumnje na recidiv neuroendokrinog tumora. Četiri meseca ranije, kod bolesnice urađena je totalna klasična histerektomija sa obostranom adneksetomijom zbog postojanja tumora levog jajnika. Patohistološka analiza pokazala je da se radi o karcinoidnom tumoru sa dominantnom pseudoglandularnom organizacijom (slika 1) i eozinofilnim intraluminalnim sadržajem. U manjem delu tumora ustanovljena je trabekularna organizacija epitelnih proliferata (slika 2). Imunohistohemijska analiza ukazivala je na pozitivnu reakciju sa antihromogranin A antitelima u svim tumorskim ćelijama (slika 3) i manje intenzivnu reakciju sa antitelima na neuron specifičnu enolazu (slika 4). Desni jajnik bio je bez patoloških promena.



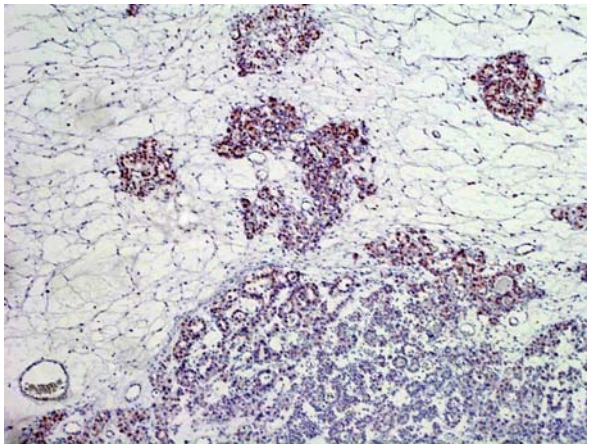
Sl. 1 – Patohistološki preparat karcinoida jajnika sa prisutnom pseudoglandularnom organizacijom i eozinofilnim intraluminalnim sadržajem (HE, 64×)



Sl. 2 – Trabekularna organizacija tumorskih epitelnih proliferata koja je bila zastupljena u manjem delu tumora (HE, 40×)



Sl. 3 – Imunohistohemijski nalaz sa pozitivnom reakcijom na antihromogranin A-antitela (HE, 64×)



Sl. 4 – Manje intenzivna citoplazmatska reakcija sa antitelima na neuron specifičnu enolazu (HE, 40×)

Na prijemu, nivo karcinoembrionskog antigena (CEA) kod ove bolesnice bio je normalan, tumorski marker CA 125 umereno povišen (31 U/mL, gornja granica referentnih vrednosti 20 U/mL), a dva puta ponovljene vrednosti 5-hidroksiindolsirćetne kiseline (5-HIAA) u 24-časovnom urinu visoke (129 µl/L i 158 µl/L, gornja granica referentnih vrednosti 52 µl/L). Hormoni štitaste žlezde bili su u granicama referentnih vrednosti, kao i nivoi kateholamina u 24-časovnom urinu.

Skener abdomena ukazivao je na potencijalnu tumorsku formaciju u maloj karlici. Urađena je relaparotomija pri čemu je konstatovano postojanje retroperitonealne fibroze bez znakova tumorskog recidiva. Šest meseci posle operacije po-

novljene vrednosti 5-HIAA bile su normalne (31 μl/L), a nalaz nuklearne magnetne rezonance (NMR) abdomena nije ukazivao na tumorski recidiv.

Diskusija

Kod prikazane bolesnice karcinoid je ispoljio specifične patohistološke karakteristike uz manje specifičnu kliničku sliku koja bi odgovarala tumorima jajnika uopšte. Karcinoidi jajnika najčešće se dijagnostikuju kao tumorska masa u maloj karlici. Patohistološki, neuroendokrina priroda ovog tumora ogleda se u prebojavanju tipičnim neuroendokrinim markerima. Karcinoidni sindrom može se javiti kod jedne četvrtine bolesnica i manifestuje se crvenilom, dijarejom, bolovima u abdomenu i desnostranom srčanom isuficijencijom [5], dok su povišene vrednosti 5-HIAA u plazmi i urinu, pozitivni tumorski markeri CEA, CA 125 i CA 19-9, kao i scintigrafija somatostatinskih receptora, analize koje mogu doprineti diferencijalnoj dijagnozi [6, 7].

Oko 10% karcinoida može se ispoljiti u sklopu multiple endokrine neoplazije tip 1 (MEN 1), što, takođe, treba uzeti u razmatranje prilikom ispitivanja i tretmana ovih bolesnika.

Karcinoidi predstavljaju relativno retke benigne tumore jajnika koji se češće javljaju kod mlađih žena. Definitivna dijagnoza moguća je samo na osnovu patohistološkog pregleda uz upotrebu imunohistohemijskih metoda obrade preparata, čime je omogućena njihova diferencijacija u odnosu na tumore jajnika poreklom iz polnih traka i ependimome.

Prognoza kod karcinoidnih tumora povoljna je jer svega 1,4–2% ispoljava malignu alteraciju, a komplikacije se javljaju kod 14% bolesnica [3]. Naročito povoljan ishod može se očekivati u slučajevima sa primarnim tumorom koji je ograničen na jajnik u momentu postavljanja dijagnoze, kada stopa preživljavanja iznosi više od 90% [8]. I pored toga što su primarni karcinoidi jajnika retki, posebnu pažnju trebalo bi obratiti na bolesnike sa prisutnim elementima karcinoidnog sindroma u kliničkoj slici i adneksalnim tumefaktom [9, 10].

Zaključak

Karcinoidi predstavljaju neuroendokrine neoplazme sa tendecijom javljanja na neuobičajenim antomskim lokalizacijama, što uz nespecifičnu kliničku sliku otežava pravovremenu dijagnozu i lečenje. Primarno hirurško lečenje i praćenje, predstavljaju terapiju izbora kod bolesnica sa ovim tumorima.

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CASE REPORT

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Reconstruction of the columella and the tip of the nose with an island-shaped forehead flap

Rekonstrukcija kolumele i vrha nosa ostrvastim čeonim režnjem

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Abstract

Background. Posttraumatic and postoperative defects of columella and the tip of the nose are difficult to reconstruct. There are several operative methods described in the literature, and many of them are step-by-step procedures with long duration. The aim of this study was to present one-step procedure for reconstruction of the columella and the tip of the nose with island-shaped arterial forehead flap. **Case report.** A 45-year old man was submitted to surgical excision of basocellular skin cancer. After the excision, a defect of the columella and tip of the nose the remained, 3 × 2.5 cm in dimensions, with exposed alar cartilages. During the same operation, the defect was covered with an island-shaped arterial forehead flap. Postoperative one-year course was uneventful, without signs of tumor recurrence after one year, and further surgical corrections were unnecessary. **Conclusion.** Considering the results of our operative technique, we believe that middle island-shaped forehead flap is suitable for reconstruction of the columella and the tip of the nose, due to the following reasons: safe vascularization of flap, similarity of the transferred tissue with the excised one, the procedure is completed in one step, simple surgical technique and uncomplicated healing of a flap-harvesting site.

