ЗВАНИЧАН ЧАСОПИС СРПСКОГ ЛЕКАРСКОГ ДРУШТВА

СРПСКИ АРХИВ

ЗА ЦЕЛОКУПНО ЛЕКАРСТВО Осн.1872

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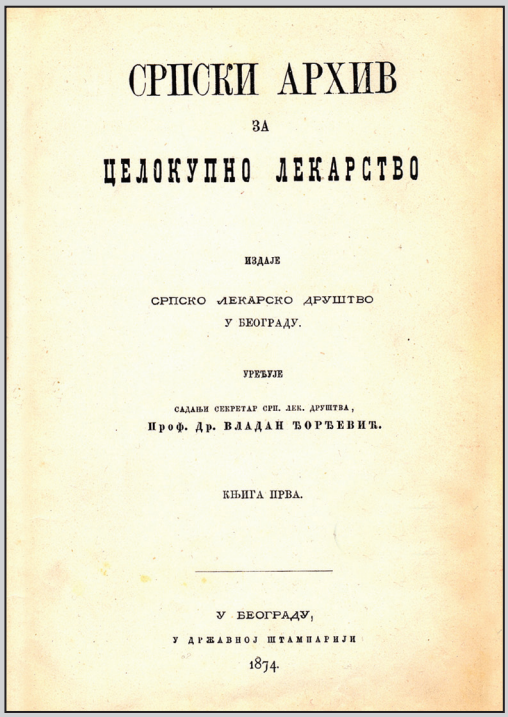

СРПСКИ АРХИВ

ЗА

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ИЗДАЈЕ

СРПСКО ЛЕКАРСКО ДРУШТВО

У БЕОГРАДУ.

УРЕЂУЈЕ

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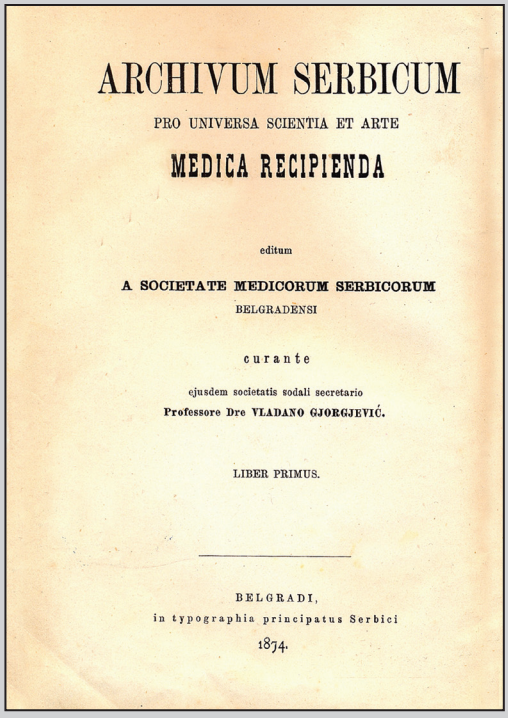
КЊИГА ПРВА.

У БЕОГРАДУ,

У ДРЖАВНОЈ ШТАМПАРИЈИ

1874.

Прва страна првог броја часописа на српском језику



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The title page of the first journal volume in Latin

Корице/Cover
Председник Српског лекарског друштва
Младен Јанковић (1831–1895)
Часопис се уређивао на састанцима Друштва (1879–1894)

President of the Serbian Medical Society
Mladen Janković (1831–1895)
The editorial process of the journal used to take place at the Society meetings (1879–1894)

Српски архив за целокупно лекарство је часопис Српског лекарског друштва основан 1872. године, у којем се објављују радови чланова Српског лекарског друштва, претплатника часописа и чланова других друштава медицинских и сродних струка. Часопис објављује: оригиналне радове, саопштења, приказе болесника, прегледе литературе, актуелне теме, радове из историје медицине, радове за праксу, радове који се односе на језик медицине, радове из медицинске етике (клиничка етика, етика публиковања, регулаторни стандарди у медицини), извештаје с конгреса и стручних састанака, стручне вести, приказе књига и дописе за рубрике Сећање, *In memoriam* и *Promemoria,* као и коментаре и писма Уредништву.

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УВОДНИК • EDITORIAL

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УВОДНИК / EDITORIAL

Српске мајке из стране службе

Миле Игњатовић
Академија медицинских наука Српског лекарског друштва

Велики рат је много проучаван протеклих 100 година. Међутим, утисак је да ниједна тема није толико запостављена као улога жена у том рату. За Србију је то од посебног значаја, јер су жене имале суштински битну улогу у спасавању српске нације, не само од већег страдања већ и од биолошког нестајања. Улога српских жена је сигурно највећа, али посебно је значајна улога свих оних жена из иностранства које су дошле да помогну у спасавању српске нације. Њима морамо бити вечно захвални и не смемо их никада заборавити. Управо о њима у Србији и изван Србије говоре радови Славице Поповић-Филиповић [1–4].

Ниједан рат није нормалан, али Први светски рат је од почетка за Србију био катастрофалан. Непријатељ је био толико острашћен да је Србија морала нестати. Није било довољно Србију војнички поразити, чак згазити. С друге стране, Србија је ове ратове дочекала потпуно исцрпљена после тек завршених балканских ратова. Недостајало је свега. Санитетска средства су потрошена, нова нису набављена. Највећи недостатак је био у лекарима и осталом санитетском особљу. На срећу, у Европи почетком XX века били су изузетно развијени човекољубље и милосрђе, жеља и спремност да се помогне. Тако су, као и у балканским ратовима, стране санитетске мисије дошле Србији у помоћ.

У Првом светском рату, у периоду 1914–1915. године, од страних санитетских мисија биле су четири руске мисије са 16 лекара, три грчке мисије, 14 енглеских мисија и три америчке мисије, које су имале (без руске и француске) 82 лекара и 429 болничара и другог особља [5]. Ове мисије су отварале нове болнице или ређе користиле већ постојеће са помоћним људством. После епидемије, према речима пук. др Генчића, начелника санитета у то време, „у земљи је било 90 разних болница, са преко 100 000 болесничких постеља, а само на војишту радило је, поред наших лекара, још 200 страних лекара и око 500 школованих сестара ... ми смо крајем лета 1915. били у санитетском погледу за рат спремни боље но икада пре тога". У току рата отворено је 58 привремених или резервних болница са више од 50 000 кревета. Према др Недоку, цела Србија се претворила у сиромашну војну болницу [6].

Посебно место заузимају Болнице шкотских жена (*The Scottish Women's Hospitals for Foreign Service*) (слике 1 и 2), по свом значају, обиму, жртвовању, улози за време и после рата [7]. Наше мајке из иностранства нису нас заборавиле ни после рата. Пружале су помоћ и подршку још много година после рата. Поред материјалне и организационе помоћи, оне су преносиле истину о Србима, који су били сатанизовани као никада раније. Од више од 600 Британки које су биле у Србији у току Првог светског рата, посебно место заузима др Елси Инглис, као оснивач и покретач ових болница. Сер Винстон Черчил (1874–1965), у то време политичар, рекао је 1918. године да ће „слава др Елси Инглис светлети у историји". Амбасада Велике Британије у Београду названа је њеним именом 15. марта 2015, а Денис Киф (*Denis Keefe*), британски амбасадор у Београду, говор је завршио са: „Елси Инглис је била једна од првих високообразованих жена у Шкотској и пионирка медицине. Енергично се борила против предрасуда, за друштвену и политичку еманципацију жена Британије. Била је неуморна волонтерка, храбра организаторка болница жена Шкотске и посвећена хуманитарка. Елси Инглис нажалост није дочекала крај рата и дефинитивни тријумф неких својих идеја, али је направила огроман утицај на друштвена кретања у нашој земљи. У Шкотској је постала лекарка, а у Србији светица" [8].

Заборавност и немарност Срба су познате, али Срби не заборављају своје мајке и светице. Сећају се и то обележавају на најбоље начине, почев од 1918. године, када су јој подигнути споменици у Србији, а Иван Мештровић (1883–1962) урадио њену бисту у бронзи по наруџби краља Александра (Слика 3), преко бројних спомен-плоча

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Слика 1. Типична Болница шкотских жена
Figure 1. A typical Scottish Women's Hospital

Слика 2. Снимак из ваздуха Британске опште болнице у Солуну [7]
Figure 2. Aerial view of No. 64 British General Hospital in Salonica [7]

Слика 3. Иван Мештровић: Бронзана биста Елси Инглис, 1918 (Национална галерија Шкотске)
Figure 3. Ivan Meštrović: Bronze bust of Elsie Inglis, 1918 (National Galleries of Scotland)

Слика 4. Британске хероине Првог светског рата у Србији
Figure 4. British heroines of the First World War in Serbia

посвећених њој и њеном делу, све до изванредног издања Поште Србије (Слика 4) и ових радова Славице Поповић-Филиповић. После 100 година било би неумесно подизање било каквих споменика. Ово су прави начини да се освежи сећање и прикаже рад свих тих жена из иностранства које су дошле и жртвовале се за добробит српског народа. Као и све мајке, оне су нам биле већи пријатељи од нас самих.

Она се толико сродила са Србима да је почела делити њихову злу судбину и после своје смрти. Наиме, Меморијални фонд др Елси Инглис из Лондона (формиран после њене смрти у Лондону) доделио је 1927. године значајна средства Физиолошком институту у Београду за научноистраживачки рад, када су формирани виваријум, библиотека и једна лабораторија, која је названа њеним именом. Тим поводом откривена је и спомен-плоча октобра 1929. на којој је писало: *In memoriam* / *Elsie Inglis* / *M.D.* / *amicae Serborum Certissimae* / *quae currans milites Serbos* / *malates et vulmeratos* / *obiit* 26. 11. 1917 (У спомен др Елси Инглис, пријатељици Срба, одлучној да лечи болесне и рањене српске војнике, преминуле 26. 11. 1917) [9]. Зграда Института и спомен-плоча су нестале у бомбардовању од истог непријатеља 6. априла 1941. Слична спомен-плоча је постављена 1952. године.

Ако је тачно оно што пише на крају Меморијала Елси Инглис у Катедрали Св. Егидија (*St. Giles Cathedral*) у Единбургу – *Mors janva vitae (Death is the door of life*), онда је Елси Инглис својим деловањем и пожртвовањем обезбедила себи бесмртност.

Људи умиру када нестане сећање на њих. Код Срба ће Елси Инглис увек бити жива.

ЛИТЕРАТУРА

1. Popović-Filipović S. Elzi Inglis (1864–1917) i Bolnice škotskih žena u Srbiji u Velikom ratu. 1. deo. Srp Arh Celok Lek 2018; OnLine-First: September 5, 2017; (00):167–167. [DOI: https://doi.org/10.2298/SARH170704167P]
2. Popović-Filipović S. Elzi Inglis (1864–1917) i Bolnice škotskih žena u Srbiji u Velikom ratu. 2. deo. Srp Arh Celok Lek 2018; OnLine-First: September 5, 2017; (00):168–168. [DOI: https://doi.org/10.2298/SARH170704168P]
3. Popović-Filipović S. Srbi na Korzici u Velikom ratu. 1. deo. Srp Arh Celok Lek 2018; OnLine-First: September 8, 2017; (00):169–169. [DOI: https://doi.org/10.2298/SARH170704169P]
4. Popović-Filipović S. Srbi na Korzici u Velikom ratu. 2. deo. Srp Arh Celok Lek 2018; OnLine-First: September 8, 2017; (00): 170–170. [DOI: https://doi.org/10.2298/SARH170704170P]
5. Popović-Filipović S. Iz postojbine javora. Kanadsko-britanska medicinska i humanitarna pomoć Srbiji u Prvom svetskom ratu. Beograd: Srpsko lekarsko društvo; 2013.
6. Nedok A. Srpski vojni sanitet na početku rata i u velikim bitkama 1914. godine. U: Nedok A, Popović B. Srpski vojni sanitet 1914–1915. godine. Beograd: Uprava za vojno zdravstvo Ministarstva odbrane Republike Srbije i Akademija medicinskih nauka Srpskog lekarskog društva; 2010. p. 28–76.
7. British Army Medical Services. Aerial view No 64 British General Hospital Salonica (James Cotter collection, AMS Archives). (Accessed February 25, 2018) Available from: http://maltaramc.com/imghosps/map64genhospsal.jpg
8. Britanska rezidencija u Beogradu imenovana po dr Elsi Inglis. (Accessed February 25, 2018) Available from: https://www.gov.uk/world/organisations/british-embassy-belgrade.sr
9. Đurić DM. Dr. Elsie Maud Inglis (1864–1917). (Accessed July 2017). Available at: http://www.mfub.bg.ac.rs/global/pdf/instituti/medicinska_fiziologija/istorijat/ODRELSIEINGLISIISTOIMENOMFONDU.pdf

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The influence of intravitreally applied triamcinolone acetonide on vitreal hemorrhage resorption and visual acuity in patients with proliferative diabetic retinopathy

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SUMMARY

Introduction/Objective Vitreal hemorrhage is one of the possible complications of diabetic retinopathy, followed by intensive decrease of visual acuity. Corticosteroids are commonly used in treatment of different retinal diseases, due to their anti-inflammatory and anti-angiogenetic effect. Triamcinolone acetonide applied intravitreally remains in the eye for several months, releases its crystals, and decreases the density of vitreal hemorrhage.

The main goal of this study is to evaluate the efficacy of 20 mg intravitreal triamcinolone acetonide for the management of long-lasting vitreal hemorrhage, occurred as a complication of proliferative diabetic retinopathy in non-vitrectomized eyes.

Methods In a prospective study performed between January 1, 2015 and January 1, 2016, 24 patients with vitreal hemorrhage who received intravitreal triamcinolone acetonide were compared to 21 patients from the control group. The control group consisted of patients with proliferative diabetic retinopathy and similar degree of vitreal hemorrhage. All the patients underwent an ophthalmological examination at the beginning of the study, seven days, one, three, six, nine, and 12 months after intravitreal administration of 20 mg of triamcinolone acetonide. In addition to vitreal hemorrhage and visual acuity, intraocular pressure and cataract development were also analyzed.

Results Statistically significant difference in the density of vitreal hemorrhage and visual acuity was recorded during the first and the third month after administering triamcinolone. Twenty-nine percent of the patients had a temporary rise in intraocular pressure after intravitreal triamcinolone application, and 4.1% of the patients finished the study with a developed cataract.

Conclusion Intravitreally applied triamcinolone acetonide has a moderate and temporary influence on the velocity of vitreal hemorrhage reabsorption, probably by the mechanism of sedimentation of triamcinolone's crystals with blood elements. It can be a useful treatment option when vitrectomy in not possible.

Keywords: triamcinolone acetonide; vitreal hemorrhage; intravitreal injection; intraocular pressure

INTRODUCTION

Vitreal hemorrhage (VH) represents a significant complication of proliferative diabetic retinopathy which causes serious decrease of visual acuity [1]. There are many factors that distinguish VH from other hemorrhages: long-term survival of intact red blood cells, instant clot formation, slow fibrin lysis, inactivated early polymorphonuclear cellular response. It is known that VH has clearance of only 1% per day [2]. The accepted method for treatment of vitreous hemorrhage is pars plana vitrectomy [1].

Due to their anti-inflammatory and anti-angiogenetic influences, corticosteroids are commonly used in treatment of different retinal disorders. As it is reported by many studies, triamcinolone acetonide applied intravitreally (IVTA) has shown an effect in the treatment of macular edema or proliferative diabetic retinopathy and proliferative vitreoretinopathy [3, 4, 5]. Serving as an adjuvant therapy, IVTA acts like a depot, releasing crystals into the vitreal cavity [5]. The effect of triamcinolone acetonide is the reduction of intra- and postoperative inflammation, vascular permeability and re-proliferation [6]. Triamcinolone acetonide can also be effective for rapid clearing of recurrent post-vitrectomy diabetic VH [6].

The study was conducted with the aim to evaluate the efficacy of 20 mg IVTA in the adjuvant treating of long-lasting VH, in patients with proliferative diabetic retinopathy in non-vitrectomized eyes. We measured the density of VH and recorded the influence that IVTA had on the visual acuity, cataract development, and the increase of intraocular pressure (IOP).

METHODS

The prospective, comparative study included two groups of patients. The first group (IVTA

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group) contained 24 patients with long-lasting VH of various density which occurred as a complication of proliferative diabetic retinopathy. They were recruited for intravitreal application of triamcinolone acetonide. The second group had 21 participants with proliferative diabetic retinopathy and with a similar degree of VH (control group). Sex and age were matched between the groups. The study was carried out between January 1, 2015 and January 1, 2016 at the Ophthalmology Clinic of the Kragujevac Clinical Centre, Serbia. With the approval of the institutional ethics committee and according to the tenets of the Declaration of Helsinki, all enrolled patients gave their written consent at the beginning of the investigation. All the patients from the first group were acquainted that this was an off-label use of triamcinolone acetonide and signed an informed consent.

The patients had passed a complete ophthalmological examination: visual acuity, intraocular pressure measurement, slit lamp, fundus examination, and ocular ultrasonography. These examinations were performed before the IVTA application, on visits after seven days, one month, three months, six, nine, and 12 months.

The degree of intravitreal hemorrhage was scaled according to the diabetic retinopathy vitrectomy study grading system (Table 1) [7]. In this study, we examined patients who received IVTA, by comparing the IVTA effect on VH resorption and visual acuity with the control group. The IOP rise and cataract development were also follow-up parameters as possible complications after ocular steroid administration [8].

Table 1. Diabetic retinopathy vitrectomy study grading system

Grade 0	No vitreous hemorrhage
Grade I	Mild vitreous hemorrhage with visible fundus details
Grade II	Moderate vitreous hemorrhage with no visible fundus details but with an orange fundus reflex
Grade III	Severe vitreous hemorrhage with no retinal details and no orange fundus reflex

Exclusion criteria for the patients were preexisting glaucoma, uveitis, myopia, ocular trauma, earlier intraocular surgery, cataract, and retinal detachment confirmed by ocular ultrasonography or fundoscopic examination. Patients with previous exposure to the topical, intraocular, or systemic steroids were also excluded. If any patients had developed some other complication of diabetic retinopathy during the period of the study, such as diabetic macular edema, they would have been excluded as well.

The intravitreal injection of 20 mg triamcinolone acetonide was given to all the patients in the operation theatre under sterile conditions. As we mentioned earlier, patients agreed to receive an off-label triamcinolone acetonide and signed an informed consent. Multiple sedimentation was performed to obtain a wanted dose of 20 mg of triamcinolone acetonide. The crystalline cortisone was adopted after aspirating a 1 mm bottle which contained about 40 mg of triamcinolone acetonide (Kenalog®, Bristol-Myers Squibb, New York City, NY, USA) into syringe of 1 mm. After leaving the syringe in the vertical position for 20 minutes, the first sedimentation was done. The upper, unsedimented part, was gently ejected trough the syringe. Sedimented part, about 0.2 ml, was then mixed with Ringer's solution until the syringe was filled again. After five minutes in vertical position, unsedimented part, about 0.8 ml, was again eliminated from the syringe. This procedure was repeated once more. After this triple sedimentation, there was about 0.2 ml left in the syringe, with about 20 mg triamcinolone acetonide.

Periocular and ocular area were sterilized using 5% and 10% povidone iodine. Triamcinolone acetonide was injected into the central parts of the vitreal cavity. Under the topical anesthesia, using a 27 gauge needle, 3.5 mm from the limbus, triamcinolone acetonide was implemented. When the procedure was done, the patients remained in the upright position for the next two hours. Topical ciprofloxacin (Floxal®, DR. Gerhard Mann, Chem.-Pharm. Fabrik GmbH, Berlin, Germany) was prescribed five times per day, for the next seven days.

Statistical methods

IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA) was used for all calculations in the study. We used Freidman's test in testing the evolution of VH through the period of 12 months. For comparison of the variables, such as the IOP, visual acuity, or cataract development, Student's t-test was used. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

Examined patients from the first group had a mean age of 56.24 ± 5.5 years, while that of the control group members was 54.15 ± 4.8 years. No statistical significance was found among the patients' age ($p = 0.43$). In both groups female to male ratio was approximately equal.

Every patient passed a complete ophthalmological examination on every visit during the follow-up period (Figures 1, 2, and 3). According to the density of VH, examined patients were divided into four grades and statistically analyzed. Visual acuity was measured for every grade separately. Mean visual acuity in grade 0 was 0.9 ± 0.1, in grade I it was 0.6 ± 0.17. Grades II and III were characterized by an intensive decrease of visual acuity, 0.3 ± 0.15 and 0.03 ± 0.01, respectively.

At the beginning of the research, in the IVTA group there were 0 patients with grade 0, seven with grade I, 10 with grade II, and seven patients with grade III of VH. The control group also had 0 patients with the grade 0, but six patients with grade I, nine patients with grade II, and six patients with the grade III. No statistical significance ($p = 0.99$) was found between the groups. At that time, none of the patients had the IOP over 21 mmHg or any sings of cataract development. Mean visual acuity in the first group was 0.30 ± 0.05, while in the second group it was 0.31 ± 0.03, without any statistically significant difference between the groups ($p = 0.68$).

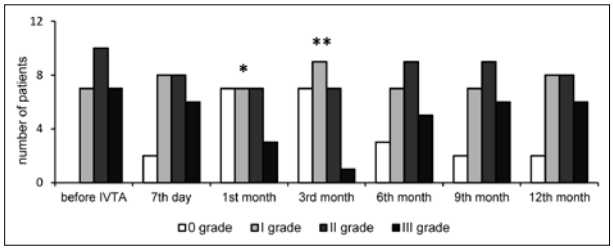

Figure 1. Grading the patients who received triamcinolone acetonide applied intravitreally (IVTA) during a period of one year

*p < 0.05
**p < 0.001

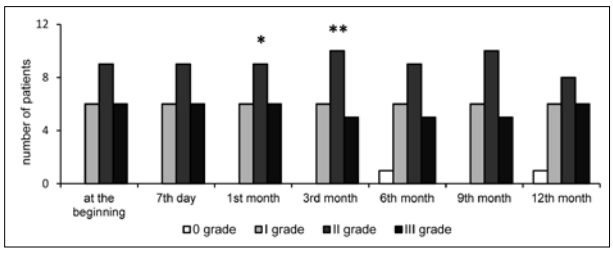

Figure 2. Grading the patients from the control group during a period of one year

*p < 0.05
**p < 0.001

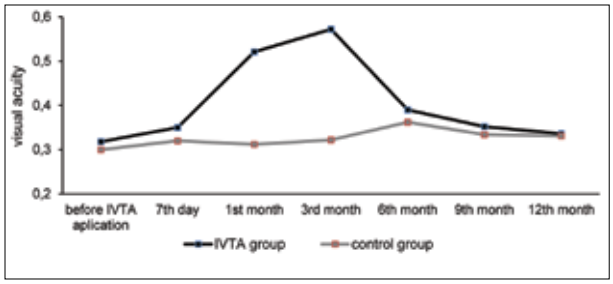

Figure 3. Comparison of visual acuity in patients who received triamcinolone acetonide and the patients from the control group

IVTA – triamcinolone acetonide applied intravitreally

Seven days after the IVTA application, no statistically significant differences were recorded in the density of VH ($p = 0.54$) and the visual acuity ($p = 0.08$).

At the third measurement, one month after the IVTA procedure, we detected a statistically significant difference for the first time. Twenty-one patients divided equally among the first three grades and only one patient with severe VH were detected in the IVTA group. Compared with the control group, where the patients were still in the same schedule as they were at the beginning of the study (grade 0 – zero, grade I– six, grade II – nine, grade III – six) statistical significance was noticed ($p = 0.04$). This was followed by an improvement of visual acuity to 0.51 ± 0.08 in the first group, while it remained the same in the second group, 0.34 ± 0.04. Again, we recorded statistically significant difference, $p = 0.02$.

The statistically significant difference among the groups was captured three months after triamcinolone acetonide application, $p < 0.05$; $p < 0.001$. Both VH and visual acuity were much better in those who received triamcinolone acetonide then in patients from the control group ($p = 0.01$; $p = 0.001$).

The last three measurements, six, nine, and 12 months after the administration of IVTA, passed without statistically significant differences ($p > 0.05$). VH and visual acuity were quite similar in both groups (Figures 1 and 3).

During this one-year study, the IOP measurements and detailed ophthalmological examinations were constantly performed. Three and six months after receiving triamcinolone acetonide, seven patients (29.1%) had a temporary IOP rise of over 5 mmHg in relation to the IOP values they had before the triamcinolone acetonide injection. They were efficiently treated by appropriate antiglaucomatous medications – dorzolamide/timolol eye drops (Cosopt®, Merck Sharp & Dohme, Kenilworth, NJ, USA) two times a day. One patient from the first group (4.1%) ended the study with the diagnosis of cataract. No endophthalmitis was recorded among those who underwent intravitreal application of triamcinolone acetonide.

DISCUSSION

The collagen fibrils and hyaluronic acid, contained inside the vitreal gel, are responsible for the integrity of the vitreal matrix. Fibrils are arranged as a fine network, with the glycosaminoglycans filling the gaps between them. When hemorrhage in the vitreal cavity occurs, the polymorphonuclear neutrophils and macrophages get activated to phagocytize erythrocytes [9]. Intact erythrocytes leave the eye through the trabecular meshwork. Related to the slow vitreal lyses of fibrin, because of low tissue fibrinolytic activity, elimination of the vitreal fibrin is also very slow [10]. Despite the fact that erythrocytes leave the eye through the trabecular meshwork, intact blood cells can be histologically detected in vitreal cavity many months after the incident. These erythrocytes provoke realizing of the macrophages' lysosomal enzymes, which decompose them by the process of the hemolysis. The velocity of VH reabsorption is approximately 1% per day [2]. The quantity of VH as well as its occurrence frequency and the level of communication of the anterior and posterior segment of the eye determine the clearance rate [11]. Vitrectomy has an important role in the process of the VH clearing. Based on the reachable data, cleared vitreal cavity, after vitrectomy, expedites reabsorption of the remaining erythrocytes [12].

Corticosteroids can be useful for the treatment of retinal vascular and inflammation disorders by inhibition of different genes expression responsible for the synthesis of different mediators of inflammation and angiogenesis [13]. Intravitreally applied triamcinolone acetonide due to its low water solubility and its sustained crystal releasing, has prolonged action duration [12].

The real mechanism of triamcinolone acetonide intravitreally applied on hemorrhage reabsorption is still not clear. Triamcinolone acetonide crystals deposit along the retinal vasculature, making them look like frosted angiitis [14]. These phenomena have certain effect on the VH

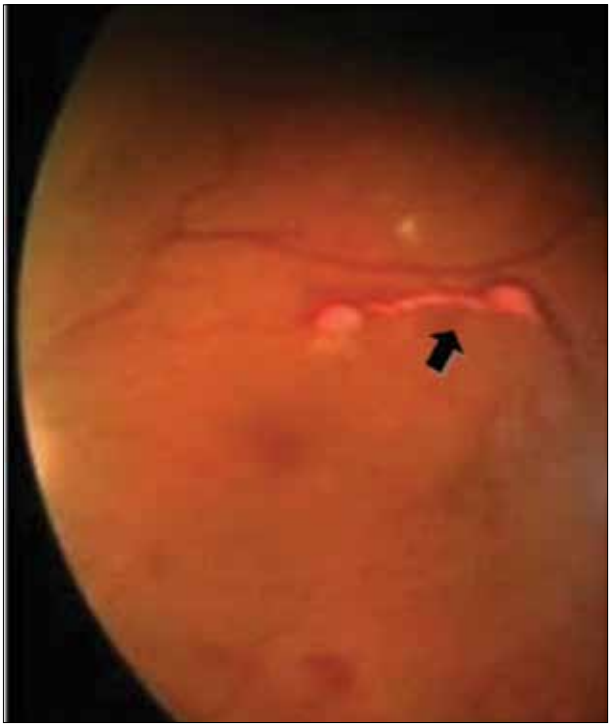

Figure 1. Crystals of triamcinolone acetonide spotted one month after the intravitreal application of 20 mg of triamcinolone acetonide

reabsorption. Despite the fact that posterior vitreous detachment can often be detected in these eyes, remnants of it persist along the retinal vasculature elements, and prolonged its action on the vascular elements [5]. By the mechanism of sedimentation of triamcinolone crystals with retinal blood elements and vascular stabilization, triamcinolone acetonide has its role in the cleaning of VH in patients with proliferative diabetic retinopathy [15]. Using detailed ophthalmoscopic examination, we managed to identify these crystals, stationed along the retinal vasculatures, one month after the application of intravitreal triamcinolone acetonide (Figure 4). According to our results, the crystals remained in the vitreal cavity for three months, which is in correlation with the improvement of the density of VH, and consequently with better visual acuity. After this period, the crystals of triamcinolone acetonide were not noticed in the vitreal cavity, and the results were quite similar to the control group. Temporary rise of the IOP, which was recorded in some patients three to six months after triamcinolone acetonide injection, indicated that triamcinolone was still present in the eye, even it wasn't identified during the ophthalmological examination. That IOP rise was efficiently treated by locally applied medical therapy – antiglaucomatous eye drops, without unwanted influence on the optic nerve, which was confirmed at the next control examination, three months later. Some studies reported much longer duration after the application of 20 mg of triamcinolone intravitreally [16, 17]. Non-existence of the unique opinion among the scientists, of the mechanism and duration of IVTA provides new possibilities for future investigations.

CONCLUSION

Intravitreal application of the triamcinolone acetonide has a temporary and limited effect in the treatment of VH, followed by the transitory improvement of the visual acuity. Triamcinolone acetonide can serve as the alternative therapy for the diabetic patients with massive VH, in those cases where vitrectomy is not recommended. Existence of ocular comorbidities or contraindications for general anesthesia, such as abnormally high blood pressure, cardiopulmonary insufficiency, extreme obesity, senility, gives space for the use of intravitreal triamcinolone acetonide. By this treatment we improve the patients' quality of life for a while. Also, the intravitreal application can be repeated after a few months. Following the rules of sepsis and antisepsis, as well as the guide for secondary glaucoma treatment, complications of this intervention can be reduced.

REFERENCES

1. Spraul CW, Grossniklaus HE. Vitreous hemorrhage. Surv Ophthalmol.1997; 42(1):32–9.
2. Aiello LP, Brucker AJ, Chang S, Cunningham Jr ET, D Amico DJ, Flynn Jr HW, et al. Evolving guidelines for intravitreous injections. Retina. 2004; 24:S3–19.
3. Kriechbaum K, Prager S, Mylonas G, Scholda C, Rainer G, Funk M, et al. Intravitreal bevacizumab (Avastin) versus triamcinolone (Volon A) for treatment of diabetic macular edema: one-year results. Eye (Lond). 2014; 28(1):9–15.
4. Jonas JB, Hayler JK, Panda-Jonas S. Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative vitreoretinopathy. Br J Ophthalmol. 2000; 84(9):1064–7.
5. Spaide RF, Sorenson J, Maranan L. Photodynamic therapy with verteporfin combined with intravitreal injection of triamcinolone acetonide for choroidal neovascularization. Ophthalmology. 2005; 112(2):301–4.
6. Lee SY, Yoon YH, Lee HG, Chung H, Kim JG. Intravitreal triamcinolone acetonide in eyes with recurrent postvitrectomy diabetic vitreous hemorrhage. Am J Ophthalmol. 2006; 142(3):501–3.
7. Diabetic Retinopathy Vitrectomy Study (DRVS). Two-year course of visual acuity in severe proliferative diabetic retinopathy with conventional management. Report No 1. Ophthalmology. 1985; 92(4):492–502.
8. Nath Razeghinejad MR, Katz LJ. Steroid-induced iatrogenic glaucoma. Ophthalmic Res. 2012; 47(2):66–80.
9. Swann DA. On the integrity of vitreous structure, in Freeman HM, Hirose T, Schepens CL (eds): Vitreous Surgery and Advances in Fundus Diagnosis and Treatment. New York: Appleton-Century Crofts; 1977. p. 3
10. Cuevas P, Outeiriño LA, Azanza C, Angulo J, Giménez-Gallego G. Dramatic resolution of vitreous hemorrhage after an intravitreal injection of dobesilate. Mil Med Res. 2015; 2:23.
11. Agarwal D, Gelman R, Prospero Ponce C, Stevenson W, Christoforidis JB. The vitreomacular interface in diabetic retinopathy. J Ophthalmol. 2015; 2015:392983.
12. Steel DH, Connor A, Habib MS, Owen R. Entry site treatment to prevent late recurrent postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy. Br J Ophthalmol. 2010; 94(9):1219–25.
13. Jonas JB, Kreissig I, Degenring RF. Neovascular glaucoma treated by intravitreal triamcinolone acetonide. Acta Ophthalmol Scand. 2003; 81(5):540–1.
14. Silva PS, Singh RJ, Bakri SJ, Lising RS, Santiago DE, Harvey S. Vitreous concentration of triamcinolone acetonide after a

single transseptal depot injection. Ocular Immunology and inflammation. 2009; 17(3):216–20.
15. Vedantham V, Kolluru C, Ramasamy K. Persistent depot of triamcinolone acetonide after a single intravitreal injection. Indian J Ophthalmol. 2005; 53(1):65–6.
16. Wei Y, Wang HZ, Chen FH, Wang RS, Yang XG. Triamcinolone intravitreal injection and intraocular pressure in macular edema associated with retinal vein occlusion. Eye Sci. 2012; 27(4):182–7.
17. Jonas JB. Intraocular availability of triamcinolone acetonide after intravitreal injection. Am J Ophthalmol. 2004; 137(3):560–2.

Утицај интравитреално апликованог триамцинолон-ацетонида на ресорпцију витреалне хеморагије и видну оштрину код болесника са пролиферативном дијабетесном ретинопатијом

Ненад Петровић[1,2], Душан Тодоровић[1], Сунчица Срећковић[1,2], Татјана Шаренац-Вуловић[1,2], Мирјана Јанићијевић-Петровић[1,2], Светлана Пауновић[2], Катарина Јанићијевић[3], Светлана Јовановић[1,2]

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САЖЕТАК

Увод/Циљ Витреална хеморагија (ВХ) једна је од могућих компликација дијабетесне ретинопатије, која је праћена интензивним падом видне оштрине. Кортикостероиди се учестало користе у лечењу различитих ретиналних обољења, захваљујући свом антиинфламаторном и антиангиогенетском ефекту. Триамцинолон-ацетонид апликован интравитреално задржава се у оку неколико месеци, отпушта своје кристале и смањује густину ВХ.

Циљ ове студије је да процени ефикасност 20 милиграма интравитреално апликованог триамцинолон-ацетонида у третману дуготрајне ВХ као компликације пролиферативне дијабетесне ретинопатије (ПДР) код невитректомисаних очију.

Методе У проспективној студији, у 2015. години, упоређена су 24 болесника са ВХ и интравитреално апликованим триамцинолон-ацетонидом са 21 болесником из контролне групе (болесници са ПДР и сличним степеном ВХ). Сви болесници су имали комплетан офталмолошки преглед на почетку студије, 7 дана, 1, 3, 6, 9 и 12 месеци после интравитреалне апликације 20 милиграма триамцинолон-ацетонида. Поред ВХ и видне оштрине, анализирани су и интраокуларни притисак и развој катаракте.

Резултати Статистички значајна разлика у густини ВХ и видној оштрини забележена је 1. и 3. месеца после употребе триамцинолона. Код 29% болесника забележен је привремени скок интраокуларног притиска после интравитреалне примене триамцинолона, а 4,1% болесника завршило је студију са развијеном катарактом.

Закључак Интравитреално апликован триамцинолон-ацетонид има умерен и привремен ефекат на брзину реапсорпције ВХ. То може представљати корисну терапијску могућност када витректомија није могућа.

Кључне речи: триамцинолон-ацетонид; витреална хеморагија; интравитреална инјекција; интраокуларни притисак

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Comparing characteristics of the optic nerve head among subjects with suspected glaucoma in different ages of onset

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SUMMARY

Introduction/Objective Evaluation of the optic nerve head (ONH) is an inevitable procedure in the diagnosis of glaucoma. One of the most common imaging techniques for a quantitative assessment of the topography of the ONH is the Heidelberg retinal tomography II (HRT II).

The aim of this study was to determine quantitative stereometric parameters of the ONH by using HRT II and to investigate any damage of neuroretinal rim in children with suspected glaucoma and compare these data with a group of adults also with suspected glaucoma.

Methods This comparative study included 167 children (167 eyes) aged between five and 16 years (mean age of 11 ± 3 years) with suspected juvenile glaucoma and 175 adult participants (175 eyes), aged 55–66 years (mean age of 60 ± 3 years) also with suspected glaucoma. All of them were examined between January 2013 and April 2014. ONH topography and retinal nerve fiber layer thickness measurements were assessed using HRT II.

Results Data analysis in this study showed that the average mean values for children/adults were as follows: disc area (mm^2) 2.828 ± 0.489 / 2.663 ± 0.412 ($p < 0.001$); rim area (mm^2) 1.873 ± 0.391 / 1.667 ± 0.275 ($p < 0.001$); cup/disc area ratio 0.369 ± 0.125 / 0.369 ± 0.101 ($p = 0.530$); mean retinal nerve fiber layer thickness (mm) 0.223 ± 0.078 / 0.219 ± 0.055 ($p = 0.494$). Statistically significant difference in damage of neuroretinal rim, between children and adults, was found in the temporal and temporal-inferior segments.

Conclusion There were differences in some of the investigated quantitative parameters of the ONH between children and adults, as optic disc size, cup and rim area, and rim volume. By using Moorfields regression analysis, differences in the damage of the neuroretinal rim, when comparing children and adult optic discs, appeared only in the temporal and temporal-inferior segments, which means that optic disc cupping has spread more in the children than in the adults.

Keywords: Heidelberg retina tomography; optic disc; stereometric parameters; primary open angle glaucoma; juvenile glaucoma

INTRODUCTION

Evaluation of the optic nerve head (ONH) is an inevitable procedure in the diagnosis of juvenile glaucoma. However, it is not easy to detect the first glaucomatous changes on a disc because of the great variability in the appearance of the optic nerve that often makes an accurate distinction between glaucomatous and healthy optic nerve rather difficult [1, 2]. On the other hand, the problems in the diagnosis of juvenile glaucoma are usually difficult in getting useful visual field information in children (especially young children). In the absence of a reliable visual field result, ophthalmologists must rely on an evaluation of structural changes on the optic disc, which according to the reported results, may precede the development of the reproducible perimetry defects by several years [3, 4, 5]. A confocal scanning laser tomography, Heidelberg retina tomography (HRT; Heidelberg Engineering, Heidelberg, Germany), is one of the promising tools for the evaluation of the ONH in glaucoma patients due to high reproducibility and ability to measure three-dimensional parameters [6, 7]. HRT has been used in recent years to perform quantitative measurements of the ONH and provides measures of ONH topography [8]. It has been proved to be highly reproducible and also shows good agreement with clinical estimates between ONH structure and visual function [9, 10, 11].

Glaucoma has been categorized by the age of onset and the angle characteristics. It is accepted to a certain extent that juvenile-onset primary open-angle glaucoma (JOAG) is a subset of adult primary open-angle glaucoma (POAG) with an earlier age of onset. However, JOAG and POAG differ from each other with regard to their inheritance, prevalence, and severity of presentation [12]. There is a lack of papers on comparative morphometric analysis of the ONH using confocal scanning laser ophthalmoscopy among primary open-angle glaucoma and juvenile-onset primary open-angle glaucoma, or their suspects.

The aim of this study was to determine quantitative stereometric parameters of the ONH by using Heidelberg retina tomography II (HRT II)

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and to investigate any damage of neuroretinal rim in children with suspected glaucoma and compare these data with the group of adults also with suspected glaucoma.

METHODS

This prospective comparative study included 167 children (167 eyes) aged 5–16 years (mean age of 11 ± 3 years) with suspected juvenile glaucoma and 175 adult participants (175 eyes), aged 55–66 years (mean age of 60 ± 3 years) also with suspected glaucoma. All of them were examined between January 2013 and April 2014 at the Clinic for Eye Diseases, Clinical Center of Serbia, Belgrade. All subjects underwent a complete ophthalmic examination by a glaucoma specialist including visual acuity (Snellen chart), slit-lamp biomicroscopy, gonioscopy, IOP measurement with Goldmann applanation tonometry, and fundus examination using indirect ophthalmoscopy with Volk Superfield lens 90D. Diagnostic observation also included a visual field test using the Threshold C 24-2 Swedish Interactive Testing Algorithm (SITA) standard program with Humphrey visual field analyzer II (Carl Zeiss, Oberkochen, Germany) and scanning laser ophthalmoscopy – HRT II (version 2.02; Heidelberg Engineering, GmbH, Dossenheim, Germany). Central corneal thickness values were measured by ultrasonic pachymeter (Alcon Laboratories, OcuScan® RxP Ophthalmic Ultrasound system, Fort Worth, TX, USA) by trained ophthalmic technicians. The pachymetry measurement recorded for each eye was the average of three measurements taken per eye. Refractive error was measured with KR-7000 auto kerato-refractometer (Topcon, Tokyo, Japan) and was calculated as spherical equivalent in diopters (D), as the sum of the sphere and half of the refractive astigmatism.

Subjects included in the study were glaucoma suspects with either glaucomatous-appearing optic disc and IOP under 22 mmHg or healthy appearing optic disc and IOP of 22 mmHg or above. The criteria for determining the glaucomatous-appearing optic disc were assessed by the clinical impression of a glaucoma specialist. "Glaucomatous-appearing optic disc" must include one or more of the following: 1) excavation – undermining of the neuroretinal rim; 2) notching – it was considered if it involved two clock hours; 3) focal or diffuse atrophy of neuroretinal rim area – neuroretinal rim thinning involving two or more clock hours; 4) vertical cup-disc ratio of more than 0.6 or 5) vertical cup-disc asymmetry between the eyes of 0.2 or more [1]. Participants included in the study did not receive anti-glaucoma medications nor did they undergo surgery.

Inclusion criteria were as follows: 1) best-corrected visual acuity better than 0.8; 2) spherical refraction within ±5.0 D; 3) cylindrical correction within ±1.5 D; 4) open angle on gonioscopy, and 5) normal visual field.

Exclusion criteria were the coexistence of any other ophthalmic pathology other than glaucoma and IOP above 26 mmHg.