Key words:
skin neoplasms; reconstructive surgical procedures; nose neoplasms; treatment outcome.

Apstrakt

Uvod. Posttraumatski i postoperativni defekti kolumele i vrha nosa su teški za rekonstrukciju. Ima više opeativnih metoda opisanih u literaturi. Većina njih su višeaktovne i obavljaju se korak po korak. Cilj ovog rada bio je da se prikaže jednofazna procedura rekonstrukcije kolumele i vrha nosa primenom ostrvastog arterijalnog čeonog režnja. **Prikaz bolesnika.** Bolesnik, star 45 godina, bio je podvrgnut hirurškom uklanjanju bazocelularnog karcinoma kože. Posle hirurške intervencije ostao je defekt veličine 3 × 2,5 cm na kolumeli i vrhu nosa sa eksponiranom alarnom hrskavicom. Tokom operacije defekt je pokriven ostrvastim arterijskim čeonim režnjem. Postoperativni tok u narednih godinu dana bio je bez komplikacija, bez znakova recidiva tumora, te dalje hirurške korekture nisu bile potrebne. **Zaključak.** Na osnovu rezultata hirurške tehnike koju smo primenili možemo zaključiti da je ostrvasti čeoni režanj pogodan za rekonstrukciju kolumele i vrha nosa jer ima pogodnu vaskularizaciju, tkivo mu je slično uklonjenom, a procedura se obavlja u jednoj fazi, hirurška tehnika je jednostavna i postoperativni tok je bez komplikacija.

Ključne reči:
koža, neoplazme; hirurgija, rekonstruktivne procedure; nos, neoplazme; lečenje, ishod.

Introduction

Reconstruction of the nose is one of the oldest operations of its kind, but it is still a challenge to surgeons because of the complex anatomy of the nose and its functional and aesthetic importance [1–6]. A number of studies on this issue have shown that the tip of the nose, especially columella are the most complex structures for reconstruction, because of their specific localization [7–15].

Isolated defects of the skin at the tip of the nose are usually covered by local skin flaps. Collumella defects may be partial or total, also associated with defects of adjacent structures [10–16]. The literature describes numerous reconstructive methods. According to existing records, the first reconstruction of the columella was done by Diefenbach in 1833 when he applied a skin flap from the upper lip. This method was later modified several times [9]. Then Joseph published the results of reconstruction of the columella by chon-

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drocutaneous transplant, and as giving region he used the nasal wing. Others were applying composite graft from auricle or mastoid region [17]. Other reconstructive methods were also described: nasolabial flaps [18–21], flaps of the lower lip, frontal lobes [22–27], dermal or fascial flaps from the dorsum of the nose, skin flaps from the nasal wings or from the nasal vestibule and the nasal septum [28], cheek flaps, or tubule or island-shaped flaps from the neck regions, periauricle flaps, scalp flaps, a skin tubule from the upper arm or back of the hand and microvascular muscle flaps from the ear [29].

One of the known methods of multiple procedures methods of the columella and the tip of the nose reconstruction is the pedicled interpolar frontal lobe flap. Island-shaped arterial frontal lobe of supratrochlear blood vessels was used for reconstruction of larger nose defects or partial defects in the upper and middle part of the nose [3, 5, 6,13, 14, 22–27, 30–32]. Because there are different methods for reconstruction of the columella and the tip of the nose, we thought it reasonable to demonstrate experience in using the frontal island-shaped flap in resolving defect of the columella and the tip of the nose.

Case report

A patient, aged 45, was hospitalized because of skin tumor on the columella and the tip of the nose. The tumor by its morphological features resembled basal cell carcinoma (Figure 1). Radical excision was done after which there was a skin defect of the folowing dimensions - 3 × 2.5 cm, as well as exposed cartilage. In further surgical procedure reconstruction of the central island-shaped frontal lobe was performed. It was flapped with supratrochlear blood vessels on the left side. Secondary lobe defect was closed by direct suture. The operation was performed under general endotracheal anesthesia and lasted about 60 min. During postoperative period the flap was vital, and there was a shorter venous congestion of the flap and mild swelling of the nose that lasted for several days (Figure 2). Histopathological results confirmed that it was a basal cell carcinoma, which was radically excised at the periphery and depth. The patient was discharged from the hospital seven days after the operation, when the stitches were removed also. During the control examinations the last of which was performed one year after the surgery, there were no signs of recurrence, the results of the operation were satisfactory and with no need for additional corrections (Figures 3, 4).

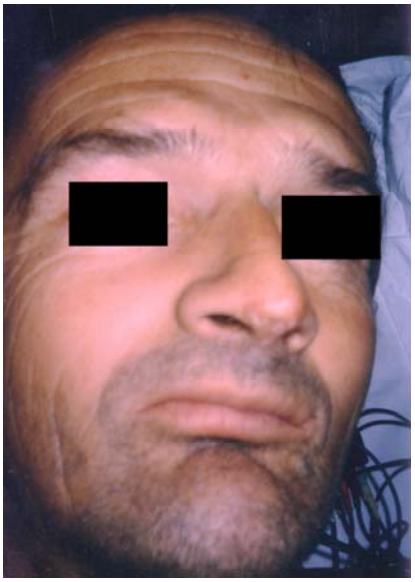

Fig. 1 – Basal cell carcinoma of the columella and the tip of the nose

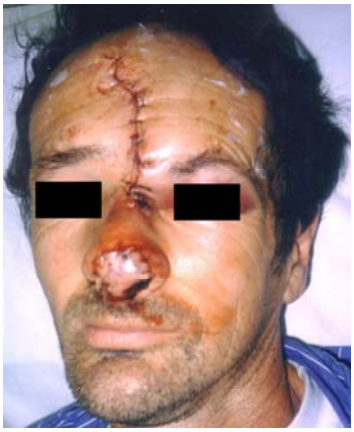

Fig. 2 – Island-shaped arterial forehead flap for reconstruction of the columella and the tip of the nose, 24 hours after the procedure

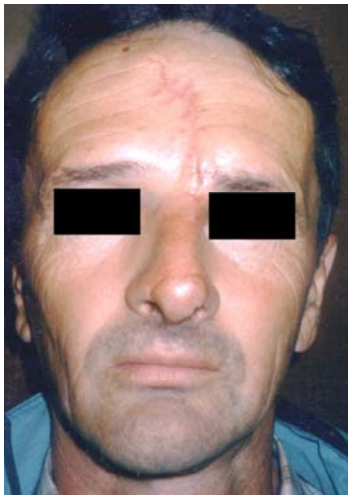

Fig. 3 – The result of reconstruction one month after the surgical procedure

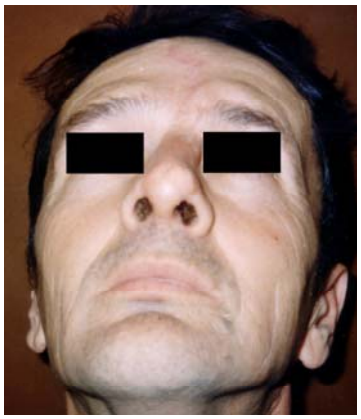

Fig. 4 –The result of reconstruction one year after the surgical procedure

Disscusion

If we consider the number and type of the presented methods for columella reconstruction so far, the conclusion is that none of them is ideal.