All subjects received a detailed explanation about the study and signed an informed consent form in accordance with the principles embodied in the Declaration of Helsinki. An informed consent to participate in the study was taken from all adult participants or from the guardians (if participants were below 18 years of age). The Ethics Committee of the Clinical Center of Serbia, where the study was undertaken, approved this study.

Study participants underwent ocular imaging with the commercially available HRT II version 2.02. HRT is a confocal scanning laser ophthalmoscope that provides software-generated measurements describing the topography of the surface of the optic disc and adjacent peripapillary retina. The right eye of each participant selected for the study was examined for the first time by means of HRT II. The same observer analyzed all HRT images after proper adjustment for refractive error and astigmatism.

Twelve stereometric parameters [disc area (mm^2), cup area (mm^2), rim area (mm^2), cup-to-disc area ratio (C/D ratio), cup volume (mm^3), rim volume (mm^3), mean retinal nerve fiber layer (RNFL) thickness, RNFL cross sectional, height variation contour (mm), mean cup depth (mm) and maximum cup depth (mm), and cup shape measure (mm)] of children and adults have been taken into consideration in this study. We also investigated data for the mean RNFL thickness, rim area, rim volume and C/D ratio in each of the six segments (temporal, temporal-inferior, temporal-superior, nasal, nasal-superior, and nasal-inferior).

Moorfields regression analysis (MRA) is a part of the HRT program, which represents the method for analyzing regression logarithmic of the global and six segment rim areas (temporal, temporal-inferior, temporal-superior, nasal, nasal-superior, and nasal-inferior) to the matching disc areas and compares the results to a normative database. It defines these areas as damaged or outside normal limit, borderline, and normal based on the 95% and 99.9% confidence intervals (CI): "normal" if all of the measurements fall within the 95% CI) "borderline" if at least one falls between the lower 95% and 99.9% CI; and "outside normal limits" if at least one rim area measurement is less than the lower 99.9% CI.

By using the MRA, the percentage of the participants who had normal, borderline, and/or outside normal limit neuroretinal rim (temporal, temporal-superior, temporal-inferior, nasal, nasal-superior, and nasal-inferior) was determined, so these data were compared between children and adult groups.

Statistical analysis

Standard descriptive statistics were used. Student's t-test and Mann–Whitney test was used for comparison of the variables between studied groups; χ^2 test was used to evaluate the significance of the differences between categorized data. Individual differences were considered to be statistically significant for $p < 0.05$. IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) was used for all statistical calculations.

RESULTS

During the observation period, 167 children and 175 adults were enrolled in this study. Baseline demographic characteristics of enrolled participants, IOP, best-corrected visual acuity, and refractive error in diopter are shown in Table 1.

The mean children's age was 11.2 ± 3.1 years (range of 5–16 years); the children were predominantly male (54%). In the adult group the mean age was 60.1 ± 3.2 years (range of 55–65 years); they were predominantly female (66%). The children's mean IOP was 16.5 ± 3.1 mmHg (range of 10–25 mmHg) and in the adults it was 19.7 ± 2.8 mmHg (range of 12–26 mmHg) (p = 0.584). There was a statistically significant difference in mean central corneal thickness in two studied groups, children/adults: 578 ± 35 μm (range of 503–620 μm) / 547 ± 35 μm (range of 453–60 μm) (p = 0.032). Visual acuity in both children and adults were 0.8 or better. They were predominantly myopic and spherical equivalent in children ranged between –5.00 and +1.00 D and in adults between -4.50 and +2.00 D.

Summary statistics for the optic disc morphometric characteristics of interest are presented in Tables 2, 3, 4, 5, and 6.

These summary statistics include the range, the mean, and standard deviation for each characteristic in each group. Table 2 shows a comparison of global ONH parameters by HRT II between the two groups. There were statistically significant differences between the children and the adults in the following stereometric parameters: disc area (mm^2): 2.828 ± 0.489 vs. 2.663 ± 0.412, (p < 0.001), cup area (mm^2): 1.157 ± 0.527 vs. 1.011 ± 0.381 (p = 0.0024), rim area (mm^2): 1.873 ± 0.391 vs. 1.667 ± 0.275 (p < 0.001), rim volume (mm^3: 0.437 ± 0.196 vs. 0.382 ± 0.132 (p = 0.039) and RNFL cross sectional 1.357 ± 0.473 vs. 1.262 ± 0.327 (p = 0.048). However, no significant differences were found in the mean C/D ratio, cup volume, mean RNFL, mean and maximum cup depth (p > 0.05).

We further analyzed C/D ratio, rim area, rim volume, and mean RNFL in each segment. Values of C/D area ratio in each of the six segments in both studied groups are summarized in Table 3. In temporal, temporal-inferior, nasal, and nasal-superior segments C/D ratio was larger in the children than in the adult group; with it, there were statistically significant differences in the temporal [0.592 ± 0.106 vs. 0.543 ± 0.146 (p = 0.044)] and the temporal-inferior [0.388 ± 0.122 vs. 0.349 ± 0.144 (p = 0.045)] segments. Rim area was larger in each of the six segments in children than in adults (Table 4) and statistically significant in all segments. Also, rim volume was greater in all segments in children than in adults, but it was statistically significant in temporal (p = 0.006), temporal-inferior (p < 0.001), and nasal (p = 0.0026) segments (Table 5). Analyzing the mean RNFL we did not find statistically significant differences in each of the 6 segments between two studied groups (Table 6).

By analyzing the MRA findings of both groups, statistically significant difference between children and adults in damage of neuroretinal rim was found in the temporal (p < 0.001) and the temporal-inferior segment (p = 0.0046) (Table 7).

Data for the temporal segment for children/adults were (in percent) normal (77.2/96.1%), borderline (21.3/3.9%), outside normal limit (1.6/0%); for the temporal-inferior

Table 1. Characteristics of the participants in both studied groups

Variables	Children	Adults	p
Number of participants, n	167	175	
Male / female, n (%)	90 (54) / 77 (46)	59 (34) / 116 (66)	0.001
Age (years), mean ± SD (range)	11.2 ± 3.1 (5–16)	60.1 ± 3.2 (55–65)	< 0.001
IOP (mmHg) (range)	16.5 ± 3.1 (10–25)	19.7 ± 2.8 (12–26)	0.584
CCT (μm), mean ± SD (range)	578 ± 35 (503–620)	547 ± 35 (453–601)	0.032
Best corrected VA (range)	0.98 ± 0.048 (0.8–1.0)	0.98 ± 0.027 (0.8–1.0)	0.755
Refractive error, SE (D), (range)	-2.50 (-5.00–+1.00)	-1.50 (-4.50–+2.00)	0.313

IOP – intraocular pressure; VA – visual activity; SE – spherical equivalent; D – diopter; CCT – central corneal thickness

Table 2. Values of global optic nerve head parameters in both studied groups

Stereometric parameters	Children		Adults		p
	Range	Mean ± SD	Range	Mean ± SD	
Disc area (mm^2)	1.685–4.571	2.828 ± 0.489	1.780–3.745	2.663 ± 0.412	< 0.001
Cup area (mm^2)	0.042–2.758	1.157 ± 0.527	0.187–1.957	1.011 ± 0.381	0.0024
Rim area (mm^2)	1.873–3.593	1.873 ± 0.391	0.908–2.630	1.667 ± 0.275	< 0.001
Cup/disc area ratio	0.021–0.639	0.369 ± 0.125	0.081–0.599	0.369 ± 0.101	0.530
Cup volume (mm^3)	0.001–1.122	0.387 ± 0.262	0.028–1.078	0.327 ± 0.203	0.065
Rim volume (mm^3)	0.123–1.343	0.437 ± 0.196	0.127–0.850	0.382 ± 0.132	0.039
mRNFL	0.052–0.467	0.223 ± 0.078	0.091–0.398	0.219 ± 0.055	0.494
RNFL cross section (mm^2)	0.034–2.873	1.357 ± 0.473	0.522–2.190	1.262 ± 0.327	0.048
Mean cup depth (mm)	0.074–0.677	0.307 ± 0.096	0.111–0.631	0.309 ± 0.098	0.889
Maximum cup depth (mm)	0.200–1.316	0.744 ± 0.181	0.379–1.278	0.758 ± 0.180	0.552
Height variation contour	0.171–1.553	0.370 ± 0.149	0.183–0.655	0.356 ± 0.081	0.706
Cup shape measure	-0.412–0.058	-0.144 ± 0.078	-0.309–0.048	-0.152 ± 0.081	0.264

mRNFL – mean retinal nerve filter layer

Table 3. Values of cup-to-disc area ratio in each of the six segments in both studied groups

Cup-to-disc area ratio segments	Children		Adults		p
	Range	Mean ± SD	Range	Mean ± SD	
Temporal	0.081–0.864	0.592 ± 0.106	0.230–0.822	0.543 ± 0.146	0.044
Temporal-superior	0.000–0.724	0.408 ± 0.133	0.069–0.704	0.430 ± 0.123	0.133
Temporal-inferior	0.010–0.813	0.388 ± 0.122	0.007–0.737	0.349 ± 0.144	0.045
Nasal	0.000–0.738	0.239 ± 0.162	0.000–0.680	0.218 ± 0.149	0.084
Nasal-superior	0.000–0.636	0.317 ± 0.154	0.000–0.588	0.303 ± 0.135	0.588
Nasal-inferior	0.000–0.524	0.207 ± 0.124	0.000–0.662	0.219 ± 0.128	0.686

Table 4. Values of rim area in each of the six segments in both studied groups

Rim area segments	Children		Adults		p
	Range	Mean ± SD	Range	Mean ± SD	
Temporal	0.081–0.651	0.301 ± 0.096	0.087–0.464	0.265 ± 0.069	< 0.001
Temporal-superior	0.103- 0.443	0.257 ± 0.063	0.079–0.326	0.233 ± 0.043	< 0.001
Temporal-inferior	0.076–0.650	0.257 ± 0.071	0.058–0.345	0.214 ± 0.043	< 0.001
Nasal	0.199–1.086	0.545 ± 0.133	0.206–1.021	0.510 ± 0.106	0.022
Nasal-superior	0.069–0.555	0.257 ± 0.154	0.141–0.334	0.233 ± 0.430	< 0.001
Nasal-inferior	0.168–0.554	0.292 ± 0.065	0.123–0.446	0.255 ± 0.053	< 0.001

Table 5. Values of rim volume in each of the six segments in both studied groups

Rim volume segments	Children		Adults		p
	Range	Mean ± SD	Range	Mean ± SD	
Temporal	0.010–0.100	0.029 ± 0.016	0.000–0.080	0.024 ± 0.012	0.006
Temporal-superior	0.008–0.131	0.049 ± 0.023	0.008–0.126	0.045 ± 0.019	0.211
Temporal-inferior	0.006–0.259	0.061 ± 0.033	0.010–0.134	0.048 ± 0.021	< 0.001
Nasal	0.000–0.272	0.063 ± 0.059	0.000–0.237	0.044 ± 0.046	0.144
Nasal-superior	0.004–0.253	0.066 ± 0.036	0.015–0.167	0.064 ± 0.026	0.927
Nasal-inferior	0.024–0.268	0.091 ± 0.039	0.018–0.175	0.078 ± 0.030	0.0026

Table 6. Values of the mean retinal nerve filter layer (mRNFL) in each of the six segments in both studied groups

mRNFL segments	Children		Adults		p
	Range	Mean ± SD	Range	Mean ± SD	
Temporal	0.096–0.168	0.079 ± 0.030	0.038–0.142	0.075 ± 0.020	0.114
Temporal-superior	0.021–0.493	0.252 ± 0.088	0.104–0.501	0.262 ± 0.077	0.526
Temporal-inferior	0.024–0.628	0.265 ± 0.107	0.055–0.453	0.242 ± 0.082	0.706
Nasal	0.050–0.700	0.246 ± 0.113	0.030–0.460	0.233 ± 0.079	0.059
Nasal-superior	0.198–0.615	0.284 ± 0.122	0.089–0.569	0.303 ± 0.088	0.258
Nasal-inferior	0.109–0.648	0.330 ± 0.110	0.137–0.512	0.323 ± 0.083	0.474

Table 7. Moorfields regression analysis results

Segments (%)	Children			Adults			p
	IN	BL	OUT	IN	BL	OUT	
Temporal	98 (77.2)	27 (21.3)	2 (1.6)	122 (96.1)	5 (3.9)	0 (0)	< 0.001
Temporal-superior	119 (93.7)	6 (4.7)	2 (1.6)	114 (89.8)	12 (9.4)	1 (0.8)	0.2695
Temporal-inferior	101 (79.5)	21 (16.5)	5 (3.9)	117 (92.1)	9 (7.1)	1 (0.8)	0.0046
Nasal	93 (73.2)	21 (16.5)	13 (10.2)	106 (83.5)	13 (10.2)	8 (6.3)	0.1498
Nasal-superior	95 (74.8)	23 (18.1)	9 (7.1)	95 (74.8)	29 (22.8)	3 (2.4)	0.8285
Nasal-inferior	105 (82.7)	14 (11)	8 (6.3)	105 (82.7)	13 (10.2)	9 (7.1)	0.9772

IN – normal; BL – borderline; OUT – outside normal limit

segment they were normal (79.5/92.1%), borderline (16.5/7.1%), and outside normal limit (3.9/0.8%). There was no statistically significant difference in other segments.

DISSCUSION

In the present study, we evaluated stereometric parameters of the ONH in suspected primary open-angle glaucoma in different ages of onset. Our first purpose was to evaluate morphometric features of the optic disc in children, and the second one was to compare these data with the data of the group of adults. The optic disc characteristics have been extensively studied with regard to adult onset of POAG, but there are few studies relating to the morphometry of primary juvenile glaucoma discs [13, 14]. On the other hand, HRT has been used in normal children in a few studies [15–18]. Ruberto et al. [15] reported normal values for HRT in comparison with children with cerebral visual impairment, and Tong et al. [16] presented values of myopic 11–12-year-old Singaporean children. Recently, He et al. [17] used HRT to analyze disc and cup area in a twin

study of children. Larsson et al. [18] investigated the normal values but also repeatability and interocular difference of the ONH, using HRT, in 5–16-year-old full term children. They had smaller disc area than in the present study (2.16 mm^2 vs. 2.83 mm^2), as well as rim area (1.75 mm^2 vs. 1.87 mm^2) and cup area (0.41 mm^2 versus 1.15 mm^2). Chinese twins, studied by He et al. [17], also had smaller disc area [2.83 mm^2 (present study) vs. 1.97 mm^2] and smaller cup area [1.15 mm^2 (present study) vs. 0.50 mm^2]. The differences were obvious especially in the cup area because in our study most of the children had a glaucomatous-appearance disc and Larsson et al. [18] and He and al. [17] studied normal children. Also, the reason for large discs and large cupping could be the reason why children in our study had myopic refractive errors like in the study by Jung et al. [19], in which they suggested that highly hyperopic eyes have significantly smaller optic discs and highly myopic eyes have significantly larger discs than emmetropic eyes.

There were not many studies on comparative morphometric analyses of ONH using confocal scanning laser ophthalmoscopy among primary glaucoma in different ages of onset. Jonas and Grundler [13] compared ONH between JOAG and POAG patients in 1996, and recently Gupta et al. [12] analyzed differences in optic disc characteristics between primary congenital glaucoma, juvenile, and adult onset open angle glaucoma patients.

The present study found optic discs to be larger among patients with suspected JOAG compared with suspected glaucoma in adults. Our parameters were larger than in the recent study by Gupta et al. [12] – optic disc size in JOAG patiens was 2.61 mm^2 vs. 2.83 mm^2 (present study); the parameters were also significantly larger than in adult POAG eyes [2.44 mm^2 vs. 2.663 mm^2 (present study)]. It can be observed that in the study by Gupta et al. [12] the patients were presenting with a confirmed diagnosis of glaucoma, while in our study participants were presenting with suspected glaucoma. One of explanations that children may have larger optic disc sizes might be that a larger disc size may also be inherited with a genetic susceptibility to develop glaucoma. It is known that genetic susceptibility plays a greater role in the causation of glaucoma in children (congenital and juvenile) compared to adults, where causation is, more often, multifactorial. Hence, genetic segregation of children affected by glaucoma could also account for the larger optic discs seen within our observations of these young participants compared with our adult participants [20].

On other hand, Jonas and Grundler [13] studied the optic disc morphometry of 37 JOAG and 382 adult POAG patients using stereo disc photographs but did not find a difference in the disc area between the juvenile and adult onset POAG eyes in their population. They used the planimetric method for calculations, which is known to give larger measurements because of image magnification compared with the confocal scanning laser ophthalmoscope (CSLO).

Measurement of the optic disc and neuroretinal rim is important for the diagnosis and management of glaucoma [21]. It is increasingly recognized that the disc size is a major determinant of other disc parameters such as neuroretinal rim area or cup area or volume [13, 19, 22]. When comparing our data compiled from the children and the adults groups, in addition to larger disc sizes, the children also had larger rim areas, which is consistent with the results in previous published studies [23, 24].

In our study, children also had greater average cup area and cup volume than adults. Jonas and Grundler [13] also found that cup volume in children with JOAG were larger than in POAG patients. In the study by Gupta et al. [12], the cup characteristics demonstrated significantly greater means among JOAG compared with POAG and primary congenital glaucoma eyes, including cup depth ($p = 0.001$), cup volume ($p = 0.024$), and C/D area ratio ($p = 0.049$). C/D ratio as a measure for determining structural change is most often used clinically by glaucoma specialists to assess structural damage of the optic disc. In the present study there was no significant difference in the mean C/D ratio between children and adults (children 0.369 ± 0.125, adults 0.369 ± 0.101).

We mentioned that previous studies have suggested a correlation of neuroretinal rim area and optic cup area to the optic disc size but the question is the correlation between disc size and RNFL [13, 19, 22]. Budenz et al. [25] have demonstrated thicker RNFL in larger optic discs. In our study, RNFL was thinner in adults but we need to take into consideration the fact that age is recognized as a significant factor affecting RNFL thickness [26, 27], and that normal individuals lose ganglion cells in an age-dependent manner, at an estimated rate of up to 5,000 axons/year, which may translate into considerable axon loss during a 70-year life span [24]. On the other hand, our results coincide with results in a study by Savini et al. [22], showing that RNFL thickness was positively correlated with ONH size. Such a correlation may be the result of either an increased number of nerve fibres in eyes with larger discs or a smaller distance between the circular scan and the true ONH margin [22].

Besides quantitative parameters of the ONH in children and adults, we investigated differences in damage of the neuroretinal rim with MRA, comparing children's and adult optic discs in which damage was only appearing in the temporal and temporal-inferior segments; our conclusion is that the optic disc cupping spread more in children than in adults. MRA indicates normal, borderline, and outside normal limits on the basis of a comparison between an examined optic disc and a dedicated database of normal eyes and is highly capable of clinically discriminating normal and glaucomatous patients. In our study, there was a statistically significant difference of the percentage distribution in normal, borderline, and outside normal limit between children and adults group in the temporal and temporal-inferior segments; in these segments neuroretinal rim was more damaged in children than in adults. Several clinical studies support the idea that damage to the optic nerve and the RNFL can be identified before an alteration in the visual field [28]. This fact is very important in the examination of children, because determination of the visual field and interpretation of the results

may prove challenging. Detection and monitoring of glaucoma patients are based on identification of structural and functional changes. We mentioned that in the absence of reliable visual field results in children, ophthalmologists must rely on evaluating structural changes on the optic disc. We also know that structural alterations of the optic disc nerve fiber layer complex provide the earliest reliable signs of damage from glaucoma [24, 29]. Accurate and objective quantitative measurements of the ONH and nerve fiber layer are required to improve our ability to regularly recognize early glaucomatous damage. It follows that it is important to evaluate the ONH by using well-established confocal scanning laser ophthalmoscope, HRT II, and to improve detection of early damage [30]. Also, HRT is a quick and non-invasive technique and therefore is applicable in children.

Our study has some limitations. While HRT has mostly been used in the diagnosis of glaucoma, it has also been the requirement that the operator manually defines a contour line marking the inner border of the ONH margin as defined by the sclera ring. Many of the quantitative measurements are derived from the contour line placement, thereby inducing measurement variability. Second, the problem is that there is a lack of normative database for subjects under the age of 18 and consequently HRT use in children has not been extensively studied. Also, it should be noted that the mean age of these two groups was different, which makes the comparison less accurate. We did not present age-matched control data because the aim of this study was to compare morphologic appearance of optic disc in glaucoma suspects in different ages of onset. In addition, it should be taken into account that all the participants underwent visual field testing with a limitation, which implies that most of the children did not have reliable visual field testing results. Finally, it is important to highlight that participants with suspected glaucoma were enrolled in the study. Even though JOAG is, by definition, characterized by elevated IOP, in the clinical practice, most children with suspected JOAG have glaucomatous-appearing optic disc with IOP in the normal range and therefore a certain number of these children were included in the study.

CONCLUSION

The results of the present study showed that there were differences in some of the investigated quantitative parameters of the ONH between children and adults, such as optic disc size, cup and rim area, and rim volume. When comparing children's and adult optic discs by using MRA, the difference in the damage of the neuroretinal rim appeared only in the temporal and temporal-inferior segments, which means that optic disc cupping spread more in children than in adults.