Concerning the fact that skin is thicker in the lower half of the nose, free skin grafts are rarely used in that region because the aesthetic result is worse, and besides, that cannot be applied when cartilage is exposed without perichondrium. Isolated and fewer defects at the top of the nose can usually be covered with local skin flaps.

In columella defect, the use of local flap is limited because of its specific localization and morphology. Composite graft from the nasal alae, ear or mastoid region may be applied for partial columella defects and is commonly used with children with congenital retrusion of the tip of the nose [17]. In addition, this region is very ungrateful for the immobilization of grafts. Flaps from the nose vestibule or perialae region can be applied for minor defects of the columella, and, for larger defects, it is necessary that they are bilateral, and therefore the scars are more conspicuous. Furthermore, functional consequences may also occur, because the structure of the nasal aperture is disrupted. When using a flap from the upper or lower lip, a scar on the secondary defect is obvious. Tubule mucosal flap from the upper lip is a multiple method, and the tissue is of a different texture and color. Nasolabial flap [18–21] can be used as an interpolar which is multiple step method, or it can be used on the subcutaneous pedicle, and in this process the nasal wing is cut; pedicle is nevertheless often tense. It is usually suggested in the elderly with a relaxed face skin. Distant flaps from the neck, shoulders or hands are a multiple step method in which the forced position of a patient is required and a long-term cure [9]. In men, the flaps from the upper or lower lip, the nasolabial region and neck contain hair, and the aesthetic result is worse. Reconstructions of the columella with the frontal lobe or periauricle scalp flaps described so far are multiple step methods. Microvascular tissue transfer involves a long-term operation and cuts on the face in the area of recipient blood vessels. When a defect catches both the columella and the tip of the nose, some of these methods cannot be applied because of the size of the defect.

Island-shaped front flap is usually used in reconstruction of partial defects in the upper two-thirds of the nose or for total nose reconstruction [3, 5, 6, 13, 14, 22–27].

The method we applied involves accurate planning of the position of non-hairy part of the forehead. Preparation of the flap should be done carefully because it is necessary that the vascular pedicle is long enough. Preoperative supratrochlear artery Doppler-ultrasound is not necessary because its anatomy is constant, but vascular status of a patient needs to be examined. It is important that a vascular pedicle flap is not compressed after the transposition, and that is why it is necessary that subcutaneous space to the part of the defect is large enough. Partial resection of the *m. procerus* proposed by some authors, is not necessary, in our opinion.

The postoperative results of this method showed that the flap was vital in total and that it did not require additional corrective procedures. Benefits of this technique are in our view multiple: secure flap vascularization, satisfactory color, texture and thickness of the flap, reconstruction in one procedure, a surgery that is relatively simple and no long lasting, quick recovery of a patient and aesthetically acceptable scar on the secondary lobe defect.

Conclusion

Reconstruction of the nose must enable optimal functional, aesthetic and economic results. The columella and the tip of the nose are in reconstructive terms very complex regions, and therefore there are a number of proposed surgical methods. Most of the reported techniques are multiple steps or long-term surgical procedures. Bearing in mind the result of operational methods which are applied, we believe that the central island-shaped frontal lobe is suitable for reconstruction of the columella and/or the tip of the nose and that it meets all the requirements of optimal reconstruction. There is a safe flap vascularization, transfer of the tissue that is similar to the tissue from the defected region, simplicity and one-step procedure method and minimal morbidity in donor region.

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H I S T O R Y O F M E D I C I N E UDC: 355.088:61-051]:581-051(091)

Medical Corps Colonel Doctor Sava Petković "Flora of the town of Niš Region" – inheritance for the future

Sanitetski pukovnik dr Sava Petković „Flora Niša i njegove okoline" – ostavština za budućnost

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Ključne reči:
physicians; therapeutics; military personnel; pharmacopoeias.

Key words:
lekari; lečenje; vojni kolektiv; botanika; farmakopeje.

Introduction

Medical Colonel Dr Sava Petrovic (Figure 1) was born on 14 January 1839 in the town of Šabac. His father Jovan was a craftsman and his mother Marija a housewife [1–3]. By profession he was a doctor, Medical Colonel of the Serbian Army and a botanist. He became elected member of the Serbian Learned Society in 1869 and a corresponding member of the Serbian Royal Academy in 1889.

Medical Colonel Dr. Sava Petrović lost his father early in his life and his mother made him learn the tailor's trade. Dissatisfied with the prospect of his future profession, he left this school and started elementary school in the town of Šabac, then attended lower secondary school in Šabac, a higher secondary school in Belgrade, and the Lyceum in Belgrade (Natural Science Department).

During his schooling in Belgrade Dr. Sava Petrović met Dr Josif Pančić, who directed him towards the study of flora [1, 2]. Upon completion of his studies at the Lyceum in Belgrade, Sava Petrović was awarded a state scholarship and went to Paris (France) to study medicine and surgery. Upon arrival in Paris Sava got ill and was forced to abandon his medical studies and return to Serbia for treatment. Due to the disease Sava Petrović lost the state scholarship, and when he recovered he was forced to work privately in order to provide funds for the completion of the previously enrolled medical school in Paris.

Dr. Sava Petrović graduated at the Medical School in Paris on 22 November 1866. His PhD thesis *De la mastomanie* was written in French and had 11 chapters on 44 pages [3, 4].

Having acquired the academic title, Dr Sava Petrović returned to Serbia, where he became employed as District Physicus in the town of Kruševac. After eight months of work in the town of Kruševac, he got a job in the military medical service in Belgrade, where he advanced to the rank of medical corps colonel, then to the position of the main Serbian military doctor, ultimately becoming the personal physician of Prince Milan Obrenović in 1873.

Fig. 1 – Medical Colonel Dr. Sava Petrović (born on January 14, 1839 in Šabac, died on January 22, 1889 in Belgrade) is a world known botanist. He was a member of the Serbian Learned Society (1869) and a corresponding member of the Serbian Royal Academy (1889). He contributed to the study and understanding of the geographical position of the town of Niš, its surroundings and the whole of southeastern Serbia in terms of the floral abundance of that area

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During the Serbian-Turkish Wars (1876–1878), Dr. Sava Petrović was appointed state commissioner for providing private help to the wounded and refugees, he supervised donations coming from the world and coordinated work of foreign volunteering medical missions in the Principality of Serbia. Dr. Sava Petrović was promoted to colonel, the highest rank in the medical corps service at the time.

Accompanying Prince Milan Obrenović on a trip to Serbia and the territories of Serbia newly liberated from the Turks Dr. Sava Petrović had an opportunity to meet people in Serbia, to learn about their customs and about the flora and fauna of Serbia.

At Prince Milan Obrenović's insistence Dr. Sava Petrović began studying the flora of the town of Niš and its surroundings.

Dr. Sava Petrović got married to Draga in 1868. They had a son, who unfortunately died very young. The great loss they suffered was a personal tragedy that left a mark in their life and work.

Medical Colonel Dr. Sava Petrović died on 22 January 1889 in Belgrade. He left his property in his will to patriotic and charitable purposes. Thus, for example, his herbarium and his rich personal botanical library he gave to the Niš High School (today First Niš High School „Stevan Sremac"). Unfortunately this priceless gift never arrived at this high school. Parts of his herbarium are known to be kept in the Institute of Botany and Botanical Garden – Jevremovac (Belgrade, Serbia), Natural History Museum in Belgrade (Serbia) and the Natural Sciences University in Zagreb (Croatia). His other assets (houses, land, money, securities, etc.) Dr. Sava Petrovic intended for establishing a fund to finance young scientists studying the flora of Serbia.

Professional and research work

Medical Colonel Dr. Sava Petrović wrote nine professional and scientific research works [1–4]:

1. *De la mastomanie* - PhD thesis written in French (Paris, 1866);
2. Conversion and concealment of disease among soldiers (London, 1875);
3. Protection from tuberculosis (London, 1880);
4. Military-medical statistics for the year 1879 (London, 1882);
5. Flora of Niš Region (*Flora Agri Nyssani*) (London, 1882);
6. Medicinal plants in Serbia (Belgrade, 1883);
7. Supplement to Flora of Niš Region (*Additamenta ad Flora Agri Nyssani*) (London, 1885);
8. *Ramondia in Serbia and family Cirtandracia* (Belgrade: Journal of the Serbian Learned Society 1885; LXII: 101–123);
9. Stachys Milanii Petrović, In: Magnier C, ed. *Florae Scrinia Selectae*, 6, 117 (Saint-Quientin, 1887).

According to Randjelović [1] medical works of Dr. Sava Petrović belong to the older works of Serbian medicine, particularly in the field of military medicine.

In addition to his regular duties Dr. Sava Petrović was in charge of social, hygienic and dietary regime of soldiers and officers of the Serbian Army, and in his work "Military medical statistics for the year 1879" published in 1882 he said: "No one can allow for one's life to be risked just to find out whether or not one is pretending... it is better for a doctor to be fooled than for one's illness to get worse or cause death... If the doctor notices that the nostalgia is the cause of the pretence, such a soldier should be sent home for a while to avoid any bad consequences of his condition" [1].

Dr. Sava Petrović was a founding member and signatory of the decision to establish the Serbian Medical Association, Srpsko lekarsko društvo (SLD), in Belgrade in 1872. At that time the SLD was the first public organization in Serbia, the oldest medical society in the Balkans and one of the oldest medical associations in the world. The idea to found SLD was introduced in Serbian newspapers in 1859, four years after founding the English Royal Medical Society (1855) [5, 6].

Dr. Sava Petrović as a florist

Dr. Sava Petrović was far more famous as a botanist, than as a doctor. His work on the study of plants began with his first employment in the town of Kruševac. Namely, Dr Sava Petrović formed a small botanical garden in the town of Kruševac in which he cultivated plants growing in Kruševac and its surroundings. When he moved to Belgrade, Dr Sava Petrović influenced Prince Milan Obrenović to assist in the formation of the first botanical garden in Serbia. So, in 1874 the botanical garden was founded in Belgrade, the first in Serbia. Its first manager was Dr. Josif Pančić, until his retirement in 1887 [1–4].

Following the example of Belgrade Dr. Sava Petrović tried to establish botanical gardens in other Serbian town – Niš, Kragujevac, Kruševac, etc... In liberated Niš (11 January 1878) Dr. Sava Petrović formed a botanical garden, located in the area of the park across the street from the Niš Fortress, on the banks of the river Nišava (unfortunately, this botanical garden does not exist any more).

In 1882, during his tenure in the town of Niš, he wrote his book "Flora of the town of Niš Region" (*Flora Agri Nyssani*) of 950 pages (Figure 2). The book was


ФЛОРА

ОКОЛИНЕ НИША

Др. Ѕ. Петровић

FLORA

AGRI NYSSANI

Dus S. PETROVIĆ

БЕОГРАД

Fig. 2 – Cover of the book „Flora of the town of Niš Region" (*Flora Agri Nyssani*) by Dr. Sava Petrović, printed in Belgrade in 1882

written according to the model of the book "Flora of the Principality of Serbia" by Josif Pančić from 1874. In the book he wrote: "Sir, during your stay in Niš in 1879 you expressed the wish to study the flora of Niš. That wish of Your Majesty I have taken as a commandment, and I immediately began to collect and study the plants around Niš".

The book offers an analysis of classes which provide the key to the comparison of genera and key to the comparison of species within genera that are of various types. He described 1,400 plant species, of which 60 new ones, while some of them were part of floristics (*Ramonda Nathaliae* Pančić *et* Petrović*, Tragopagon pterodes* Pančić and *Crosus sulphurea x biflorus* Petrović are significant for today's science, while *Trifolium lecotrichum* Petrović is a synonym for the type *T. leucanthum Bieb* and *Ornitogalum nyssanum* Petrović a synonym for the type *O. montanum* Cr. et al.). For each type, there is a description of the plant, information on where it grows and where it was found.

For this book Dr. Sava Petrović received plants from the following sites: Niš Fortress, Čair Park, Vinik, Gorica, Gabrovačka Hill, Suvodolsko Hill, Niška Banja, Jelašnica Gorge, Kunovačko Hill, Čamurlijsko Hill, Gorge, Mount Seličevica and Dry Mountain, areas surrounding the arnauts border (today it is the territory of Kosovo and Metohia of the Republic of Serbia) and the Balkans (today Old Mountain).

New species of Serbian flora that Dr. Sava Petrović presented in the book "Flora of the town of Niš region" (*Flora Agri Nyssani*) are given in Table 1 [1].