Diagnosis of glaucoma in children remains a challenge for clinicians. The assessment of the optic disc and peripapillary RNFL damage in pediatric subjects can be quite challenging; visual field testing in young children is often especially unreliable or even impossible. Although diagnostic imaging methods lack a normative database for subjects under the age of 18 years and their use in children has not been extensively studied, the clinicians would appreciate support by objective methods to differentiate between normality and abnormality in borderline cases. Hence, the aim of this study was to give insight into the characteristics of the ONH in children with suspected glaucoma by using HRT and to underline the similarities and differences between children and adults with suspected glaucoma. Furthermore, we hope that it will be helpful in the diagnosis of glaucoma in children.

REFERENCES

1. Hentova-Sencanic P, Sencanic I, Trajkovic G, Bozic M, Bjelovic N. Agreement in identification of glaucomatous progression between the optic disc photography and Heidelberg retina tomography in young glaucomatous patients. Int J Ophthalmol. 2014; 7(3):474–9.
2. Breusegem C, Fieuws S, Stalmans I, Zeyen T. Agreement and accuracy of non-expert ophthalmologists in assessing glaucomatous changes in serial stereooptic disc photographs. Ophthalmology. 2011; 118(4):742–6.
3. Weinreb RN, Zangwill LM, Jain S, Becerra LM, Dirkes KA, Piltz-Seymour JR, et al. Predicting the onset of glaucoma: The confocal scanning laser ophthalmoscopy ancillary study to the Ocular Hypertension Treatment Study. Ophthalmology. 2010; 117(9):1674–83.
4. Gardiner SK, Johnson CA, Demirel S. Factors predicting the rate of functional progression in early and suspected glaucoma. Invest Ophthalmol Vis Sci. 2012; 53(7):3598–604.
5. Zangwill LM, Jain S, Dirkes K, He F, Medeiros FA, Trick GL, et al. Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study. The rate of structural change: the confocal scanning laser ophthalmoscopy ancillary study to the ocular hypertension treatment study. Am J Ophthalmol. 2013; 155(6):971–82.
6. Danesh-Meyer HV, Gaskin BJ, Jayusundera T, Donaldson M, Gamble GD. Comparison of disc damage likelihood scale, cup to disc ratio, and Heidelberg retina tomograph in the diagnosis of glaucoma. Br J Ophthalmol. 2006; 90(4):437–41.
7. Naithani P, Ramanjit S, Parul S, Tanuj D, Viney G, Dimple K. Evaluation of optical coherence tomography and Heidelberg retinal tomography parameters in detecting early and moderate glaucoma. Invest Ophthalmol Vis Sci. 2007; 48(7):3138–45.
8. Vessani RM, Moritz R, Batis L, Zagui RB, Bernardoni S, Susanna R. Comparison of quantitative imaging devices and subjective optic nerve head assessment by general ophthalmologists to differentiate normal from glaucomatous eyes. J Glaucoma. 2009; 18(3):253–61.
9. Ferreras A, Pablo LE, Larrosa JM, Polo V, Pajarín AB, Honrubia FM. Discriminating between normal and glaucoma-damaged eyes with the Heidelberg retina tomography 3. Ophthalmology. 2008; 115(5):775–81.
10. Wang YX, O'Leary N, Strouthidis NG, White ET, Ho TA, Garway-Heath DF. Comparison of neuroretinal rim area measurements made by the Heidelberg Retina Tomograph I and the Heidelberg Retina Tomograph II. J Glaucoma. 2013; 22(8):652–8.
11. Harizman N, Zelefsky JR, Ilitchev E, Tello C, Ritch R, Liebmann JM. Detection of glaucoma using operator-dependent versus operator-independent classification in the Heidelberg retinal tomograph-III. Br J Ophthalmol. 2006; 90(11):1390–2.
12. Gupta V, James MK, Singh A, Kumar S, Gupta S, Ajay Sharma A. Differences in Optic Disc Differences in Optic Disc Characteristics of Primary Congenital Glaucoma, Juvenile, and Adult Onset Open Angle Glaucoma Patients. J Glaucoma. 2016; 25(3):239–43.
13. Jonas JB, Grundler A. Optic disc morphology in juvenile primary open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol. 1996; 234(12):750–4.

14. Jonas JB, Budde WM. Optic nerve head appearance in juvenile-onset chronic high-pressure glaucoma and normal-pressure glaucoma. Ophthalmology. 2000; 107(4):704–11.
15. Ruberto G, Salati R, Milano G, Bertone C, Tinelli C, Fazzi E, et al. Changes in the optic disc excavation of children affected by cerebral visual impairment: a tomographic analysis. Invest Ophthalmol Vis Sci. 2006; 47(2):484–8.
16. Tong L, Chan YH, Gazzard G, Loon SC, Fong A, Selvaraj P, et al. Heidelberg retinal tomography of optic disc and nerve fiber layer in Singapore children: variations with disc tilt and refractive error. Invest Ophthalmol Vis Sci. 2007; 48(11):4939–44.
17. He M, Liu B, Huang W, Zhang J, Yin Q, Zheng Y, et al. Heritability of optic disc and cup measured by the Heidelberg retinal tomography in Chinese: the Guangzhou twin eye study. Invest Ophthalmol Vis Sci. 2008; 49(4):1350–5.
18. Larsson E, Nuija E, Alm A. The optic nerve head assessed with HRT in 5–16-year-old normal children: normal values, repeatability and interocular difference. Acta Ophthalmol. 2011; 9(8):755–8.
19. Jung JJ, Baek SH, Kim US. Biometry and spectral domain optical coherence tomography parameters in children with large cupping. Grafes Arch Clin Exp Ophthalmol. 2013; 251(9):2213–7.
20. Ramdas WD, van Koolwijk LM, Ikram MK, Jansonius NM, de Jong PT, Bergen AA, et al. A genome-wide association study of optic disc parameters. PLoS Genet. 2010; 6:e1000978.
21. Hoffmann EM, Bowd C, Medeiros FA, Boden C, Grus FH, Bourne RR, et al. Agreement among 3 optical imaging methods for the assessment of optic disc topography. Ophthalmology. 2005; 112(12):2149–56.
22. Savini GZ, Zanini M, Carelli V, Sadun AA, Ross-Cisneros FN, Barboni P. Correlation between retinal nerve fibre layer thickness and optic nerve head size: an optical coherence tomography study. Br J Ophthalmol. 2005; 89(4):489–92.
23. Miglior S, Albe´ E, Guareschi M, Rosetti L, Orzalesi N. Intraobserver and interobserver reproducibility in the evaluation of optic disc stereometric parameters by Heidelberg retina tomograph. Ophthalmology. 2002; 109(6):1072–7.
24. Mrugacz M, Bakunowicz-Lazarczyk A. Optical Coherence Tomography Measurement of the Retinal Nerve Fiber Layer in Normal and Juvenile Glaucomatous Eyes. Ophthalmologica. 2005; 219(2):80–5.
25. Budenz DL, Anderson DR, Varma R, Schuman J, Cantor L, Savell J, et al. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. Ophthalmology. 2007; 114(6):1046–52.
26. Qian J, Wang W, Zhang X, Wang F, Jiang Y, Wang W, et al. Optical coherence tomography measurements of retinal nerve fiber layer thickness in Chinese children and teenagers. J Glaucoma. 2011; 20(8):509–13.
27. Alasil T, Wang K, Keane PA, Lee H, Baniasadi N, de Boer JF, et al. Analysis of normal retinal nerve fiber layer thickness by age, sex, and race using spectral domain optical coherence tomography. J Glaucoma. 2012; 22(7):1–10.
28. Pollet-Villard F, Chiquet C, Romanet JP, Noel C, Aptel F. Structure-function relationships with spectral-domain optical coherence tomography retinal nerve fiber layer and optic nerve head measurements. Invest Ophtghalmol Vis Sci. 2014; 55(5):2953–62.
29. Horn FK, Mardin CY, Laemmer R, Baleanu D, Juenemann AM, Kruse FE, et al. Correlation between local glaucomatous visual field defects and loss of nerve fiber layer thickness measured with scanning laser polarimetry and spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2009; 50(5):1971–7.
30. Kilintzis V, Pappas T, Chouvarda I, Salonikiou A, Maglaveras N, Dimitrakos S, et al. Novel Heidelberg retina tomograph-based morphological parameters derived from optic disc cupping surface processing. Invest Ophthalmol Vis Sci. 2011; 52(2):947–51.

Топографска процена папиле видног живца код деце и одраслих са сумњом на глауком

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САЖЕТАК

Увод/Циљ Преглед папиле видног живца (ПВЖ) представља основу приликом постављања дијагнозе глаукома. Једна од најчешћих дијагностичких метода за квантитативну процену топографије ПВЖ је Хајделбергова томографија ретине II (ХТР II).

Циљ рада је био одредити помоћу ХТР II квантитативне стереометријске параметре папиле код деце са сумњом на јувенилни глауком и упоредити те параметре са групом одраслих особа такође са сумњом на глауком.

Методе У студију је укључено 167 деце узраста 11 ± 3 година са сумњом на јувенилни глауком и 175 одраслих старости 60 ± 3 година са сумњом на глауком у периоду од јануара 2013. до априла 2014.

Преглед ПВЖ и перипапиларне регије обављен је употребом ласер скенинг томографа ХРТ II.

Резултати Просечне вредности стереометријских параметара код деце/одраслих биле су: површина ПВЖ (mm^2) 2,828 ± 0,489 / 2,663 ± 0,412 ($p < 0,001$); површина неуроретиналног обода (mm^2) 1,873 ± 0,391 / 1,667 ± 0,275 ($p < 0,001$); однос пречника екскавације и пречника папиле 0,369 ± 0,125/ 0,369 ± 0,101 ($p = 0,530$); просечна дебљина слоја нервних влакана 0,223 ± 0,078 / 0,219 ± 0,055 *mm* ($p = 0,494$). Оштећење неуроретиналног обода показало је статистичку значајност у темпоралном и темпоралнодоњем сегменту код деце у односу на одрасле испитанике.

Закључак У овој студији постојала је разлика у вредностима неких од стереометријских квантитативних параметара ПВЖ између деце и одраслих, као што су: површина ПВЖ, површина и запремина неуроретиналног обода. Неуроретиналног обод је био ужи у темпоралном и темпоралнодоњем сегменту код деце, тј. више се ширила глаукоматозна екскавација.

Кључне речи: Хајделбергова ретинална томографија; глава оптичког нерва; стереометријски параметри; примарни глауком отвореног угла; јувенилни глауком

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Influence of different forms of calcium hydroxide and chlorhexidine intracanal medicaments on the outcome of endodontic treatment of teeth with chronic apical periodontitis

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SUMMARY

Introduction/Objective The aim of this study was to determine clinical and radiographic periapical healing of teeth with apical periodontitis treated with different formulations of calcium hydroxide (CH) – paste (CH-paste) and gutta-percha points (CH-GP) – as well as those of chlorhexidine (CHX) – gel (CHX-gel) and gutta-percha points (CHX-GP) –12 months after therapy.

Methods Eighty patients with chronic apical periodontitis were randomly allocated to four treatment groups according to the intracanal medicament used: CH-paste, CH-GP, CHX-gel, and CHX-GP group. Seventy-eight patients were analyzed clinically and radiographically 12 months postoperatively. The periapical index (PAI) was used for the radiographic evaluation of treatment.

Results Overall outcome was classified according to radiographic evaluation only, since clinical success was observed in all the patients. In all the groups, significant reduction in PAI scores was observed ($p < 0.001$). The proportions of healed teeth (PAI ≤ 2) were 73.7%, 60%, 68.4%, and 65% in CH-paste, CH-GP, CHX-gel and CHX-GP group, respectively, with no significant differences between the groups.

Conclusion The results suggest that there are no differences between investigated CH- and CHX-delivery systems regarding treatment outcome of teeth with apical periodontitis.

Keywords: calcium hydroxide; chlorhexidine; periapical diseases; root canal therapy; treatment outcome

INTRODUCTION

Microorganisms play a key role in the development and persistence of apical periodontitis and the success of endodontic therapy depends on their reduction. Mechanical instrumentation and irrigation significantly reduce but do not completely eliminate microbiota present in the root canal [1]. Therefore, the use of an interappointment intracanal dressing has been recommended to supplement the antibacterial effects of chemomechanical procedures and maximize bacterial reduction [2].

Calcium hydroxide (CH) is one of the most effective antibacterial dressings during endodontic therapy due to its antimicrobial activity, tissue-dissolving ability, detoxification of lipopolysaccharides, and induction of repair by formation of hard tissue [3]. Despite the favorable properties of CH, other substances, such as chlorhexidine (CHX), have been proposed with the aim of targeting bacteria resistant to CH [4].

Effectiveness of intracanal medicament depends not only on its antibacterial effect but also on its bioavailability directly influenced by the delivery system. CH is commonly mixed with aqueous, viscous, or oily vehicles, while CHX has been used in the form of liquid or gel. Another delivery method for intracanal dressing is the use of gutta-percha points impregnated with medicament, either CH or CHX. According to the manufacturer, these points are easy to insert and remove from the canal, and they have the ability to release large quantities of medicament from their surface in a time-dependent fashion. To date, almost all research about medicated gutta-percha points considered only their in vitro antibacterial activity, with contrasting results [5–11]. More recently, antibacterial effects of medicated gutta-percha points were evaluated in clinical settings [12, 13]. Investigations found no difference between CH gutta-percha points (CH-GP) and CH paste [12, 13] or CHX gutta-percha points (CHX-GP) [13]. Regardless of the reported antibacterial efficacy of medicated gutta-percha points from some in vitro and in vivo studies, clinical decision making should be based

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on the outcome of clinical research, because antibacterial efficacy and successful therapeutic treatment might not always coincide with each other [5–13]. Long-term effectiveness of CH-GP as intracanal medicament was investigated in just a few studies, mainly case reports. CH-GP were showed to be successful in the treatment of different types of periapical lesions [14], root resorption [14, 15], and for apexification treatment [16].

Thus, the aim of this study was to determine the 12-month clinical and radiographic periapical healing of teeth with apical periodontitis treated with different formulations of CH (paste and gutta-percha points) and CHX (gel and gutta-percha points). The null hypothesis tested was that the type of intracanal medicament (CH vs. CHX) or its formulation (paste and gel vs. gutta-percha points) had no influence on the clinical and radiographic healing of teeth with apical periodontitis.

METHODS

Patient selection

The study was approved by the Ethics Committee of the Faculty of Medicine and conformed to the principles embodied in the Declaration of Helsinki. A sample was selected from patients referred to the Endodontic Department of the Faculty for nonsurgical root canal treatment between 2011 and 2013.

The inclusion criteria for the study were as follows: 1) healthy subjects age 18 years and older, both sexes; 2) single-rooted and single-canalled teeth with nonvital pulps, confirmed by negative response to sensitivity pulp test (cold and electric stimulation tester); 3) the presence of periapical radiolucencies (minimum size ≥ 2 × 2 mm); 4) no previous endodontic therapy of the involved tooth; 5) the absence of tooth or root fracture of the involved tooth; 6) the absence of periodontal pocket (> 4 mm) of the involved tooth.

The exclusion criteria were the following: 1) the absence of enough tooth structure for rubber dam isolation; 2) patients with contributory medical history; 3) patients who received antibiotic therapy during previous six months.

Once eligibility was confirmed and after written and verbal informed consent was obtained, the patient was randomly assigned to one of the following four groups according to the intracanal medicament used: CH-paste (Calxyl-blue, OCO Products GMBH, Dirnstein, Germany), CH-GP (Roeko Calcium hydroxide Plus Points, Coltene/Whaledent, Langenau, Germany), CHX-gel (Consepsis V, Ultradent, South Jordan, UT, USA), and CHX-GP (Roeko Active Points, Coltene/Whaledent, Langenau, Germany). The sample was randomized using computer-generated random numbers, by a person who did not belong to the research group. The group assignment was passed on to the clinician, endodontic specialist, only at the time of treatment. Operator blinding could not be performed due to different colors and forms of used medicaments.

The minimum sample size per group was determined with the method described by Zhong [17]. Sixteen teeth per group were calculated to be required to obtain a power of 80% at the 5% level of significance, with minimal clinically significant mean difference between groups of 0.5 units (standard deviation ± 0.5 unit) using the periapical index (PAI) scale [18]. Assuming possible losses of 20% during the 12-month follow-up period, the number of teeth per group was adjusted to 20.

Clinical procedures

Each tooth was polished with pumice and isolated from the oral cavity with a rubber dam. Antisepsis of the crown and operative field was conducted according to a previously described decontamination protocol [19]. All subsequent procedures were performed aseptically. Caries lesion and/or leakage restoration were removed and a standard access cavity was prepared. The canal working length was established using the apex locator (Raypex® 5, VDW, GmbH, Munich, Germany) and confirmed radiographically. Canal instrumentation was performed using the step-back technique with K-type files (0.02 taper ISO) and Gates–Glidden drills (both from Dentsply/Maillefer, Ballaigues, Switzerland) to the apical size of at least #35 depending on both the initial size of the root canal and root anatomy. Canal was irrigated with 2 mL of 1% sodium hypochlorite after each file size. When instrumentation was completed, the canal was flushed with 5 mL of 17% ethylenediaminetetraacetic acid followed by 5 mL of 1% sodium hypochlorite. After drying the canal with sterile paper points, intracanal medicament was placed in the root canal. For teeth assigned to the CH-paste group, a lentulo spiral was used to fill the canal with the paste. In the CHX-gel group, the gel was placed into the root canals by means of a syringe and needle. Teeth in the CH-GP and CHX-GP groups were dressed by using medicated gutta-percha point inserted to full working length into the canal with a drop of sterile water, according to the manufacturer's instructions. The access cavity was sealed with temporary filling (Cavit, 3M ESPE AG, Seefeld, Germany) and glass ionomer cement (Fuji IX, GC, Tokyo, Japan). After 15 days with intracanal medication, root canal was obturated with gutta-percha and AH Plus sealer (Dentsply, DeTrey, GmbH, Konstanz, Germany) using cold lateral compaction technique. Definitive restoration was obtained within one month after the completion of treatment.

Assessment of treatment outcome

The comparisons of clinical and radiographic findings at the 12-month follow-up with that documented at preoperative examination were used for the assessment of outcome of endodontic therapy. One investigator, uninvolved in the treatment of the subjects, performed all follow-up examinations.

Clinical outcome measures were the evaluation of the presence of pain, percussion, and palpation sensitivity, soft tissue status, tooth mobility, marginal bone level at 12 months. Absence of spontaneous pain and percussion or palpation sensitivity, absence of sinus tract, absence

of soft-tissue swelling, absence of tooth mobility and no increase in periodontal probing depth compared with baseline values were used as clinical criteria for treatment success (healing).

Radiographic outcome measure was the change in periapical radiolucencies at the 12-month follow-up. The radiograph at the follow-up was made by using the individual patient's bite registration and the same exposure settings used for the preoperative image. PAI score was used for radiographic evaluation of treatment success [18]. The index consists of five categories numbered 1–5 as follows: 1 – normal periapical structures; 2 – small changes in bone structure; 3 – changes in bone structure with some mineral loss; 4 – periodontitis with well-defined radiolucent area; 5 – severe periodontitis with exacerbating features; scores of 3 or higher represent disease.

All radiographic films obtained preoperatively and at follow-up were coded blind and organized in a random order. To improve calibration and inter-examiner agreement, two experienced endodontists who had not been involved in the treatment or the follow-up appointments analyzed a series of radiographs (not related to the study samples) representing a wide range of periapical bone densities, before study evaluation. After this, they independently analyzed the study radiographs under moderate illumination at a light table. In cases of disagreement, joint re-evaluation was performed and consensuses were achieved. After one month, the examiners repeated the entire analysis of study radiographs. Inter- and intra-examiner agreement produced a Cohen kappa above 0.71 and 0.81, respectively.

At 12-month follow-up, a tooth was classified as healed if it presented no clinical signs or symptoms and had PAI ≤ 2, or as unhealed if clinical signs or symptoms were presented and/or had PAI ≥ 3.

Statistical analysis

SPSS 19.0 for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The distribution of the variables: sex, dental arch involved and tooth type was evaluated using the χ^2 test, while age was analyzed using ANOVA. The Kruskal–Wallis followed by Mann–Whitney U-test and Wilcoxon signed rank test were used for intergroup and intragroup comparison of PAI scores, at baseline and at the 12-month follow-up, respectively. To determine the difference in proportion of healed teeth between the groups and to identify variables that may influence the treatment outcome, the χ^2 was used. The level of $p < 0.05$ was chosen for statistical significance.

RESULTS

Demographic data

At the start of the treatment, 80 healthy persons (29 males) were recruited. The mean age was 37.58 (range 18–76) years. From each patient, only one tooth was included; 20 teeth per each group. Two of the 80 teeth included in the study were lost at the 12-month follow-up (one in the CH-paste and one in the CHX-gel group).

Comparisons between the groups showed no statistical difference in the distribution of age, sex, tooth type, or dental arch involved (Table 1).

Treatment outcome

At 12-months examination none of the patients had any clinical symptoms and/or abnormal findings. The PAI scores at baseline and at the 12-month follow-up for CH-paste, CH-GP, CHX-gel and CHX-GP are presented in Table 2. No significant differences between the groups were observed for both baseline examination and the 12-month control. Intragroup analysis revealed that in all treatment protocols PAI score decreased significantly ($p < 0.001$). An improvement in the PAI score was found in all patients except for three cases (15%) in the CH-GP group. Successful healing (PAI ≤ 2) was observed in 73.7%, 60%, 68.4%, and 65% of cases in groups CH-paste, CH-GP, CHX-gel and CHX-GP, respectively ($p = 0.832$).

Influence of other selected variables on treatment outcome in the total material is presented in Table 3. The only factor that showed a positive favorable influence on radiographic healing was the existence of a preoperative periapical lesion smaller than 5 mm ($p = 0.001$).

Table 1. Demographic characteristics of study population, tooth type, and dental arch by group

Intracanal medicament form	n	Age mean ± SD	Male n (%)	Female n (%)	Tooth type			Dental arch	
					incisor n (%)	canine n (%)	premolar n (%)	maxilla n (%)	mandible n (%)
CH-paste	19	39.58 ± 10.96	7 (36.8)	12 (63.2)	9 (47.4)	4 (21)	6 (31.6)	12 (63.2)	7 (36.8)
CH-GP	20	37.55 ± 17.86	5 (25)	15 (75)	13 (65)	2 (10)	5 (25)	10 (50)	10 (50)
CHX-gel	19	39.53 ± 17.32	6 (31.6)	13 (68.4)	10 (52.6)	3 (15.8)	6 (31.6)	14 (73.7)	5 (26.3)
CHX-GP	20	34.65 ± 11.12	9 (45)	11 (55)	9 (45)	2 (10)	9 (45)	14 (70)	6 (30)
Total	78	37.78 ± 14.56	27 (34.6)	51 (65.4)	41 (52.6)	11 (14.1)	26 (33.3)	50 (64.1)	28 (35.9)
p		0.692	0.596		0.765			0.424	

CH-paste – calcium hydroxide paste; CH-GP – calcium hydroxide gutta-percha points; CHX-gel – chlorhexidine gel; CHX-GP – chlorhexidine gutta-percha points

Table 2. Periapical status according to Periapical Index (PAI) before and after a 12-month follow-up for each group

PAI	Before treatment				12-month control				p
	CH-paste n = 20	CH-GP n = 20	CHX-gel n = 20	CHX-GP n = 20	CH-paste n = 19	CH-GP n = 20	CHX-gel n = 19	CHX-GP n = 20	
1	0	0	0	0	12	8	10	10	< 0.001
2	0	0	0	0	2	4	3	3	< 0.001
3	3	2	4	5	5	4	5	7	< 0.001
4	13	12	10	11	0	3	1	0	< 0.001
5	4	6	6	4	0	1	0	0	< 0.001
p	0.681				0.434				

CH-paste – calcium hydroxide paste; CH-GP – calcium hydroxide gutta-percha points; CHX-gel – chlorhexidine gel; CHX-GP – chlorhexidine gutta-percha points

Table 3. Bivariate association between selected variables and success rate (PAI ≤ 2) in total sample

Variables	n	Success (PAI ≤ 2) n (%)	p
Age (years)			
< 38	46	30 (65.2)	0.810
≥ 38	32	22 (68.8)	
Sex			
Female	51	33 (64.7)	0.801
Male	27	19 (70.4)	
Tooth type			
Anteriors	52	32 (61.5)	0.210
Premolars	26	20 (76.9)	
Tooth location			
Maxilla	50	30 (60)	0.134
Mandible	28	22 (78.6)	
Size of lesion (mm)			
< 5	62	47 (77)	0.001
≥ 5	26	14 (23)	
Root-filling*			
Acceptable	64	46 (71.9)	0.058
Unacceptable	14	6 (42.9)	

n – number of teeth;

*Acceptable filling – the filling ends 0–2 mm short of the radiographic apex with no voids visible within the material or between the material and the root canal walls; unacceptable filling – the filing material ends more than 2 mm from the radiographic apex or extruded beyond the apex and/or visible voids within or between the material and the root canal walls

DISCUSSION

In this study, clinical and radiographic parameters of apical periodontitis healing were evaluated concerning different form of intracanal medicaments, paste and gutta-percha points for CH, and gel and gutta-percha points for CHX. To the best of our knowledge, this is the first clinical study assessing the effect of these points on periapical healing. All types of medicaments resulted in similar periapical healing patterns.

In the present study, the patients were randomly assigned to treatment groups and no significant difference was found between them in terms of preoperative factors (age, sex, tooth type, dental arch, and PAI score at baseline). Root canal treatment was performed according to a standardized protocol by one experienced endodontist, representing specialty practice settings. Since clinical success of treatment was observed in all the patients, overall outcome was classified according to radiographic evaluation. Limited diagnostic ability of periapical radiography has been well reported on. It has been shown that cone-beam computed tomographic imaging is more accurate than radiography for identifying periapical lesions. However, periapical radiography has been used in almost all endodontic outcome studies so far and has been adopted as a standard of practice. In addition, cone-beam computed tomographic is not recommended for routine diagnosis of periapical pathosis and the assessment of the root canal treatment outcome [20]. The applied criteria for treatment outcome were based on those suggested by Ørstavik et al. [18] accepted as a valid and reliable tool for measuring radiographic changes in apical bone density. The variability in radiographic reading is well recognized due to subjectivity of radiographic assessment. To overcome this shortcoming radiographic evaluation in our study was performed by two examiners with a substantial level of intra- and inter-examiner agreement. One-year observation period for radiological outcome in this study was chosen as most of the teeth with preoperative apical periodontitis heal during the first year after treatment [21, 22].

All treatment protocols led to significant decrease in PAI scores. About 73.7% of teeth could be judged as healed in the CH-paste group, 60% in the CH-GP, 68.4% in the CHX-gel, and 64% in the CHX-GP group. The healing rate observed in the CH-paste group corroborates the results of previous studies in which the calcium hydroxide has been used for intracanal medication of teeth with apical periodontitis [21, 22, 23]. Concerning CHX, the only available clinical report showed a healing rate of 94% in two to four years of follow-up after treatment with 2% CHX in the form of liquid, a rate much higher than for CHX in our study [24]. Disagreement with our findings may be due to difference in chemomechanical preparation, delivery system used for medication, and the time frame for outcome observation. However, if a decrease in PAI score was used as a favorable outcome, the number of healed teeth in our study would concur well with that obtained by the mentioned study [24].

Calcium hydroxide was used as a dressing material in most studies dealing with treatment outcome, with very few exceptions [23]. There are only a few studies which demonstrated that the type of intracanal medicaments significantly influence the outcome. The use of calcium hydroxide medicament resulted in better treatment outcome than no dressing or the one containing corticosteroids [20, 25]. In the present study, the outcome of endodontic therapy of teeth with apical periodontitis did not significantly differ between the groups. Thus, from the clinical point of view, the healing pattern seems largely unrelated

to the type and delivery system of intracanal medicament used, suggesting that both CH- and CHX-based medicaments can be used in therapy of primary chronic apical periodontitis. However, there was a tendency toward more favorable outcome in teeth medicated with CH-paste (75%) in comparison with CH-GP (60%). Considering the facts that both CH formulations placed in root canal for 15 days showed similar efficacy in periapical healing, and that CH-GP contain more than two times as much CH than CH-paste (58% vs. 23%), it can be assumed that bioavailability of CH in CH-GP is lower. Accordingly, release kinetics of calcium and hydroxyl ions from CH-GP was lower than that of other form of CH [12, 26, 27]. In addition, CH-GP presented short-term alkalinity and minor antimicrobial activity in comparison to CH-paste [9, 10, 11, 28]. In contrast to CH, CHX by itself possess significant pharmacokinetics characteristics, adsorption on oral mucosa and the microbial cell wall (antimicrobial substantivity), which enable its long-lasting antibacterial effect. Some authors found that CHX gel seemed to be more effective than CHX-GP in the reduction of bacterial counts in situ and in the inhibition of bacterial colonization of the dentin in vitro [5, 29]. Comparing mentioned in vitro and in situ findings considering only bacterial effectiveness with our results concerning outcomes obtained from clinical settings gel of 2% CHX and gutta-percha points of 5% CHX showing similar rate of periapical healing, it could be suggested that in clinical settings there are no differences between investigated CHX delivery systems in their bioavailability. Considering the influence of medicated gutta-percha points on periapical tissue healing, there is only data about CH-GP, mainly from clinical case series showing CH-GP to be very successful in treating teeth with persistent periapical inflammation [14]. Moreover, Bezgin et al. [16] found acceptable results in apexification treatment using CH-GP and recommended these points as an apexification agent in cases where CH apexification is indicated. However, direct comparison of the present study with studies mentioned above concerning healing outcome is difficult to make, due to differences in the study population, diagnosis, and the treatment protocol. Further studies, including larger sample sizes, are needed to elucidate clinical effectiveness of medicated gutta-percha points on periapical healing.

In this study we also analyzed possible influence of other variables on treatment outcome. For the total material, only the size of the periapical lesion had significant impact. Teeth with a preoperative lesion greater than 5 mm had lower healing rate than teeth with smaller lesions. Having in mind that the healing process is a function of time, a favorable outcome of a smaller-sized lesion should be applicable to a larger-sized lesion if sufficient time was allowed for healing to take place [30].

CONCLUSION

Under the conditions of this study, there are no differences between investigated CH- and CHX-delivery systems regarding treatment outcome of teeth with apical periodontitis. Definitive conclusions about the influence of the type of intracanal medicament on periapical healing cannot be drawn and further randomized controlled trials to identify the most appropriate medication regime (type and method) are needed.

REFERENCES

1. Sjögren U, Figdor D, Persson S, Sundqvist G. Influence of infection at the time of root filling on the outcome of endodontic treatment of teeth with apical periodontitis. Int Endod J. 1997; 30(5):297–306.
2. Paiva SS, Siqueira JF Jr, Rôças IN, Carmo FL, Leite DC, Ferreira DC, et al. Molecular microbiological evaluation of passive ultrasonic activation as a supplementary disinfecting step: a clinical study. J Endod. 2013; 39(2):190–4.
3. Siqueira JF Jr, Lopes HP. Mechanisms of antimicrobial activity of calcium hydroxide: a critical review. Int Endod J. 1999; 32(5):361–9.
4. Ercan E, Dalli M, Dülgergil CT. In vitro assessment of the effectiveness of chlorhexidine gel and calcium hydroxide paste with chlorhexidine against *Enterococcus faecalis* and *Candida albicans*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006; 102(2):e27–31.
5. Barthel CR, Zimmer S, Zilliges S, Schiller R, Göbel UB, Roulet JF. In situ antimicrobial effectiveness of chlorhexidine and calcium hydroxide: gel and paste versus gutta-percha points. J Endod. 2002; 28(6):427–30.
6. Podbielski A, Spahr A, Haller B. Additive antimicrobial activity of calcium hydroxide and chlorhexidine on common endodontic bacterial pathogens. J Endod. 2003; 29(5):340–5.
7. Ebert J, Roggendorf MJ, Frank K, Petschelt A. Antimicrobial activity of various 'active' gutta-percha points against *Enterococcus faecalis* in simulated root canals. Int Endod J. 2008; 41(3):249–57.
8. de Lucena JM, Decker EM, Walter C, Boeira LS, Löst C, Weiger R. Antimicrobial effectiveness of intracanal medicaments on *Enterococcus faecalis*: chlorhexidine versus octenidine. Int Endod J. 2013; 46(1):53–61.
9. Atila-Pektaş B, Yurdakul P, Gülmez D, Görduysus O. Antimicrobial effects of root canal medicaments against *Enterococcus faecalis* and *Streptococcus mutans*. Int Endod J. 2013; 46(59):413–8.
10. Jhamb A, Chaurasia VR, Masamatti VK, Agarwal JH, Tiwari S, Nair D. In vitro evaluation of antimicrobial activity of different gutta-percha points and calcium hydroxide pastes. J Int Soc Prev Community Dent. 2014; 4(2):92–5.
11. Gupta SP, Bhati M, Jhajharia K, Patel H, Paliwal A, Franklin S. Evaluation of antimicrobial and antifungal efficacy of inter appointment intracanal medicaments against *Enterococcus* and *Candida albicans*: an in vitro study. J Int Oral Health. 2015; 7(6):97–102.
12. Sirén EK, Kerosou E, Lavonius E, Meurman JH, Haapasalo M. $Ca(OH)_2$ application modes: in vitro alkalinity and clinical effect on bacteria. Int Endod J. 2014; 47(7):628–38.
13. Stojanović N, Krunić J, Popović B, Stojičić S, Živković S. Prevalence of *Enterococcus faecalis* and *Porphyromonas gingivalis* in infected root canals and their susceptibility to endodontic treatment procedures: a molecular study. Srp Arh Celok Lek. 2014; 142(9-10):535–41.
14. Hedge MN, Niaz F. Case reports on the clinical use of calcium hydroxide points as an intracanal medicament. Endodontology. 2006; 18:23–7.
15. Oktem ZB, Cetinbaş T, Ozer L, Sönmez H. Treatment of aggressive external root resorption with calcium hydroxide medicaments: a case report. Dent Traumatol. 2009; 25(5):527–31.
16. Bezgin T, Sönmez H, Orhan K, Ozalp N. Comparative evaluation of $Ca(OH)_2$ plus points and $Ca(OH)_2$ paste in apexification. Dent Traumatol. 2012; 28(6):488–95.
17. Zhong B. How to calculate sample size in randomized controlled trial? J Thorac Dis. 2009; 1(1):51–4.
18. Ørstavik D, Kerekes K, Eriksen HM. The periapical index: a scoring system for radiographic assessment of apical periodontitis. Endod Dent Traumatol. 1986; 2(1):20–34.

19. Ng Y, Spratt D, Skriskantharajah S, Gulabivala K. Evaluation of protocols for field decontamination before bacterial sampling of root canals for temporary microbiology techniques. J Endod. 2003; 29(5):317–20.
20. European Society of Endodontology, Patel S, Durack C, Abella F, Roig M, Shemesh H, et al. European Society of Endodontology position statement: the use of CBCT in endodontics. Int Endod J. 2014; 47(6):502–4.
21. Trope M, Delano EO, Orstavik D. Endodontic treatment of teeth with apical periodontitis: single vs. multivisit treatment. J Endod. 1999; 25(5):345–50.
22. Manfredi M, Figini L, Gagliani M, Lodi G. Single versus multiple visits for endodontic treatment of permanent teeth. Cochrane Database Syst Rev. 2016; 12:CD005296.
23. Wong AW, Tsang CS, Zhang S, Li KY, Zhang C, Chu CH. Treatment outcomes of single-visit versus multiple-visit non-surgical endodontic therapy: a randomised clinical trial. BMC Oral Health. 2015; 15:162.
24. Tervit C, Paquette L, Torneck CD, Basrani B, Friedman S. Proportion of healed teeth with apical periodontitis medicated with two percent chlorhexidine gluconate liquid: a case-series study. J Endod. 2009; 35(9):1182–5.
25. Cheung GS. Survival of first-time nonsurgical root canal treatment performed in a dental teaching hospital. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002; 93(5):596–604.
26. Azabal-Arroyo M, Menasalvas-Ruiz G, Martín-Alonso J, Arroquia JJ, Vega-del Barrio JM. Loss of hydroxyl ions from gutta-percha points with calcium hydroxide in their composition: an in vivo study. J Endod. 2002; 28(10):697–8.
27. Ardeshna SM, Qualtrough AJ, Worthington HV. An in vitro comparison of pH changes in root dentine following canal dressing with calcium hydroxide points and a conventional calcium hydroxide paste. Int Endod J. 2002; 35(3):239–44.
28. Ho CH, Khoo A, Tan R, Teh J, Lim KC, Sae-Lim V. pH changes in root dentin after intracanal placement of improved calcium hydroxide containing gutta-percha points. J Endod. 2003; 29(1):4–8.
29. Lenet BJ, Komorowski R, Wu XY, Huang J, Grad H, Lawrence HP, et al. Antimicrobial substantivity of bovine root dentin exposed to different chlorhexidine delivery vehicles. J Endod. 2000; 26(11):652–5.
30. Zhang MM, Liang YH, Gao XJ, Jiang L, van der Sluis L, Wu MK. Management of apical periodontitis: healing of post-treatment periapical lesions present 1 year after endodontic treatment. J Endod. 2015; 41(7):1020–5.

Утицај различитих облика калцијум-хидроксида и хлорхексидина као интерсеансних медикамената на исход ендодонтског лечења зуба са хроничним периапексним лезијама

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САЖЕТАК

Увод/Циљ Циљ овог истраживања је био да се испита клинички и радиографски исход лечења зуба са апексним периодонтитисом 12 месеци после завршене терапије и примене различитих облика калцијум-хидроксида (КХ): паста (КХ-паста) и гутаперка поени (КХ-ГП) и хлорхексидина (ХХ): гел (ХХ-гел) и гутаперка поени (ХХ-ГП).

Методе Рандомизовано је 80 испитаника са хроничним периапексним лезијама у четири групе на основу врсте коришћеног интерсеансног медикамента: КХ-паста, КХ-ГП, ХХ-гел и ХХ-ГП. Дванаест месеци после завршеног лечења прегледано је 78 испитаника и урађени су ретроалвеоларни снимци. За процену радиографског успеха лечења коришћен је периапикални индекс (ПИ).

Резултати Исход лечења је класификован на основу радиолошког налаза јер је код свих испитаника забележен клинички успех лечења. У свим испитиваним групама је забележено значајно смањење вредности ПИ ($p < 0,001$). Излечење (ПИ ≤ 2) уочено је код 73,3% зуба у групи КХ-паста, 60% у КХ-ГП групи, 68,4% у групи ХХ-гел и код 65% зуба у групи ХХ-ГП, при чему разлике између група нису биле статистички значајне.

Закључак Резултати овог истраживања показују да не постоји разлика у исходу лечења зуба са апексним периодонтитисом после примене испитиваних облика КХ и ХХ.

Кључне речи: калцијум-хидроксид; хлорхексидин; периапексно обољење; ендодонтски третман; исход лечења

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Effects of three types of functional appliances in Class II malocclusion treatment – sagittal and vertical changes

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SUMMARY

Introduction/Objective Class II malocclusions are sagittal malocclusions characterized by a distal relationship of posterior teeth. Depending on the underlying problem, Class II malocclusions can be skeletal or dentoalveolar. Class II malocclusion treatment modality will depend on the cause, severity, and age. Growth modification is the best treatment option in growing patients with skeletal Class II malocclusions. The aim of this study was to establish and compare sagittal and vertical skeletal and dental changes in patients treated with the "M block" appliance, the Fränkel functional regulator, and the Balters' bionator.

Methods The sample consisted of 70 patients diagnosed with skeletal Class II malocclusions (ANB > 4°) and mandibular retrognathism (SNB < 80°). The patients were divided into three groups according to the type of appliance. All the patients went through the standard diagnostic procedure (anamnesis, clinical and functional analysis, study model, panoramic radiograph, and cephalometric analysis), and dental and skeletal age was determined. Treatment effects were analyzed on study models and cephalograms at the end of treatment.

Results All the appliances led to significant mandibular anterior movement and sagittal growth, which reduced the ANB values. All three groups of patients presented with neutral growth pattern, upper incisor retrusion, and lower incisor protrusion at the end of treatment.

Conclusion The results of this study indicate efficacy of all three appliances in skeletal Class II malocclusion treatment.

Keywords: class II malocclusion; functional treatment; M block appliance; Fränkel appliance; bionator

INTRODUCTION

Class II malocclusions are sagittal malocclusions characterized by a distal relationship of posterior teeth. Depending on the underlying problem, Class II malocclusions can be skeletal or dentoalveolar. Skeletal Class II malocclusions are characterized by a distal maxillo-mandibular relationship. This could be a consequence of mandibular retrognathism and/or underdeveloped mandible, maxillary prognathism and/or overdeveloped maxilla, or a combination of the two [1, 2]. Depending on the cause of the malocclusion, Class II can be treated by growth modification, dental camouflage, or orthodontic-surgical treatment. Whenever there is a skeletal discrepancy, best treatment option would be growth modification. However, this treatment modality could be used only if the patient is still growing [3, 4]. Growth modification treatment uses the patient's residual growth in order to change jaw dimensions and position and establish proper occlusion. Ideal timing for this kind of treatment would be just before the pubertal growth spurt. Removable functional appliances are the most commonly used appliances in children and late-mixed dentition adolescents. Fixed functional appliances are commonly used in adolescents and permanent dentition post-adolescents, due to limited effects of removable appliances and lack of compliance [4].

Growth modifying functional appliances facilitate change in the activity of different groups of muscles by delivering forces to the jaws and teeth, therefore affecting their function and position [5]. Most commonly used functional appliances are Andresen activator, twin block appliance, Sander's bite-jumping appliance, Fränkel functional regulator, Balters' bionator, etc. A modification of the Sander's bite-jumping appliance made with the Schaneng screw (Dentaurum GmbH & Co. KG, Ispringen, Germany) instead of the Sander's functional screw (Forestadent Bernhard Förster GmbH, Pforzheim, Germany) has been successfully used at the Department of Orthodontics, Faculty of Dental Medicine, University of Belgrade, for over a decade. This appliance, also known locally (in Serbia) by the name "M block" appliance, consists of an upper and lower removable appliance. An expansion screw and the Schaneng functional screw are built into the upper appliance. The lower appliance contains an inclined plane that guides the functional screw and directs the mandible forward. The M block appliance (Figure 1) is built according to the design suggested by Sander for his bite-jumping appliance [6, 7].