In 1885 Dr. Sava Petrovic published a new book "Supplement to Flora of the town of Niš Region " (*Additamenta ad Floram Agri Nyssani*). The book was written on 281 pages and offered the description of 160 new plants growing in Niš area. In order to collect the plants for this book Dr. Sava Petrović was helped by Dr. Josif Pančić, Professor Sreta Pelivanović and Djura Ilić. New species of plants that Dr. Sava Petrović described in this book are: *Nonnea pallens, Orobanche Serbica* and *Genista Nissana*. The book also discusses some of Pančić's species: *Orobanche esulae* and *Silene pseudonutans*, and taxa *Rosa Serbica* and *Rossa Petrović* (described by Burnata and Gremlia, that still have unresolved status).

To this date, taxa *Genista Nissan, None pallens, Orobanche serbica, Ramonda nathaliae, Stachys milani, Tragopogon pterodes, Orobanche esulae, Crocus hybridus, Edeanthus Serbicus, Hypochaerismaculata* ssp. *Pelivanović, Hieraciumpraecox* ssp. *pljackovicense* and *Primulaacaulis f. alba* described by Dr. Sava Petrović have survived all previous revisions.

The following taxa discovered by Dr. Sava Petrović have changed their status, but kept the same name: *Centaurea napulifera* ssp. *Nissan, Hypocoum imberbe* ssp. *pseudograndiflorum* and *thymus jankae subvar. Serbicus*.

New species of plants that Dr. Sava Petrović presented in the book "The Supplement to the Flora of Niš Region" (*Additamenta ad Flora Agri Nyssani*) are given in Table 2 [1].

In the monograph "*Ramondia* in Serbia and family *Cirtandraceae*" written on 23 pages (1885, Beograd), Dr. Sava Petrović gave a detailed description of all types of *Ramonda* growing in the Mediterranean. Thus, for example, *Ramonda Nathaliae* (endemic species) found by Dr. Sava Petrović in Jelašnica Gorge he initially called *Ramonda nyssana*, but after consulting Dr. Josif Pančić he renamed it to *Ramonda Nathaliae* (Figure 3) in honour of Princess Natalia Obrenović [7–11]. Another *Ramonda*, *Ramonda Serbica* (Figure 4), was discovered and described by Dr. Josif Pančić and Dr. Sava Petrović.

Fig. 3 – *Ramonda Nathaliae* – endemic plant species found by Dr. Sava Petrović in Jelašnica Gorge in the vicinity of the town of Niš

Fig. 4 – *Ramonda Serbica* – endemic plant species found and described by Dr. Josif Pančić in collaboration with Dr. Sava Petrović with the habitat in Jelašnica and Sićevo gorges in the vicinity of the town of Niš

Dr. Sava Petrović, also wrote the first Serbian Pharmacopoeia "Medicinal plants in Serbia" (Belgrade, 1883) in which he described about 450 plants.

Table 1

New species of plants for the Serbian flora that Dr. Sava Petrović presented in the book "Flora of the town of Niš Region" (*Flora Agri Nyssani*)

Status according to Dr. Petrović	Today's status
Anchusa undulata L.	*Amchusa hybrida Ten.*
Androsace elongata L.	*Androsace elongata L.*
A. lactea L.	*A. lactae L.*
A. villosa L.	*A. villosa L.*
Allium atropurpuraeum W. K.	*Allium atropurpuraeum W. K.*
Alopecurus utriculatus Pers.	*Alopecurus utriculatus Pers.*
Astragalus vesicarius L.	*Astragalus vesicarius L.*
Avena amethhystina DC	*Avena pubescens Huds.*
Bromus confertus M.B.	*Bromus confertus M.B.*
Bupleurum rapunculoides L.	*Bupleurum rapunculoides L.*
Cachrys alpina M.B.	*Cachrys alpina M.B.*
Calamintha alpina L.	*Calamintha alpina L*
Centaurae axillaris Willd.	*Centaurea triumfetti All.*
Chaenopodium ticifolium Smith	*Chaenopodium ticifolium Smith*
Cirsium acarna (L.) Moench	*Cirsium acarna (L.) Moench*
Corydalis fabacea Pers.	*Corydalis fabacea Pers.*
Crassuda magnolii DC	*Crassuda magnolii DC*
Digitalis ferruginea L.	*Digitalis ferruginea L.*
Dryas octopetalla L.	*Dryas octopetalla L.*
Eucladium syriacim L.	*Eucladium syriacim L.*
Euphorbia baselicus Ten.	*Euphorbia barrelieri Savi*
E. lathyrus L.	*E. lathyrus L.*
Festuca liliacea Huds.	*Festuca liliacea Huds.*
Fumana anatolica Boiss.	*Fumana kralikii Jord.*
Gagea bochemica Schult.	*Gagea bochemica Schult.*
Galium anisophyllum Vill.	*Galium anisophyllum Vill.*
Gentiana verna L.	*Gentiana verna L.*
Godyera repens Ker.	*Godyera repens Ker.*
Heleocharis ovata R. Br.	*Heleocharis ovata R. Br.*
Hutchinsia petraea R. Br.	*Hornungia petraea (L.)Rchb.*
Hypericum atomarium Booiss.	*Hypericum atomarium Booiss.*
Hypericum repens L.	*Hypericum repens Petr. non L. (=H. linarioides bosse)*
Hypocoum grandiflorusm Benth.	*Hypocoum imberbe S.S.*
Iris pseudopumila Tin.	*Iris pumila L.*
Knautia magnifica Boiss. et Orph.	*Knautia magnifica Boiss. et Orph.*
Lactuca chondrillaeflora Bar.	*Lactuca chondrillaeflora Bar.*
Lamium longiflorum Ten.	*Lamium longiflorum Ten.*
Lathyrus cicera L.	*Lathyrus cicera L.*
L. erectus Lag.	*L. inconspicuum L.*
Orobus pubescens Panč.	*L. pancicii (Jur.) Adam.*
Lepidium perfoliatum L.	*Lepidium perfoliatum L.*
Lilium carniolicum Bernh.	*Lilium carniolicum Bernh.*
Lytospermum tenuifolium S.S.	*Lytospermum arvense L. var. Sibthorpianum (Griseb.) Hol.*
Nonea Lutea DC.	*Nonea Lutea DC.*
Orchis henrii Jord.	*Orchis henrii Jord.*
O. pseudosmbucina Ten.	*O. pseudosmbucina Ten.*
O. simia Lamk.	*O. simia Lamk.*
O. pubescens Panč.	*O. pubescens Panč.*
Ornithogalum divergens G.G.	*Ornithogalum divergens G.G.*
O. nanum Smith	*O. nanum Smith*
Platanthera montana Smith	*Platanthera montana Smith*
Picnemon acarna (L.) Kass.	*Picnemon acarna (L.) Kass.*
Pinus pumilio Haluk	*Pinus pumilio Haluk*
Potentilla apennina Ten.	*Potentilla apennina Ten.*
Ruta graveolens L.	*Ruta graveolens L.*
Ronunculuc ficaria L.	*Ronunculuc ficaria L.*
R. velutinus Ten.	*R. velutinus Ten.*
Salvia horminum L.	*Salvia horminum L.*
S. virgata Ait.	*S. virgata Ait.*
Saxifraga bulbifera L.	*Saxifraga bulbifera L.*
Scila autumnalis L.	*Scila autumnalis L.*
S. amoena L.	*S. amoena L.*
Scorsonera stricta Horn.	*Scorsonera stricta Horn.*
Scutellaria alpina L.	*Scutellaria alpina L.*
Thymus striatus Wahl.	*Thymus striatus Wahl.*
Trifolium angulatum DC.	*Trifolium angulatum DC.*
T. michelianum L.	*T. michelianum L.*
T. nigrescens L.	*T. nigrescens L.*
T. subterraneum L.	*T. subterraneum L.*
Tulipa sylvestris L.	*Tulipa sylvestris L.*
Vicia onobrychoides L.	*Vicia onobrychoides L.*
Viola macedonica Boiss. et Heldr.	*Viola macedonica Boiss. et Heldr.*