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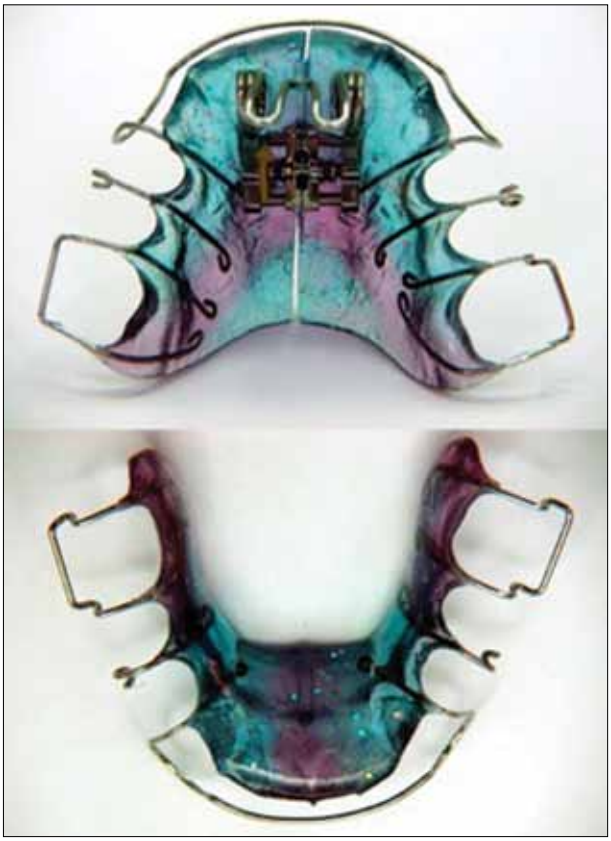

Figure 1. M block appliance

The aim of this study was to establish and compare sagittal and vertical skeletal and dental changes in patients treated with the M block appliance, the Fränkel functional regulator (Figure 2) and the Balters' bionator (Figure 3).

Figure 2. Fränkel functional regulator type I

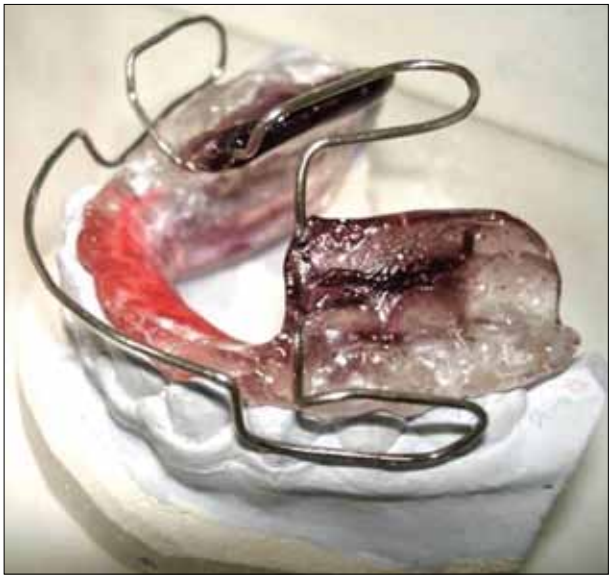

Figure 3. Balters' bionator type I

METHODS

The sample of this study consisted of 70 patients treated at the Department of Orthodontics of the Faculty of Dental Medicine, University of Belgrade. Inclusion criteria were skeletal distal bite (ANB > 4°), mandibular retrognathism (SNB < 80°), no previous orthodontic treatment, and appropriate age (prepubertal growth spurt).

According to the type of appliance used in treatment, subjects were divided into three groups: Group I: patients treated with the M block appliance (30 subjects); Group II: patients treated with the Fränkel functional regulator type I (20 subjects); Group III: patients treated with the Balters' bionator type I (20 subjects).

All three appliances are indicated for treating growing patients diagnosed with skeletal distal bite and mandibular retrognathism.

Standard diagnostic procedure was performed, which included anamnesis, clinical and functional examination, study model analysis, panoramic radiograph analysis, and cephalometric analysis. Dental age was estimated according to the method developed by Demirjian et al. [8]. Skeletal age was determined using the modified Cervical Vertebral Maturation method described by Baccetti et al. [9]. According to age assessment, all patients were in the pre-pubertal growth spurt period, which is a crucial prerequisite for functional orthodontic treatment. The average chronological age of patients before the beginning of treatment was 10 years and one month, and the average dental age was nine years and five months. Skeletal age analysis of pretreatment records revealed the following data: in Group I, three patients were in stage 1 (10%), 22 patients in stage 2 (73%), and five patients in stage 3 (17%); in Group II, nine patients were in stage 1 (45%), seven patients in stage 2 (35%), and four patients in stage 3 (20%); in Group III, four patients were in stage 1 (20%), nine patients in stage 2 (45%), and seven patients in stage 3 (35%). The average treatment time was 15 months in Group I, 20 months in Group II and 22 months in Group III. The patients' age, treatment time, and sex distribution are shown in Table 1.

Cephalometric analysis

The following cephalometric parameters were used: I sagittal parameters (angles): SNA – sagittal position of the maxilla; SNB – sagittal position of the mandible; SNPg – sagittal position of the chin; ANB – sagittal maxillo-mandibular relationship; II maxillary and mandibular development parameters (linear distances): Snp to A' – length of the maxil-

lary corpus (C max); Go' to Pg' – length of the mandibular corpus (C mand); Cd' to Go' – length of the mandibular ramus (R mand); Cd to Me – total mandibular length (Mand); III vertical parameters (angles): SN/SpP – vertical position of the maxilla; SN/MP – vertical position of the mandible; SpP/MP – vertical maxillo-mandibular relationship; IV type of growth: Bjork polygon (Σ = NSAr + SArGo + ArGoMe); anterior to posterior facial height relation (S-Go/N-Me × 100); V incisor position (angles): I/SpP – upper incisor inclination; i/MP – lower incisor inclination.

All appliances (M block, Fränkel functional regulator type I, and Balters' bionator type I) were made according to standard principles previously described in the literature [10]. Therapeutic effects of these appliances and consequential changes were recorded on study models and cephalograms at the end of treatment.

Statistical analysis

Mean values, standard deviations, minimal and maximal values were calculated as a part of descriptive statistics. Statistical analysis included two-factor analysis of the variance with repeated measuring, where the measuring was done in relation to the factor time and the time and group allocation factor. Monofactorial variance analysis was done using the ANOVA, Boneferroni, and Student's t-test for determining the statistical significance of acquired differences.

This research was approved by the Ethics Committee of the Faculty of Dental Medicine, University of Belgrade (resolution number 36/6 issued on March 21, 2012).

RESULTS

I Sagittal parameters

The SNA angle decreased slightly after the M block appliance and Fränkel functional regulator treatment, and increased significantly after bionator treatment. Two-factor analysis of the variance with repeated measuring was used to evaluate the treatment effect of three different functional appliances on the sagittal position of the maxilla in two different time periods (the beginning and the end of treatment) and it was established that there were no statistically significant changes in pre- and post-treatment values. However, statistically significant changes appeared when all three appliances were compared. The SNB angle increased significantly in all three groups of patients. Two-factor analysis of the variance with repeated measuring revealed the influence of time on the SNB value changes within groups. A statistically significant difference was also noted when comparing all three appliances over time. The SNPg angle also increased significantly after treatment in all three groups. Two-factor analysis of the variance with repeated measuring showed the influence of time on the value changes before and after treatment, as well as between groups over time (Table 2). The ANB angle decreased significantly in all three groups. Statistically significant differences were noted in the pre-treatment values of parameters between Group I and Group II and in the post-treatment values of parameters between Group I and Group II, and Group II and Group III (Table 3).

Table 1. Age, treatment time, and sex distribution

Parameter	Mean age (years, months)		Skeletal age	Treatment time (months)	Sex	
	chronological	dental			♂	♀
M block n = 30	10 y 4 m	9 y 8 m	Stage 1 (10%) Stage 2 (73%) Stage 3 (17%)	15	13	17
Fränkel n = 20	8 y 8 m	9 y 2 m	Stage 1 (45%) Stage 2 (35%) Stage 3 (20%)	20	10	10
Bionator n = 20	10 y 7 m	9 y 3 m	Stage 1 (20%) Stage 2 (45%) Stage 3 (35%)	22	9	11

Table 2. Values and statistical significance of changes – sagittal parameters SNA, SNB, and SNPg

Parameter	T1 x ± SD	T2 x ± SD	Δ (T2 - T1) x ± SD	Significance[a] (difference between groups at T1)	Significance[a] (difference between groups at T2)	Significance[b/c]	Significance[d]
SNA (°)				p			
M block n = 30	81.72 ± 2.97	81.63 ± 3.45	-0.08 ± 1.26	0.876	0.357	[b]0.075 [c]0.005*	0.720
Fränkel n = 20	81.4 ± 2.52	81.25 ± 2.49	-0.15 ± 1.14				0.562
Bionator n = 20	81.35 ± 2.66	82.55 ± 2.48	1.20 ± 1.96				0.013*
SNB (°)							
M block n = 30	76.35 ± 3.22	77.48 ± 3.13	1.13 ± 1.40	0.148	0.971	[b]0.000* [c]0.000*	0.000*
Fränkel n = 20	74.7 ± 2.56	77.65 ± 2.46	2.95 ± 1.05				0.000*
Bionator n = 20	75.5 ± 2.72	77.65 ± 2.68	2.15 ± 1.34				0.000*
SNPg (°)							
M block n = 30	77.6 ± 2.79	78.56 ± 2.86	0.96 ± 0.99	0.250	0.857	[b]0.000* [c]0.001*	0.000*
Fränkel n = 20	76.5 ± 2.44	78.55 ± 2.64	2.05 ± 0.99				0.000*
Bionator n = 20	76.5 ± 2.84	78.15 ± 2.70	1.65 ± 0.87				0.000*

*statistically significant difference; [a]monofactorial variance analysis; [b]two-factor analysis of the variance, factor time; [c]two-factor analysis of the variance, factor time * group; [d]t-test for paired samples

Table 3. Values and statistical significance of changes – sagittal parameter ANB

ANB (°)	T1	T2	Significance[a] (difference between groups at T1)	Significance[a] (difference between groups at T2)	Significance[b] (difference between groups at T1)	Significance[b] (difference between groups at T2)	Significance[c] (difference within groups T1 and T2)
M block n = 30	5.5 ± 0.81	4.38 ± 1.11	0.005*	0.002*	0.001* M vs. F	0.005* M vs. F	0.000*
Fränkel n = 20	6.6 ± 1.35	3.6 ± 1.23			0.114 M vs. B	0.154 M vs. B	0.000*
Bionator n = 20	5.9 ± 1.07	4.9 ± 1.23			0.086 F vs. B	0.002* F vs. B	0.004*

*statistically significant difference; [a]Kruskal–Wallis test; [b]Mann–Whitney test; [c]Wilcoxon matched pairs test

Table 4. Values and statistical significance of maxillary and mandibular development parameters

Parameter	T1	T2	Δ (T2 - T1)	Significance[a] (difference between groups at T1)	Significance[a] (difference between groups at T2)	Significance[b/c]	Significance[d]
C max (mm)							
M block n = 30	48.57 ± 3.28	49.80 ± 3.13	1.23 ± 0.72	0.596	0.100	[b]0.000* [c]0.011*	0.000*
Fränkel n = 20	49.30 ± 2.34	50.80 ± 2.39	1.50 ± 1.36				0.000*
Bionator n = 20	49.23 ± 2.50	51.60 ± 2.98	2.37 ± 1.83				0.000*
C mand (mm)							
M block n = 30	70.33 ± 5.37	72.02 ± 5.23	1.69 ± 0.85	0.829	0.690	[b]0.000* [c]0.168	0.000*
Fränkel n = 20	71.23 ± 5.32	73.20 ± 4.72	1.97 ± 1.40				0.000*
Bionator n = 20	71.08 ± 6.09	72.05 ± 5.35	0.97 ± 2.69				0.122
R mand (mm)							
M block n = 30	55.77 ± 3.63	57.50 ± 3.88	1.73 ± 0.93	0.515	0.537	[b]0.000* [c]0.796	0.000*
Fränkel n = 20	55.10 ± 4.08	56.55 ± 3.43	1.45 ± 2.96				0.041*
Bionator n = 20	54.47 ± 4.09	56.45 ± 3.71	1.98 ± 3.33				0.016*
Mand (mm)							
M block n = 30	108.02 ± 5.72	109.80 ± 5.78	1.78 ± 1.27	0.212	0.442	[b]0.000* [c]0.320	0.000*
Fränkel n = 20	105.70 ± 5.16	108.40 ± 5.11	2.70 ± 3.21				0.001*
Bionator n = 20	107.75 ± 2.72	110.50 ± 3.28	2.75 ± 3.15				0.003*

*statistically significant difference; [a]monofactorial variance analysis; [b]two-factor analysis of the variance, factor time; [c]two-factor analysis of the variance, factor time * group; [d]t-test for paired samples

II Maxillary and mandibular development parameters

Maxillary corpus length increased significantly after treatment in all three groups. Two-factor analysis of the variance with repeated measuring established a statistically significant change in the pre- and post-treatment values of the maxillary corpus length. Statistically significant changes were also noted when comparing all three groups of treated patients. Mandibular corpus increased significantly after M block appliance and Fränkel functional regulator treatment, while an insignificant change was established after bionator treatment. Two-factor analysis of the variance with repeated measuring revealed statistically significant influence of mandibular corpus length change within groups over time. Mandibular ramus height increased significantly in all three groups of patients. Two-factor variance analysis with repeated measuring revealed the influence of mandibular ramus length value changes within groups over time. Total mandibular length increased statistically in all three groups. Two-factor analysis of the variance with repeated measuring showed a statistically significant influence of total mandibular length change within groups before and after treatment (Table 4).

III Vertical parameters

The SN/SpP angle increased significantly after M block appliance treatment, and insignificantly after Fränkel functional regulator and bionator treatment. Two-factor analysis of the variance with repeated measuring established a statistically significant difference in value changes before and after treatment, and a lack of significance when comparing all three groups before and after treatment. The SN/MP angle decreased insignificantly in group II, while it increased significantly in groups I and III. Monofactorial variance analysis revealed statistically significant differences between groups I and III before treatment. Statistically significant differences were also noted when comparing groups after treatment. Two-factor analysis of the variance with repeated measuring established a statistically significant influence of value changes before and after treatment, as well as between groups over time. Fränkel functional regulator treatment resulted in a decrease of the SpP/MP angle, while the M block and bionator treatment resulted in an increase of the same angle. Statistically significant changes were present when comparing post-treatment values between groups, while comparing groups in pairs lacked significance. Two-factor analysis of the variance with repeated measuring revealed statistically significant differences between groups over time (Table 5).

IV Type of growth parameters

The sum of the Björk polygon angles increased in all groups, the bionator group lacking statistical significance. Two-factor analysis of the variance with repeated measuring recognized the influence of all three types of appliances on the increase at two points in time (before and after treatment). There was no significant interaction between the type of appliance and time, while a significant influence of time (before and after treatment) was confirmed in patients within each group. The percentage of the anterior to posterior facial height relation decreased, but none of the appliances caused any statistically significant differences in the pre- and post-treatment values (Table 6).

V Incisor position

Upper incisors were uprighted significantly after treatment in all three groups. Monofactorial variance analysis revealed statistically significant changes in the I/SpP angle after treatment, as well as between groups over time. Lower incisors were proclined significantly after M block and Fränkel functional regulator treatment, while the bionator group lacked statistical significance. Monofactorial vari-

Table 5. Values and statistical significance of vertical parameters SN/SpP, SN/MP, SpP/MP

Parameter	T1 x ± SD	T2 x ± SD	Δ (T2 - T1) x ± SD	Significance[a] (difference between groups at T1)	Significance[a] (difference between groups at T2)	Significance[b/c]	Significance[d]	Significance[e] (difference between groups at T1)	Significance[e] (difference between groups at T2)
SN/SpP (°)									
M block n = 30	8.25 ± 4.39	9.10 ± 4.92	0.85 ± 1.32	0.567	0.704	[b]0.001* [c]0.616	0.001*		
Fränkel n = 20	8.90 ± 2.12	9.30 ± 2.13	0.40 ±1 .90				0.359		
Bionator n = 20	9.30 ± 3.03	10.00 ± 2.96	0.70 ± 1.59				0.064		
SN/MP (°)									
M block n = 30	31.60 ± 5.56	32.50 ± 6.10	0.90 ± 2.20	0.021*	0.004*	[b]0.033* [c]0.005*	0.033*	0.437 M vs. F	1.00 M vs. F
Fränkel n = 20	33.85 ± 4.97	33.08 ± 5.31	-0.77 ± 2.29				0.261	0.018* M vs. B	0.005* M vs.B
Bionator n = 20	35.95 ± 5.19	37.85 ± 5.16	1.90 ± 2.53				0.003*	0.642 F vs. B	0.027* F vs. B
SpP/MP(°)									
M block n = 30	26.58 ± 5.12	27.17 ± 4.79	0.59 ± 1.96	0.608	0.039*	[b]0.505 [c]0.017*	0.115		0.10 M vs. F
Fränkel n = 20	25.10 ± 5.61	23.90 ± 5.07	-1.20 ± 3.03				0.930		1.00 M vs. B
Bionator n = 20	26.55 ± 6.10	27.85 ± 5.91	1.30 ± 3.51				0.114		0.058 F vs. B

*statistically significant difference; [a]monofactorial variance analysis; [b]two-factor analysis of the variance, factor time; [c]two-factor analysis of the variance, factor time * group; [d]t-test for paired samples; [e]Bonferroni test

Table 6. Values and statistical significance of the type of facial growth parameters

Parameter	T1 x ± SD	T2 x ± SD	Δ (T2 - T1) x ± SD	Significance[a] (difference between groups at T1)	Significance[a] (difference between groups at T2)	Significance[b/c]	Significance[d]
Σ Bjørk (°)							
M block n = 30	393.50 ± 4.68	395.80 ± 3.39	2.30 ± 3.51	0.733	0.901	[b]0.000* [c]0.313	0.001*
Fränkel n = 20	393.55 ± 5.34	395.70 ± 4.17	2.15 ± 2.66				0.002*
Bionator n = 20	394.60 ± 5.67	395.35 ± 2.72	0.75 ± 4.66				0.481
S-Go/N-Me × 100 (%)							
M block n = 30	65.05 ± 3.78	65.14 ± 3.50	0.09 ± 1.34	0.590	0.384	[b]0.441 [c]0.656	0.711
Fränkel n = 20	65.31 ± 3.17	65.05 ± 3.07	-0.26 ± 1.70				0.505
Bionator n = 20	64.15 ± 4.28	63.83 ± 3.77	-0.32 ± 2.23				0.524

*statistically significant difference; [a]monofactorial variance analysis; [b]two-factor analysis of the variance, factor time; [c]two-factor analysis of the variance, factor time * group; [d]t-test for paired samples

Table 7. Values and statistical significance of the incisor position parameters

Parameter	T1 x ± SD	T2 x ± SD	Δ (T2 - T1) x ± SD	Significance[a] (difference between groups T1)	Significance[a] (difference between groups T2)	Significance[b/c]	Significance[d]	Significance[e] (difference between groups T1)	Significance[e] (difference between groups T2)
I/SpP (°)									
M block n = 30	66.83 ± 4.13	71.33 ± 3.71	4.50 ± 2.27	0.006*	0.904	[b]0.000* [c]0.000*	0.000*	0.008* M vs. F	
Fränkel n = 20	70.10 ± 2.98	70.90 ± 3.07	0.80 ± 1.23				0.009*	0.059 M vs. B	
Bionator n = 20	69.35 ± 3.43	71.15 ± 3.01	1.80 ± 1.23				0.000*	1.000 F vs. B	
i/MP (°)									
M block n = 30	87.15 ± 4.34	85.76 ± 3.77	-1.38 ± 1.91	0.029*	0.001*	[b]0.000* [c]0.013*	0.000*	0.041* M vs. F	0.016* M vs. F
Fränkel n = 20	89.75 ± 2.81	88.30 ± 2.53	-1.45 ± 1.27				0.000*	0.166 M vs. B	0.001* M vs. B
Bionator n = 20	89.15 ± 2.79	89.00 ± 2.17	-0.15 ± 1.23				0.591	1.000 F vs. B	1.000 F vs. B

*statistically significant difference; [a]monofactorial variance analysis; [b]two-factor analysis of the variance, factor time; [c]two-factor analysis of the variance, factor time * group; [d]t-test for paired samples; [e]Bonferroni test

ance analysis showed statistically significant differences between groups before treatment, while in post-treatment records significance appeared when comparing the M block appliance with the Fränkel functional regulator, and the M block appliance with the bionator. Two-factor analysis of the variance with repeated measuring recognized statistically significant changes in the i/MP values after treatment, as well as significant differences between groups over time (Table 7).

DISCUSSION

Growth modification treatment improves jaw relations, resulting in a positive effect on dental structures' relations. Changes that happen during the functional appliance treatment are a result of the synergy between the appliance effects and growth that would happen regardless of treatment. The aim of this study was to determine and compare sagittal and vertical changes that occurred during the M block appliance, Fränkel functional regulator type I, and Balters' bionator type I treatment. Patients diagnosed with skeletal distal bite caused by mandibular prognathism and in the prepubertal growth spurt period treated at the Department of Orthodontics, Faculty of Dental Medicine, University of Belgrade, were involved in this research. The patients were divided into three groups according to the type of appliance used: Group I treated with the M block appliance, Group II treated with the Fränkel functional regulator, and Group III treated with the Balters' bionator. This was done in order to compare the effects of different types of functional appliances used in Class II treatment.