Table 2

New species of plants for the the town of Niš region flora that Dr. Sava Petrović presented in the book The addition to the Flora of the town of Niš Region (*Additamenta ad Flora Agri Nyssani*)

Status according to Dr. Petrović	Today's status
Ranunculus nissanus Petrović	*R. psilostachys Gris.*
Hypecoum pseudo-grandiflorum Petrović	*H. imberbe S.S. ssp. pseudograndiflorum*
Centaurea nissana Petrović	*C. napulifera Rch. ssp. nissana*
Achilea serbica Petrović	*A.. serbica Nim.*
Nonnea pallens Petrović	*N. pallens Petrović*
Nonnea commutata Petrović	*N. pallens Petrović*
Linaria nissana Petrović	*L. concolor Gris.*
Orobanche serbica Beck at Petrović	*O. serbica Beck at Petrović*
Orobanche esulae Panč.	*O. esulae Panč.*
Silene pseudonutans Panč.	*S. pseudonutans Panč.*
Hypericum boisseri Petrović	*H. rochelii Griseb.*
Genista nissana Petrović	*G. nissana Petrović*
Rossa serbica Burnat et Gremli	?
Rossa petrovići Burnat et Gremli	?
Peucedanum serbicum Petrović	*P. aegopodioides (Boiss) Vandas*
Carduus leiophyllus Petrović	*C. thoermeri Weium*
Festuca ovina var. panciciana Hack.	*F. panciciana (Hack) Rich*
Orobanche evonymi Petrović	*O. amethiestea Thill. var. evonymi*

Conclusion

Dr. Sava Petrović was one of the fathers of Serbian medicine whose work made a great contribution to the promotion of Serbian medicine, military health care and botany. He is one of the leading figures of Serbian botany, immediately after Dr. Josif Pančić. While working in the field of botany he made discoveries which used even today for processing domestic and world flora. Dr. Sava Petrović's work contributed to the study and understanding of the geographical position of the town of Niš, its surroundings and the whole of southeastern Serbia in terms of the floral abundance of that area. He pointed out the extraordinary richness and diversity of vegetation of southeastern Serbia that will later be confirmed and completed. He described the endemic and relict plant species, for which Niš and its surroundings became famous in the world. Those are the endemic plants of the *Ramonda* genus (one was discovered by Dr. Josif Pančić – *Ramonda Serbica* and another by Dr. Sava Petrović – *Ramonda Nathaliae*) which are the living fossils of tropical flora.

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P R I K A Z K N J I G E

Hronika Medicinskog fakulteta u Beogradu (1920–2010)

Istorijat, ljudi i događaji

1863 – 1920 – 2010

Autor: prof. dr Snežana Veljković
Izdavač: Beograd: Medicinski fakultet; 2010.
Štampa: Grafostil, Kragujevac
Tiraž: 1 000

Krajem prošle godine, u sklopu proslave 90. godišnjice osnivanja Medicinskog fakulteta u Beogradu, izišla je monografija Snežane Veljković, redovnog profesora Medicinskog fakulteta u Beogradu, pod nazivom „Hronika Medicinskog fakulteta u Beogradu (1920–2010). Istorijat, ljudi i događaji 1863–1920–2010“. Prema rečima same autorke, navedenim u uvodnim napomenama, ideja o ovakvoj hronici nastala je 2005. godine, kada je u potrazi za dokumentima o počecima rada Katedre za sudsku medicinu na Medicinskom fakultetu u Beogradu, otkrila obilje dokumenata i fotografija, do tada nepoznatih široj medicinskoj javnosti, iz kojih se mogao sagledati razvoj, ne samo Medicinskog fakulteta u Beogradu, već i čitavog Beogradskog univerziteta. Trebalo je uložiti ogromnu energiju i vreme da se svi ti podaci sistematizuju, obrade i hronološki postave u logičan sled da bi čitalac na sveobuhvatan način mogao da prati događaje i ličnosti koje su ostavile dubok pečat u istoriji srpske medicine i, na neki način, i celokupne akademske zajednice Srbije. Prof. dr Snežana Veljković to je uradila na način dostojan velikana istorijskih kazivanja.

Neke od najvažnijih događaja iz istorije Medicinskog fakulteta u Beogradu i Beogradskog univerziteta, autorka je stavila u okvire tadašnjih društveno-političkih prilika, tako da ova „Hronika“ predstavlja i svojevrsnu sociološku studiju jednog vremena. Knjiga je, kao što i priliči jednoj hronici, bogato ilustrovana, neke od fotografija rečitije su i od samog teksta i zajedno s njim čine neraskidivu i skladnu celinu.

Ovo delo ima preko 1 000 strana, tačnije 1 024. Na početku knjige, posle kopije članka prof. Stanoja Stanojevića „Nukleus srpskog medicinskog fakulteta u 14. veku“, objavljenog 1929. godine u časopisu Medicinski pregled, u kome se govori o počecima nastave iz medicine u okviru srpskog manastira Prodrom u Carigradu, navedena su imena sa fotografijama svih dekana Medicinskog fakulteta Univerzitata u Beogradu od 1920. do danas. Potom, sledi 14 glavnih poglavlja: 1) Osnivanje Velike škole i Univerziteta u Beogradu, 2) Univerzitet za vreme Balkanskih ratova i Velikog svetskog rata, 3) Osnivanje Medicinskog fakulteta, 4) Univerzitet u Beogradu u međuratnom periodu, 5) Medicinski fakultet u međuratnom periodu, 6) Beogradski univerzitet i medicinski fakultet za vreme okupcije i Drugog svetskog rata, 7) Univerzitet u Beogradu u posleratnom periodu, 8) Medicinski fakultet u posleratnom periodu, 9) Beogradski univerzitet u periodu socijalizma i samoupravljanja, 10) Medicinski fakultet u periodu socijalizma i samoupravljanja, 11) Univerzitet u Beogradu posle devedesetih, 12) Medicinski fakultet posle devedesetih, 13) Vojna bolnica, Medicinski fakultet i Vojnomedicinska akademija, i 14) Zakoni, uredbe, statuti i

pravilnici koji se odnose na Veliku školu, Univerzitet u Beogradu i Medicinski fakultet u Beogradu od 1863. do 2009/10. Posle toga, dat je prikaz literature sa preko 260 navoda na osnovu kojih je ispisana ova „Hronika“.

Posebnost ove knjige je i spisak diplomiranih lekara Medicinskog fakulteta u Beogradu u periodu 1926–2010. godina, sa ukupno 36 058 imena, što, samo po sebi, dovoljno govori o značaju Medicinskog fakulteta u Beogradu u stvaranju visokoobrazovanog medicinskog kadra bivše i sadašnje države (15. poglavlje „Hronike“). Na kraju, dat je Registar imena koja se pojavljuju u knjizi sa navedenim stranicama na kojima se ista pojavljuju, što olakšava snalaženje u tekstu.

Kao što se iz naslova 13. poglavlja „Hronike“ može zaključiti, u njemu je dat osvrt na razvoj vojnog saniteta i doprinos vojnih lekara razvoju Medicinskog fakulteta i medicine, uopšte, na ovim prostorima. Deo ovog poglavlja odnosi se i na razvoj VMA, od osnivanja 1844. godine, pa sve do današnjih dana, kada je akreditovana Visoka škola integrisanih akademskih studija medicine VMA i uspostavljena saradnja sa drugim medicinskim fakultetima u Srbiji. Kao kuriozitet, navodim podatak da je u knjigu ušla i vest sa sajta VMA od 13.11.2010. godine o sastanku dekana svih medicinskih fakulteta u Srbiji koji je održan u VMA, kada je postignut dogovor o zajedničkim aktivnostima za unapređenje nastave, prakse naučnoistraživačkog rada i publicističke delatnosti, što govori o izuzetnom angažovanju autorke da, čak i poslednje vesti od značaja za razvoj medicine na ovim prostorima za period o kome je reč u knjizi, ugradi u „Hroniku Medicinskog fakulteta u Beogradu“.

Knjiga je napisana jasno, zanimljivim stilom, sa puno topline, tako da nikoga ne ostavlja ravnodušnim. Verujem da delim utisak svih koji su imali ovu knjigu u rukama da je njen autor, prof. dr Snežana Veljković, učinila „poduhvat od velikog značaja kako za srpsku medicinu, tako i za kulturu srpskog naroda u celini“, kako je u svojoj recenziji napisao naš uvaženi akademik, sadašnji predsednik Srpskog lekarskog društva, prof. dr Radoje Čolović.

Stoga, toplo preporučujem knjigu svim akademskim građanima, sadašnjim i budućim, posebno onima medicinskog usmerenja, jer će među njenim koricama naći deo i svog identiteta kojeg se neretko i nehotice odričemo, prelazeći olako preko tradicije i uspomena.

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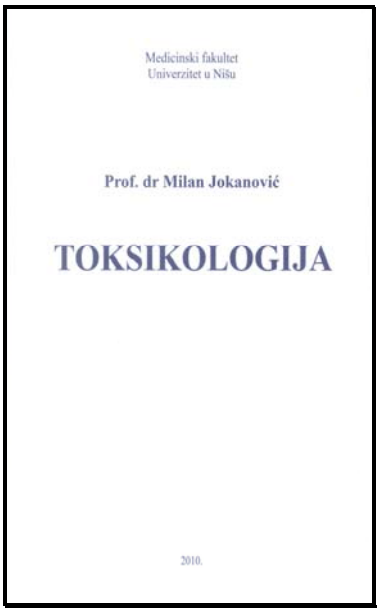
Institut za naučne informacije

P R I K A Z K N J I G E

Toksikologija



Autor: prof. dr Milan Jokanović
Izdavač: Beograd: Milan Jokanović; 2010.
Štampa: Princip Press – Portal, Beograd
Tiraž: 1 000

Krajem prošle godine izišla je iz štampe monografija „Toksikologija“, autora dr sc. pharm. Milana Jokanovića, člana Akademije nauka i umjetnosti Republike Srpske i redovnog profesora toksikologije na Medicinskom fakultetu Univerziteta u Nišu. U stvari, radi se o drugom, prerađenom i proširenom izdanju istoimene monografije objavljene 2001. godine. Kao i prethodno izdanje, i ova „Toksikologija“, po svom sadržaju i kompoziciji, predstavlja jedinstvenu monografsku publikaciju iz oblasti toksikologije na srpskom jeziku. U njoj su na pregledan i jasan način, logičkim redosledom, predstavljeni najznačajniji naučni i stručni aspekti toksikologije.

Monografija je podeljena na četiri glavna poglavlja: 1) *Opšta toksikologija*, 2) *Sistemska toksikologija*, 3) *Otrovi* i 4) *Primenjena toksikologija*.

U poglavlju *Opšta toksikologija*, kroz sedam potpoglavlja: 1) *Uvod u toksikologiju*, 2) *Mehanizam toksičnosti*, 3) *Resorpcija, distribucija i ekskrecija otrova i lekova*, 4) *Metabolizam otrova i lekova*, 5) *Osnovni toksikokinetički modeli*, 6) *Genetička toksikologij*a i 7) *Hemijska karcinogeneza*, dati su osnovni postulati toksikologije kao nauke i objašnjeni mehanizmi toksičnog oštećenja ćelija, kao i kinetičkih procesa i biotransformacije otrovnih supstancija i lekova u organizmu. Takođe, u ovom delu detaljnije su objašnjeni procesi mutageneze i karcinogeneze, kao specifični načini ispoljavanja toksičnosti pojedinih hemijskih jedinjenja, uključujući i lekove.

Poglavlje *Sistemska toksikologija* sadrži, takođe, sedam potpoglavlja u kojima su opisane najčešće manifestacije delovanja otrova na pojedine organske sisteme (nervni sistem, kardiovaskularni sistem, bubrege, jetru, reproduktivni sistem, kožu i respiratorni sistem), i objašnjeni mehanizmi ispoljavanja toksičnih efekata na glavne biohemijske procese koji stoje u osnovi funkcijske organizovanosti pojedinog sistema.

U poglavlju *Otrov*i, kroz šest potpoglavlja, detaljnije su obrađene pojedine grupe otrova od značaja za radnu i životnu sredinu čoveka. Osim uobičajenih toksičnih supstancija koje se standardno pominju u knjigama iz toksikologije (pesticidi, metali, organski rastvarači, gasovi, otrovi razvijeni za vojne i policijske potrebe), u ovom delu posebno su obrađeni i toksični efekti duvana i uličnih droga, što, samo po sebi, dovoljno govori o želji autora da na sveobuhvatan način predstavi najnovija saznanja iz ove oblasti.