Our results indicate an insignificant decrease in the SNA angle after M block and Fränkel functional regulator treatment, and a significant increase after bionator treatment. SNB and SNPg angles increased significantly in all three groups. All this resulted in the ANB angle decrease. Mandibular advancement with or without SNA angle decrease is a quintessential part of functional appliance treatment. As stated previously, the M block appliance construction and treatment principles are similar to those of the Sander's appliance. Sander [7] and Sander et al. [11] reported mesial mandibular movement and maxillary growth inhibition (similar to the high-pull headgear effect) as results of his bite-jumping appliance treatment and stressed that this kind of maxillary response could only be achieved with one other appliance – the Herbst appliance. A decrease in the SNA angle after bionator treatment was noted by Moreira Melo et al. [12], while Almeida et al. [13] found no differences between the bionator treated group and the control group. Almeida et al. [13] also found significant increase in the SNB angle after bionator treatment. Comparing patients treated with the Sander appliance and untreated Class II controls, Sander and Wichelhaus [6] established significant increase of the SNB angle in treated patients. Comparing the bite-jumping appliance, Fränkel functional regulator, and bionator treated patients, Sander and Lassak [14] found significantly greater skeletal effects after bite-jumping appliance treatment, which led to mesial mandibular movement, maxillary growth inhibition, and ANB angle decrease.

The fundamental question, "Do functional orthodontic appliances stimulate additional mandibular growth?" still remains unanswered. Results obtained in this study indicate an increase in the length of maxillary and mandibular bodies in all three groups, regardless of the type of appliance used. Total mandibular length increased significantly after M block and Fränkel functional regulator treatment, while the bionator group lacked significance.

In their meta-analysis from 2006, Cozza et al. [15] analyzed papers dealing with mandibular changes after functional Class II treatment. In more than half of the papers analyzed, researchers had found clinically significant mandibular growth as a result of functional appliance treatment, and this growth was significantly greater if patients were treated at an appropriate age, i.e. during the pubertal growth spurt. However, none of the randomized clinical studies established clinically significant growth as a result of functional appliance treatment. This is in line with the finding of dos Santos-Pinto et al. [16], who compared bionator treated patients with untreated controls and found significant growth in both groups, regardless of whether they were treated or not. On the other hand, Moreira Melo et al. [12] found an increase in total mandibular growth after bionator treatment, which was confirmed by Almeida et al. [13], who reported significant increase in the length of mandibular corpus and total mandibular length. Class II functional treatment using the bionator was also examined by Malta et al. [17], who found favorable skeletal and dental changes at the end of treatment, specifically significant increase in mandibular corpus length. Martina et al. [18] reported significant improvement in sagittal inter-maxillary relations after bite-jumping appliance treatment, primarily due to the actual increase in mandibular corpus length and minimal maxillary growth restriction. Freeman et al. [19] examined the effects of the Fränkel functional regulator and found the greatest long-term effects had been achieved at the level of sagittal maxillo-mandibular relations, with minimal maxillary growth inhibition. In their meta-analysis, Perillo et al. [20] analyzed studies that examined the effects of the Fränkel functional regulator. Even though the research included was very heterogeneous, all authors stressed the positive effect of the Fränkel functional regulator on mandibular growth, especially total mandibular length, clinical effect reported being minimal to moderate. Another meta-analysis by Marsico et al. [21] analyzed the therapeutic effects of the Fränkel functional regulator, bionator and several other functional appliances. All authors of included studies reported statistical significance of skeletal changes, but stated lack of their clinical significance. Even though this supports the claims that two-phase treatment has no advantages over one-phase treatment, Marsico et al. [21] stress the benefits of using functional appliances in the first phase of Class II treatment. Some of the advantages they mention are prevention of maxillary incisor trauma due to increased overjet, interception of dysfunction, psycho-social benefits for the growing child, stable dentoalveolar correction, and shorter treatment time with fixed orthodontic appliances.

Looking at vertical parameters, the results of our study indicate an increase after M block and bionator treatment, while Fränkel functional regulator resulted in insignificant clockwise rotation of the maxilla and counter-clockwise rotation of the mandible. This led to a decrease in the maxillo-mandibular vertical angle after Fränkel functional regulator, and its increase after M block and bionator treatment. The Björk–Jarabak analyses revealed neutral growth in all groups at the end of treatment.

Malta et al. [17] also found an increase in vertical dimensions after bionator treatment, while Martina et al. [18], who examined the effects of the Sander bite-jumping appliance, and Freeman et al. [19], who analyzed the Fränkel functional regulator effects, concluded the unwanted clockwise rotation of the maxilla and mandible was both clinically and statistically insignificant. The important thing to consider here is the type of facial growth and vertical parameter values before treatment. Most patients from our sample were horizontal growers according to the Björk–Jarabak analyses, so the increase of the Björk polygon sum of angles led to neutral growth at the end of treatment.

Finally, incisor position parameters in this study's sample indicate upper incisor retrusion and lower incisor protrusion in all three groups at the end of treatment. Even though it was statistically significant, upper incisor retrusion was clinically insignificant in groups treated with the Fränkel functional regulator and bionator, while it was clinically significant in the M block-treated group. Lower incisor protrusion was clinically insignificant in all three groups at the end of treatment.

In Class II, Division 1 patients, overjet is typically increased due to upper incisor protrusion [2]. Upper incisor uprighting is commonly achieved during Andresen activator, Balters' bionator, Herbst and Fränkel functional appliance treatment [4, 12, 13, 15, 22, 23, 24]. Lower incisor protrusion is always present at the end of Andresen activator, Balters' bionator, and Fränkel functional appliance treatment [12, 13, 24, 25]. Freeman et al. [19] found a significant upper incisor retrusion and a less pronounced lower incisor protrusion at the end of Fränkel functional regulator treatment, while Martina et al. [18] concluded lower incisor protrusion was both clinically and statistically insignificant at the end of Sander's bite-jumping appliance treatment.

CONCLUSION

The results of our study indicate efficiency in skeletal Class II malocclusion treatment of all three types of functional appliances (M block appliance, Fränkel functional regulator type I, and Balters' bionator type I) investigated. Owing to significant mesial positioning and mandibular sagittal growth, sagittal maxillo-mandibular angle values decreased. Upper incisor retrusion and lower incisor protrusion additionally decreased the overjet. All three types of appliances produced neutral facial growth in patients at the end of treatment. Our results indicate all three types of functional appliances are suitable for skeletal Class II malocclusion treatment of growing patients in everyday clinical practice.

NOTE

This paper is based on Dr. Vladimir Ristić's PhD thesis.

REFERENCES

1. McNamara JA, Jr., Peterson JE, Jr., Alexander RG. Three-dimensional diagnosis and management of Class II malocclusion in the mixed dentition. Semin Orthod. 1996; 2(2):114–37.
2. McNamara JA. Components of Class II Malocclusion in Children 8–10 Years of Age. Angle Orthod. 1981; 51(3):177–202.
3. Proffit WR, Fields Jr HW, Sarver DM. Contemporary orthodontics. St Louis: Mosby Elsevier; 2006.
4. Pancherz H, Ruf S. The Herbst appliance: research-based updated clinical possibilities. World J Orthod. 2000; 1(1).
5. Bishara SE. Textbook of orthodontics: St Louis: Elsevier; 2001.
6. Sander F, Wichelhaus A. Skeletal and dental changes during the use of the bite-jumping plate. A cephalometric comparison with an untreated Class-II group. Fortschr Kieferorthop. 1995; 56(3):127–39.
7. Sander F. Functional Processes when wearing a SII Appliance during the day. Journal of orofacial orthopedics = Fortschritte der Kieferorthopadie : Organ/official journal Deutsche Gesellschaft fur Kieferorthopadie. 2001; 62(4):264–74.
8. Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. Hum Biol. 1973; 45(2):211–27.
9. Baccetti T, Franchi L, McNamara JA, Jr. An improved version of the cervical vertebral maturation (CVM) method for the assessment of mandibular growth. Angle Orthod. 2002; 72(4):316–23.
10. Graber TM, Rakosi T, Petrovic AG. Dentofacial Orthopedics with Functional Appliances. St Louis: Mosby; 1997.
11. Sander F, Synodinos FN, Iglezos E, Sander M, Iglezou E, Sander C. The functional orthodontic-orthopedic VDP appliance (Vorschubdoppelplatte, Bite jumping appliance, Sander II). Literature review and typical clinical case presentation. Hellenic Orthodontic Review. 2007; 10(1).
12. Moreira Melo AC, dos Santos-Pinto A, Martins LP, Sakima MT. Orthopedic and orthodontic components of Class II, Division 1 malocclusion correction with Balters bionator: A cephalometric study with metallic implants. World J Orthod. 2003; 4(3).
13. Almeida MR, Henriques JF, Almeida RR, Almeida-Pedrin RR, Ursi W. Treatment effects produced by the bionator appliance. Comparison with an untreated Class II sample. Eur J Orthod. 2004; 26(1):65–72.
14. Sander F, Lassak C. The modification of growth with the jumping-the-bite plate compared to other functional orthodontic appliances. Fortschr Kieferorthop. 1990; 51(3):155–64.
15. Cozza P, Baccetti T, Franchi L, De Toffol L, McNamara Jr JA. Mandibular changes produced by functional appliances in Class II malocclusion: A systematic review. Am J Orthod Dentofacial Orthop. 2006; 129(5):599.e1–12.
16. dos Santos-Pinto PR, Martins LP, dos Santos-Pinto A, Gandini Júnior LG, Raveli DB, dos Santos-Pinto CCM. Mandibular growth and dentoalveolar development in the treatment of class II, division 1, malocclusion using Balters Bionator according to the skeletal maturation. Dental Press J Orthod. 2013; 18(4):43–52.
17. Malta LA, Baccetti T, Franchi L, Faltin K, Jr., McNamara JA, Jr. Long-term dentoskeletal effects and facial profile changes induced by bionator therapy. Angle Orthod. 2010; 80(1):10–7.
18. Martina R, Cioffi I, Galeotti A, Tagliaferri R, Cimino R, Michelotti A, et al. Efficacy of the Sander bite-jumping appliance in growing patients with mandibular retrusion: a randomized controlled trial. Orthod Craniofac Res. 2013; 16(2):116–26.
19. Freeman DC, McNamara Jr JA, Baccetti T, Franchi L, Fränkel C. Long-term treatment effects of the FR-2 appliance of Fränkel. Am J Orthod Dentofacial Orthop. 2009; 135(5):570.e1–6.

20. Perillo L, Cannavale R, Ferro F, Franchi L, Masucci C, Chiodini P, et al. Meta-analysis of skeletal mandibular changes during Frankel appliance treatment. Eur J Orthod. 2011; 33(1):84–92.
21. Marsico E, Gatto E, Burrascano M, Matarese G, Cordasco G. Effectiveness of orthodontic treatment with functional appliances on mandibular growth in the short term. Am J Orthod Dentofacial Orthop. 2011; 139(1):24–36.
22. de Almeida-Pedrin RR, Rodrigues de Almeida M, Rodrigues de Almeida R, Pinzan A, Ferreira FPC. Treatment effects of headgear biteplane and bionator appliances. Am J Orthod Dentofacial Orthop. 2007; 132(2):191–8.
23. Siara-Olds NJ, Pangrazio-Kulbersh V, Berger J, Bayirli B. Long-Term Dentoskeletal Changes with the Bionator, Herbst, Twin Block, and MARA Functional Appliances. Angle Orthod. 2009; 80(1):18–29.
24. Stamenković Z. Primena Frenklovih regulatora funkcije kod skeletno distalnog zagrižaja. Belgrade: Zadužbina Andrejević; 2012.
25. Šćepan I. Efekti terapije malokluzija II klase funkcionalnim aparatima [dissertation]. Belgrade: University of Belgrade; 1997.

Терапијски ефекти три врсте функционалних апарата у лечењу малоклузија II скелетне класе – сагиталне и вертикалне промене

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САЖЕТАК

Увод/Циљ рада Малоклузије II класе су сагиталне неправилности загрижаја које карактерише дистални однос бочних зуба. У зависности од тога које структуре су у неправилном односу, деле се на скелетне и дентоалвеоларне. Терапија II класе зависи од узрока, изражености и узраста. Најбољи вид терапије уколико пацијенти и даље расту је модификација раста.

Циљ ове студије био је да се утврде и упореде сагиталне и вертикалне промене на скелетним и денталним структурама у току лечења М блок-апаратом, Френковим регулатором функције тип I и бионатором по Балтерсу тип I.

Методе Седамдесет испитаника са дијагнозом скелетног дисталног загрижаја (*ANB* > 4°) и мандибуларног ретрогнатизма (*SNB* < 80°), према врсти апарата, подељени су у три групе. Сви су прошли кроз стандардну дијагностику (анамнеза, клиничка и функционална анализа, анализа студијских модела, ортопантомографског и профилног телерендгенског снимка). Терапијски ефекти и промене анализирани су на студијским моделима и профилном снимцима по завршетку терапије.

Резултати Сва три апарата довела су до значајног мезијалног усмеравања и сагиталног раста мандибуле, што је смањило *ANB* угао. У све три групе је утврђен неутрални раст, као и ретрузија горњих и протрузија доњих секутића.

Закључак Резултати студије указују на ефикасност сва три испитивана апарата у лечењу скелетних малоклузија II класе.

Кључне речи: малоклузије II класе; функционална терапија; М блок; Френклов апарат; бионатор

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Dosimetric comparison of two-dimensional versus three-dimensional intracavitary brachytherapy in locally advanced cervical cancer

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SUMMARY

Introduction The aim of this study was dosimetric comparison of two-dimensional (2D) with three-dimensional (3D) planning for high-dose-rate intracavitary brachytherapy (HDR-BT) in locally advanced cervical cancer by dose evaluation in given International Commission on Radiation Units and Measurements (ICRU) reference points, as well as in target volume and organs at risk.

Methods Sixty-six sessions of HDR-BT were performed in 22 patients, with 3D planning, but a virtual 2D plan for dosimetric comparison was also made. 2D planning was performed on radiography obtained by C-arm in ICRU points, and 3D planning in volumes delineated on computer tomography.

Results The comparative analysis indicated a significant mean dose difference of point A left ($p = 0.00014$) and right ($p = 0.003$), through higher doses in 2D and lower doses in 3D reconstructed points A. According to the dose volume histograms, 56.88% and 61.41% mean target volume received 100% and 90% of the prescribed dose, respectively. 2D bladder analysis showed a mean dose of 3.487 Gy in ICRU points, while in 3D analysis a maximum mean dose of 8.804 Gy and a mean dose of 4.716 Gy in 2 cm^3 volume. 2D analysis showed a rectal mean dose of 2.892 Gy in ICRU points, while 3D analysis showed maximum mean dose of 6.411 Gy and 3.947 Gy mean dose in 2 cm^3 volume.

Conclusion 2D planning showed unreal higher doses in the ICRU points for the target and lower doses for the organs at risk.

Keywords: cervical cancer; intracavitary brachytherapy; organs at risk; target volume

INTRODUCTION

Cervical cancer is the third most common malignant disease in women, with approximately 530,000 new cases and 275,000 lethal cases on the global level in 2014 [1]. In spite of the well-developed screening program for early detection of cervical cancer, the locally advanced disease is still present and demands a specific therapeutic approach.

According to cervical cancer classification of the International Federation of Gynecology and Obstetrics, locally advanced cervical cancer means inoperable disease, treated with external beam concurrent chemoradiotherapy followed by a high-dose-rate brachytherapy (HDR-BT) [2]. According to Datta and Agrawal [3], from 1999 to date this type of treatment has shown significant results in treating advanced cervical cancer. The treatment has the highest curative effect if it is finished in a period of eight weeks or 56 days [3].

HDR-BT is one of the most efficient radiotherapy techniques in the treatment of cervical cancer by which compensation of radiotherapy dose delivered by percutaneous radiotherapy is achieved [4]. This is due mainly to two factors. The first factor are anatomic conditions that allow insertion of intrauterine and intravaginal applicators, that is, injection of radioactive sources very close to or inside the tumor. The second factor is based on the principle of reducing the dose by the square of the distance, which means that the given high dose can be focused precisely in the tumor itself by quick dose decline in the surrounding normal structures.

In line with the current clinical practice in most medical centers when treating cervical cancer with HDR-BT, the dose is prescribed in reference points during conventional 2D treatment planning. These are empirical points and they do not always coincide with the specified dose. The ICRU Report 38 points out the possibility that the specified high dose may not be realized in the tumor and that precise data may not be obtained for the real dose at a certain distance from the tumor including the surrounding normal tissues and organs [5, 6]. In order to avoid this inconsistency, the conventional 2D planning treatment is most commonly replaced with 3D treatment planning.

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It enables radiation with precise dose distribution allowing a supply of a controlled high-rate dose in the tumor, which results in better local control of the disease, as well as better control and dose distribution in the organs at risk (OAR), hence reducing the adverse toxic events from radiotherapy [7].

Computerized 3D treatment planning by using computer tomography (CT) instead of 2D radiography shows precise localization of applicators, and the applicators relationship with the adjacent structures can be seen by the 3D anatomic model. At the same time, maintenance of applicators' position has to be ensured since each shift can cause deviation from the prescribed dose [6, 8].

3D brachytherapy treatment planning using image from CT simulation for cervical cancer has been available in our hospital since 2014. Both 2D and 3D planning were initially done to evaluate the dose between these two techniques, in terms of target coverage and doses to bladder and rectum.

METHODS

The study included 22 women with locally advanced inoperable cervical cancer, treated at the University Clinic of Radiotherapy and Oncology, Skopje, in the period from November 2014 to September 2015. All patients underwent definitive treatment consisting of concurrent chemoradiation therapy and successive HDR-BT. Brachytherapy was realized according to 3D prepared plan. Additionally, virtual 2D plan was made, according to the treatment protocol for 2D planning that we used before, for the purpose of dosimetric comparison of both planning techniques.

Treatment protocol

The treatment started by concurrent chemoradiation therapy. Chemotherapy consisted of administration of weekly bolus cisplatin 40 mg/m^2, five times in total, followed by radiotherapy fraction one to three hours after its application. The external beam radiotherapy was conducted after previous CT scanning, followed by delineation of the target volume and OAR. Conformal "four-field box" technique was implemented on a linear accelerator with 15 MV photon energy. The total tumor dose was 50.4 Gy in 28 fractions, with a daily dose of 1.8 Gy. After finishing the concurrent chemoradiation therapy, the treatment was continued with a HDR-BT in order to compensate the tumor dose, with additional 21 Gy in three fractions, once a week at a dose of 7 Gy per fraction.

Uterovaginal application technique

A Foley catheter was inserted, filled with 7 cm^3 contrast and fixed against the bladder neck. CT-compatible tandem-ring applicators were used for HDR-BT. After the applicators were inserted, they were stabilized, and the rectum and bladder were set apart from the applicators with vaginal gauze packing. Only for 2D planning, a rectal marker was placed deeply in the rectum to visualize it. All the patients underwent a 3D-CT simulation and additionally a virtual 2D orthogonal simulation for each session.

When the application is done, the patient is transferred to the CT simulator in order to make a 3D simulation. The main problem is the transport of the patient from the operating room to the CT simulator and later back from the CT simulator to the operating room. During the transport, there is a possibility of geometry change of the previously placed applicators. Because of this, applicator position during the irradiation will be different from the one present after the insertion by the radiation oncologist. We solved this problem with a construction of a special tabletop. The tabletop consists of two parts: the upper part of the table that ends at the patient's pelvis – during the application, patients are positioned on it as on a gynecological table; the second, lower (caudal) part, is joined with the upper part after the application is over. The patient's legs are stretched down and previously inserted applicators are fixated by a clamping device firmly attached to the lower part of the tabletop. There are handles on both the upper and the lower part of the tabletop so the patient can be lifted and put on a transport cart. The patient is positioned on the CT simulator and later returned to the operating room and/or brachytherapy bunker without any fear of applicator displacement.

Virtual 2D conventional planning (according to the 2D treatment protocol, which we used before)

The C-arm was used to generate orthogonal posteroanterior and laterolateral radiographs where reconstruction and treatment planning were defined. The prescribed dose was controlled in certain reference points for the target volume, along with monitoring the dose in the reference points for the OAR. As the critical structures are not fully visualized, the dose is prescribed in points. The ICRU reference point for the target volume in which the dose of 7 Gy is prescribed is point A (left and right). The bladder reference point (ICRUb) on the laterolateral radiograph is projected on the posterior aspect of the balloon, the nearest point to the applicators, while on the posteroanterior radiograph it is in the center of the balloon. The maximum allowed dose in the bladder reference point is 80% of the prescribed dose (5.6 Gy per fraction).

The reference point of the rectum (ICRUr) on the laterolateral radiograph is 5 mm behind the vaginal fornix or from the rectal marker, whereas on the posteroanterior radiograph it is on the inferior end of the tandem. We usually used three points along the rectal marker that are nearest to the active length of the applicators. The maximum dose (rDmax) to the rectum was the highest recorded dose at one of these three points. The maximum permitted dose in these reference points is 70% of the given dose (4.9 Gy per fraction).