Poslednje poglavlje u monografiji *Primenjena toksikologija* sadrži četiri potpoglavlja: 1) *Analitička toksikologija*, *Opšti principi kliničke toksikologije*, 3) *Antidoti* i 4) *Testovi toksičnosti*. Ovo poglavlje, kao što mu i sam naslov govori, posvećeno je aplikativnim aspektima toksikologije, odnosno

onim disciplinama u toksikologiji koje se bave analitikom toksičnih materija, dijagnostikom i lečenjem akutnih trovanja, kao i pretkliničkim ispitivanjem toksičnog potencijala lekovitih supstancija, ali i drugih jedinjenja. U ovom delu, uz navođenje najčešćih uzročnika trovanja, načina za njihovo određivanje u biološkim uzorcima i tumačenje dobijenih rezultata, dati su opisi kliničke slike najčešćih trovanja nekim lekovima i otrovima, kao i osnovne preporuke za lečenje akutno otrovanih osoba. Posebno su opisane glavne grupe antidota i njihov mehanizam dejstva. U potpoglavlju *Testovi toksičnosti* obrađeni su testovi za ispitivanje toksičnosti koji se izvode na eksperimentalnim životinjama u sklopu predkliničkih ispitivanja lekovitih supstancija namenjenih za upotrebu u humanoj i veterinarskoj medicini, kao i sredstava opšte namene, tako da čitalac može da stekne potpunu sliku o opsežnosti pretkliničkih toksikoloških ispitivanja ovih jedinjenja.

Posle svakog potpoglavlja navedena je literatura koju je autor koristio za pisanje istog. U najvećem broju slučajeva radi se o referencama iz poslednjih 10 godina, a nisu retkost ni reference iz 2010. godine, dakle, godine u kojoj je monografija izdata. Ovo dovoljno govori o želji autora da stavi na uvid stručnoj javnosti najnovije podatke iz oblasti o kojima je pisao.

Na kraju monografije dat je veoma bogat indeks pojmova i naziva koji se pominju u tekstu sa naznakom stranice na kojoj se nalaze, što znatno olakšava korišćenje knjige.

Uz već pomenutu originalnost, preglednost, sadržajnost, aktuelnost i jasnoću izraza kojom je napisana, treba napomenuti da je ovu monografiju pisao jedan od naših vodećih toksikologa srednje generacije, poznat i van granica Srbije, naučnik čiji su radovi iz oblasti, prvenstveno, eksperimentalne toksikologije objavljivani i citirani u najprestižnijim međunarodnim časopisima, što je još jedna garancija njenog kvaliteta.

Monografija je, u prvom redu, namenjena studentima farmacije i studentima doktorskih studija iz toksikologije. Međutim, ona se može preporučiti kao korisno štivo i različitim profilima stručnjaka (lekarima, farmaceutima, biohemičarima, biolozima, fizikohemičarima, tehnolozima) koji se u svom poslu, na bilo koji način, susreću sa otrovima, odnosno toksičnim supstancijma.

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Poziv na reklamiranje u 2011. godini

U prilici smo da vam ponudimo mogućnost oglašavanja i reklamiranja proizvoda i usluga u časopisu „**Vojnosanitetski pregled**“ (VSP). To je sigurno najbolji vid i najzastupljeniji način upoznavanja eventualnih korisnika sa vašim uslugama i proizvodima.

Časopis „**Vojnosanitetski pregled**“, zvanični organ lekara i farmaceuta Vojske Srbije, naučno-stručnog je karaktera i objavljuje radove iz svih oblasti medicine, stomatologije i farmacije. Radove ravnopravno objavljuju stručnjaci iz vojnih i civilnih ustanova i iz inostranstva. Štampa se na srpskom i engleskom jeziku. Časopis izlazi neprekidno od 1944. godine do sada. Jedini je časopis u zemlji koji izlazi mesečno (12 brojeva), na oko 100 strana A4 formata, a povremeno se objavljuju i tematski dodaci (suplementi). Putem razmene ili pretplate VSP se šalje u 23 zemlje sveta. Radove objavljene u VSP-u indeksiraju: *Science Citation Index Expanded (SCIE)*, *Journal Citation Reports/Science Edition*, *Index Medicus (Medline)*, *Excerpta Medica (EMBASE), EBSCO* (preko ove baze VSP je *on line* dostupan od 2002. godine u *pdf* formatu) i *Biomedicina Serbica*.

Cene reklama i oglasa u časopisu „Vojnosanitetski pregled“ u 2009. godini su:

1.	Oglas u crno-beloj tehnici A4 formata za jedan broj	20 000,00 dinara
2.	Oglas u c/b tehnici A4 formata za celu godinu (11-12 brojeva)	200 000,00 dinara
3.	Oglas u boji A4 formata za jedan broj	35 000,00 dinara
4.	Oglas u boji A4 formata za celu godinu (11-12 brojeva)	330 000,00 dinara
5.	Oglas u boji na koricama K3 za jedan broj	50 000,00 dinara
6.	Oglas u boji na koricama K3 za celu godinu (11-12 brojeva)	455 000,00 dinara
7.	Oglas u boji na koricama K2 i K4 za jedan broj	55 000,00 dinara
8.	Oglas u boji na koricama K2 i K4 za celu godinu (11-12 brojeva)	530 000,00 dinara

Za sva objašnjenja, uputstva i ponude zainteresovani kontaktiraju redakciju časopisa „Vojnosanitetski pregled“. Sredstva se uplaćuju na žiro račun kod Uprave javnih plaćanja u Beogradu broj: 840-941621-02 **VMA (za Vojnosanitetski pregled ili za VSP)**, **PIB 102116082**. Uplatnicu (dokaz o uplati) dostaviti lično ili poštom (pismom, faksom, *e-mail*-om) na adresu: Vojnosanitetski pregled, Crnotravska 17, 11000 Beograd; tel/faks: 011 2669 689, e-mail: vsp@vma.mod.gov.rs ili vmavsp@hotmail.com

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

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

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

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

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Priprema rada

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

1. ***Naslovna strana***

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

b) Ispisuju se puna imena i prezimena autora.

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

2. ***Apstrakt i ključne reči***

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

3. ***Tekst članka***

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

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

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

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

Literatura

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

Primeri oblika referenci:

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

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

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

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

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

Tabele

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

Ilustracije

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

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

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

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

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

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

Preparation of manuscript

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

1. ***Title page***

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

b) full name of each author;

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

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

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

3. ***Text***

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

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

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

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

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

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Examples of references:

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

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

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

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

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

Tables

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

Illustrations

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

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

Abbreviations and symbols

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

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