Actual 3D CT-based planning

The applicators are CT compatible, thus 3D planning was carried out by a CT simulator, where the region of interest was scanned after the application was realized. With delineation of structures of interest, the target volume (the uterus) and the OAR (the bladder, the rectum) 3D model

was provided. In this way, critical structures were clearly visualized in the reconstructed volume.

In both cases (for 2D and 3D planning), medical physicists calculated the dose by using specialized BrachyVision™ software (Varian Medical Systems, Palo Alto, CA, USA). HDR-BT was done in patients according to 3D designed plan with a Gamma Medplus apparatus (Varian Medical Systems), with iridium 192 as the radioactive source. In an outpatient setting, three fractions of HDR-BT were given to each patient once a week.

Statistical analysis

All analyses were made with the SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA) statistical program. Categorical variables are presented in absolute and relative numbers, and quantitative variables are presented with descriptive statistics (mean ± SDi). To test the distribution of data, Kolmogorov–Smirnov and Shapiro–Wilk tests were used, as well as the values of z-score as the measure of asymmetry (skewness) and of the shape (kurtosis). Student's t-test was used to compare 2D and 3D treatment planning for target coverage and dose to OAR. A p-value < 0.05 was considered statistically significant.

RESULTS

In this study we have analyzed the data obtained from 22 patients with the mean age of 51 ± 11.3 years. Detailed characteristics of the patients and of tumors are shown in Table 1.

Table 1. Baseline characteristics

Characteristics	n (%)
Patient characteristics	
Sex: female	22 (100)
Mean age (years) ± SD, (range)	51 ± 11.3 (25–71)
Tumor histological characteristics	
squamous cell carcinoma	18 (81)
mucoepidermoides carcinoma	3 (14)
adenosquamous carcinoma	1 (5)
Tumor cell differentiation	
well differentiated	5 (22)
moderately differentiated	11 (50)
poorly differentiated	6 (28)
Clinical stage	
IIB	17 (77)
IIIA	4 (18)
IIIB	1 (5)

Table 2. Mean dose values for the target volume per reference point

Reference point	2D planning (Gy)	3D planning* (Gy)	2D planning vs. 3D planning
ICRU A – left	7.241 ± 0.2 (6.632–7.818)	7.006 ± 0.05 (6.925–7.143)	t = 4.2; p = 0.00014**
ICRU A – right	7.204 ± 0.28 (6.676–7.961)	7.014 ± 0.03 (6.953–7.120)	t = 3.14; p = 0.003**

2D – two-dimensional; 3D – three-dimensional; ICRU – International Commission on Radiation Units and Measurements;
*(3D) reconstruction of ICRU reference point A;
**t (Student's t-test) p < 0.01

According to the histopathology of malignant cells, the squamous cell carcinoma prevailed in 81% of patients. Moderate rate of malignant cells differentiation was observed in 50% of patients. Concerning the clinical stage of the disease, the largest number of patients (77%) had stage IIB cancer.

Dosimetric analysis was made for all 66 brachytherapy applications and the comparison of both ways of intracavitary brachytherapy planning was done. The mean values of the obtained doses per fraction in reference points that cover the target volume for both ways of planning are presented in Table 2. Reconstruction of ICRU reference point A was made in 3D planning for the correct comparison of the data. The comparative analysis has indicated a statistically significant difference in the mean dose of reference point A left (t = 4.2; p = 0.00014) and A right (t = 3.14; p = 0.003). 2D planning showed higher doses in reference points A compared to doses received in the reconstructed reference points A in 3D planning.

3D planning through dose-volume histogram showed isodose coverage of the target volume as a whole, and not only in a point. By its analysis it was found that V100 (volume that received 100% of the prescribed dose) had a mean value of 56.88 ± 19.5% and a range of 18.573–99.163%, while V90 (volume that received 90% of the prescribed dose) had a mean value of 61.41 ± 19.7% and a range of 21.133–99.606% (Figure 1).

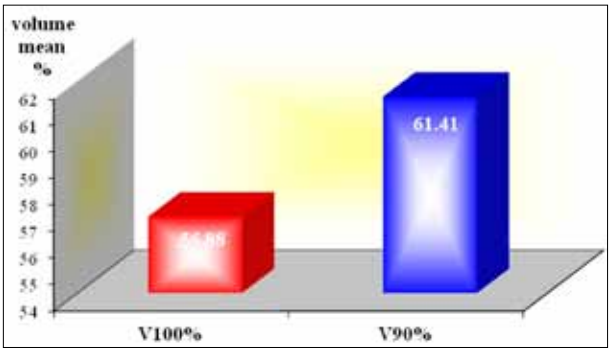

Figure 1. Percentage isodose coverage of target volume by analysis of V100 and V90 (volumes that received 90% and 100% of the prescribed dose, respectively)

Table 3 presents the obtained mean dose values in the bladder as an OAR. Regarding the evidence and control of the dose in the bladder in 2D planning, only one ICRU reference point (ICRUb) was used with the obtained mean value of 3.487 ± 1.9 Gy, which was within the tolerance limit of 80% of the prescribed dose. In 3D planning, the obtained mean values were significantly higher both for the maximum dose (bDmax), which amounted to 8.804 ± 4.9 Gy, and for the mean volume dose in 2 cm^3 ($bD2cm^3$) of 4.716 ± 1.9 Gy, but at the same time they were in the reference range. A statistically significant difference was obtained by comparing the ICRUb from 2D planning with bDmax (t = 4.7; p = 0.00003**) and $bD2cm^3$ (t = 2.2; p = 0.035*) from 3D planning.

Table 4 illustrates the obtained mean dose values in the rectum as the second analyzed OAR. In 2D planning, three

Table 3. Mean dose values in the bladder

2D planning (Gy)	3D planning (Gy)	2D vs. 3D
ICRUb	bDmax	
3.487 ± 1.9	8.804 ± 4.9	
(1.444–8.856)	(3.459–26.830)	t = 4.7; p = 0.00003**
ICRUb	bD2cm^3	
3.487 ± 1.9	4.716 ± 1.9	
(1.444–8.856)	(2.357–10.467)	t = 2.2; p = 0.035*

2D – two-dimensional; 3D – three-dimensional; ICRUb – International Commission on Radiation Units and Measurements – bladder reference point; bDmax – bladder point with the maximal dose; bD2cm^3 – dose in the bladder volume of 2 cm^3; t – Student's t-test;
*p < 0.05
**p < 0.01

Table 4. Mean dose values in the rectum

2D planning (Gy)	3D planning (Gy)	2D vs. 3D
ICRUr	rDmax	
2.892 ± 0.6	6.411 Gy ± 1.8	
(1.577–3.676)	(3.689–11.433)	t = 8.8; p < 0.0001
ICRUr	rD2cm^3	
2.892 ± 0.6	3.947 Gy ± 0.8	
(1.577–3.676)	(2.391–5.247)	t = 4.8; p = 0.00002

2D – two-dimensional, 3D – three-dimensional, ICRUr – International Commission on Radiation Units and Measurements-rectum reference point, rDmax – rectum point with maximal dose; rD2cm^3 – dose in the rectum volume of 2 cm^3; t – Student's test p < 0.01

rectal reference points were used for dose evidence and control in the rectum. The obtained mean value (ICRUr) of 2.892 ± 0.6 Gy was within the tolerance limit. In 3D planning, significantly higher mean values were obtained for both the maximum dose (rDmax), which amounted to 6.411 ± 1.8 Gy and the dose in volume of 2 cm^3 (rD2cm^3) with a mean value of 3.947 ± 0.8 Gy, ranging within the tolerance limit. A statistically significant difference was obtained by comparing the ICRUr from 2D planning with rDmax (t = 8.8; p < 0.0001) and rD2cm^3 (t = 4.8; p = 0.00002) from 3D planning. Voluminously realized dose was obtained by analyzing the dose-volume histogram in 3D planning.

It can be clearly seen that unlike in 3D planning, significantly lower values for the absorbed dose in the OAR were obtained in 2D planning. However, this is due to the limited capabilities of 2D planning, which gives information on the dose in a point, while the higher dose values in 3D planning are a result of the option for displaying the maximum dose and the absorbed volume dose.

DISCUSSION

As individualized treatment based on CT or nuclear magnetic resonance, 3D brachytherapy is more commonly used in the treatment of cervical cancer. The aim is to improve the dose control and its real presentation. 2D brachytherapy is a standard and routine treatment in our institution. Traditionally, this has been done using plain film X-rays only, but this technique has its limitations. Our modest experience with 3D planning was aimed at improving the treatment of these patients. However, in the literature, there are numerous studies reporting their results. A study by Potter et al. [9] presents the similarity in the dose of the rectum in both ways of planning, but, on the other hand, it points out the possibility for late rectal complication as an adverse effect. In addition, higher bladder toxicity is emphasized. Nevertheless, the recommendations of the Gynaecological European Society for Therapeutic Radiology and Oncology inform about certain tolerance by the OAR [10]. Ling et al. [11] studied the maximum doses of the bladder and the rectum by using CT evaluation and they found out that bladder dose in 3D planning was almost two times higher than that in ICRU reference points during 2D planning. However, some studies present no statistically significant differences in the dose in the OAR between the two ways of planning. In the study by Jamema et al. [12] there was no significant difference between the mean values in dose-volume histograms and ICRU reference points.

The variations in the dose are explained by several factors such as the possible difference during reconstruction of the points and applicators in planning since they should be carried out by the same medical physicist, while difficulties very often appear due to the presence of metal artifacts. Another factor is different techniques used in different centers when applying a rectal retractor (placed in the vagina) or marking the rectum with rectal marker (placed in the rectum). Certain centers position the reference points along the marker, while in other centers, such as ours, they are positioned in front of the marker, that is, in the rectal wall. The contour correctness in 3D delineating is important, as well as the time for making the orthogonal radiographs for 2D and CT scanning for 3D planning (the best time is up to 30 minutes).

Regarding the target volume, a significant difference between 2D and 3D planning was observed in our study. During 2D planning, the planner rotates slightly the applicators around the sagittal axes in order to get line projection of the ring applicator. This causes a different space position of points A between 2D and 3D planning, which results in dose difference with inherent uncertainty regarding image reconstructions in these two planning approaches. However, it has to be pointed out that 3D planning offers a possibility for detailed monitoring of isodose coverage of the target volume through dose-volume histogram. A good isodose schedule secures better local control of the disease. In lack of opportunity for accurate visualization and setting a safety margin around the cervix, CT delineation encompasses target volume which covers the uterus entirely. This must be taken into consideration when analyzing isodose coverage of the target volume. In case of a large uterine volume it is logical to get a smaller 100% and 90% isodose coverage. Magnetic resonance imaging (MRI) is superior to CT and exceeds this limitation with the possibility of a clear visualization of the cervix and surrounding clinical target volume of high risk [7]. As it would be difficult to perform MRI-based brachytherapy for logistic reasons, CT-based image planning is a reasonable substitute.

In addition, specific radiobiological characteristics of the HDR-BT has to be taken into consideration. The prescribed high dose (higher than the dose in external

beam radiation therapy) is well tolerated due to the volume–effect ratio (small volumes can tolerate high doses) showing the main difference between 2D and 3D dose reporting – during 2D in point and during 3D in volume. With reference to the OAR (the bladder and the rectum), the comparison has shown significantly lower dose values in 2D and higher in 3D planning. The higher dose values that appear in 3D planning refer to the volume and are within the tolerance limits of OAR, but it has to be taken into account as a possibility for underlining the postirradiation adverse effects. Cumulative radiotherapy dose biologically weighted (from external radiotherapy and HDR-BT) in point A reaches up to 85 Gy_{EQD}^2, in our study 79.3 Gy_{EQD}^2 (α/β = 10 Gy). OAR tolerance limit is confined to cumulative weighted dose in volume of 2 cm^3 to 95 Gy_{EQD}^2 (α/β = 3 Gy) for the bladder and 65 Gy_{EQD}^2 (α/β = 3 Gy) for the rectum [4].

In the conclusions of the majority of studies, 3D planning is recommended as a more precise way of planning and provides easier overcoming of all previously presented errors. It is expected that therapeutic ratio analyzed through the adequate dose coverage of the target volume on one side and dose decline in OAR on the other side could be substantially enhanced if the radiation dose is prescribed according to 3D model of brachytherapy planning [4, 13–17].

ICRU Report 89 [7] provides the latest comprehensive recommendations on prescribing, recording, and reporting brachytherapy focusing on volumetric imaging in cervix cancer brachytherapy. However, it is well recognized that the majority of advanced cervix cancer patients in developing countries are and will be treated with limited resources. Patients in these countries are usually treated with simple radiotherapy methods and with the "minimal standard" for reporting the parameters.

CONCLUSION

This study demonstrated that 3D HDR-BP planning using CT is an improved individual treatment method of planning compared to 2D HDR-BP planning using orthogonal radiography. CT-based image planning allows more realistic, precise identification and dose optimization in the target volume and in the OAR. Each institution has to inspect its resources and the number of patients in order to ensure the most sophisticated treatment of patients. Further research and development of sophisticated brachytherapy techniques in locally advanced cervix cancer is of great importance having in mind long survival of these patients.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebeo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015; 136(5):E359–86.
2. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. Int J Gynaecol Obstet. 2009; 105(2):103–4.
3. Datta NR, Agrawal S. Does the evidence support the use of concurrent chemoradiotherapy as a standard in the management of locally advanced cancer of the cervix, especially in developing countries? Clin Oncol. 2006; 18(4):306–12.
4. Potter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, et al. Recommendations from Gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy – 3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol. 2006; 78(1):67–77.
5. International Commission on Radiation Units and Measurements (ICRU). Dose and volume specification for reporting intracavitary therapy in gynaecology. Oxford, United Kingdom: Oxford University Press; ICRU Report 38, 1985.
6. Datta NR, Kumar S, Das KJ, Pandey CM, Halder S, Ayyagari S. Variations of intracavitary applicator geometry during multiple HDR brachytherapy insertions in carcinoma cervix and its influence on reporting as per ICRU Report 38. Radiother Oncol. 2001; 60(1):15–24.
7. International Commission on Radiation Units and Measurements (ICRU). Prescribing, recording, and reporting brachytherapy for cancer of the cervix. Oxford, United Kingdom: Oxford University Press; ICRU Report 89, 2016.
8. Nag S. Controversies and new developments in gynecologic brachytherapy; image-based intracavitary brachytherapy for cervical carcinoma. Semin Radiat Oncol. 2006; 16(3):164–7.
9. Potter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, et al. Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol. 2006; 78(1):67–77.
10. Haie-Meder C, Potter R, Van Limbergen E, Briot E, De Brabandere M, Dimopoulos J, et al. Recommendations from gynaecological (GYN) GEC-ESTRO working group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol. 2005; 74(3):235–45.
11. Ling CC, Schell MC, Working KR, Jentzsch K, Harisiadis L, Carabell S, et al. CT-assisted assessment of bladder and rectum dose in gynecological implants. Int J Radiat Oncol Biol Phys. 1987;13(10):1577–82.
12. Jamema SV, Saju S, Mahantshetty U, Pallad S, Deshpande DD, Shrivastava SK, et al. Dosimetric evaluation of rectum and bladder using imaged-based CT planning and orthogonal radiographs with ICRU 38 recommendations in intracavitary brachytherapy. J Med Phys. 2008; 33(1):3–8.
13. Chottaweesak P, Shotelersuk K, Amornvichet N, Khorprasert C, Oonsiri P. Comparison of bladder and rectum doses between conventional 2D and 3D brachytherapy treatment planning in cervical cancer. Biomed Imaging Interv J. 2014; 10(1).
14. Vinod SK, Caldwell K, Lau A, Fowler AR. A comparison of ICRU point doses and volumetric doses of organs at risk (OARs) in brachytherapy for cervical cancer. J Med Imaging Radiat Oncol. 2011; 55(3):304–10.
15. Shin KH, Kim TH, Cho JK, Kim JY, Park SY, Kim DY, et al. CT-guided intracavitary radiotherapy for cervical cancer: Comparison of conventional point A plan with clinical target volume-based three-dimensional plan using dose-volume parameters. Int J Radiat Oncol Biol Phys. 2006; 64(1):197–204.
16. Nag S, Cardenes H, Chang S, Das IJ, Erickson B, Ibbott GS, et al. Proposed guidelines for image-based intracavitary brachytherapy for cervical carcinoma: Report from Image-Guided Brachytherapy Working Group. Int J Radiat Oncol Biol Phys. 2004; 60(4):1160–72.
17. Purdy JA. Advances in three-dimensional treatment planning and conformal dose delivery. Semin Radiat Oncol. 1997; 24(6):655–71.

Дозиметријско упоређивање дводимензионалне са тродимензионалном интракавитарном брахитерапијом код локално узнапредовалог карцинома цервикса

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САЖЕТАК

Увод/Циљ Циљ овог рада је био дозиметријско упоређивање дводимензионалног (2Д) са тродимензионалним (3Д) планирањем интракавитарне брахитерапије високе брзине дозе (ВБД-БТ) код локално узнапредовалог цервикалног карцинома са евалуацијом дозе у референтним тачкама датим од Интернационалне комисије за радијационе јединице и мере (ИКРЈ), као и у циљном волумену и органима ризика.

Методе Код 22 болеснице са 3Д планирањем реализоване су 66 сесије ВБТ-БТ, али је урађено, ради поређења, и 2Д планирање на радиографији са *C-arm* апаратом у ИКРЈ тачкама, а 3Д планирање на компјутерској томографији у делинеираним волуменима.

Резултати Компаративна анализа је показала значајну разлику у дози у левој тачки А ($p = 0,00014$) и у десној ($p = 0,003$), преко виших доза у 2Д и нижих доза у 3Д реконструисаним тачкама А. Према дозноволуменским хистограмима просечно је 56,88% волумена примило 100% од преписане дозе, док је 61,41% волумена примило 90% преписане дозе. Анализа бешике као органа ризика показала је да добија просечну дозу од 3,487 *Gy* у ИКРЈ тачки, у 3Д анализи просечни максимум у тачки је био 8,804 *Gy*, а у 2 cm^3 волумена добија просечну дозу од 4,716 *Gy*. 2Д анализа ректума показала је да ректум добија просечно 2,892 *Gy* у ИКРЈ тачки, док је у 3Д анализи максимална просечна доза у тачки била 6,411 *Gy* и 3,947 *Gy* просечне дозе у 2 cm^3 волумена.

Закључак 2Д планирање је показало нереално високе дозе у ИКРЈ тачкама и ниже дозе у органима ризика.

Кључне речи: цервикални карцином; интракавитарна брахитерапија; органи ризика; циљни волумен

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Risk factors for intraoperative variations in blood pressure and cardiac dysrhythmia during thyroid surgery

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SUMMARY

Introduction/Objective Intraoperative variations in blood pressure and/or cardiac dysrhythmias (IOVBP/CD) represent one of the most common causes of morbidity and mortality in surgical patients. The aim of the study was to determine the incidence and risk factors for IOVBP/CD in thyroid surgery patients with comorbidities.

Methods The study included 1,252 euthyroid patients with ASA 2 and ASA 3 status (American Society of Anesthesiologists – physical status classification) who underwent thyroid surgery. The following risk factors were examined: sex, age, body mass index (BMI), ASA status, admission diagnoses, type of operation, duration of surgery, time under general anesthesia, difficult intubation of trachea, and coexisting diseases – hypertension, cardiomyopathy, cardiac arrhythmias, angina pectoris, diabetes mellitus, kidney disease. The following intraoperative events were recorded: hypertension, severe hypertension, hypotension, and cardiac arrhythmias. We used Pearson χ^2 square test, univariate, and multivariate logistic regression for statistical analysis.

Results The majority of patients were female (86.3%). In 903 (72.1%) patients IOVBP/CD were detected. The most common problem was intraoperative hypertension (61.4%). Eight risk factors for IOVBP/CD were registered by univariate analysis: advanced age, ASA 3 status, BMI > 25 kg/m^2, duration of surgery, time under general anesthesia, hypertension, and cardiomyopathy as a coexisting disease. The multivariate regression model identified three independent predictors for IOVBP/CD: age, hypertension, and cardiomyopathy.

Conclusion IOVBP/CD are common in thyroid surgery. The most common is intraoperative hypertension. Older age, hypertension, and cardiomyopathy as a coexisting disease are independent risk factors for IOVBP/CD.

Keywords: thyroidectomy; hypotension; hypertension; arrhythmias, cardiac

INTRODUCTION

Intraoperative variations in blood pressure and/or cardiac dysrhythmias (IOVBP/CD) represent one of the most common causes of morbidity and mortality in surgical patients. According to different reports, the incidences of IOVBP/CD are between 4.9% and 17.5% [1, 2]. However, these studies are methodologically different, and they use different definitions of IOVBP/CD and different ways of recording complications [1–4].

The type of surgery and advanced age were identified as significant risk factors in most studies [5, 6]. Previous studies have mostly observed the occurrence of IOVBP/CD in cardiac or non-cardiac surgery [7, 8]. In the case of non-cardiac surgery, most studies focus on so-called "major" surgery which involves major abdominal, orthopedic and urological surgery. However, there is little data in the literature about the incidence of IOVBP/CD in low risk and intermediate risk surgery. To the best of our knowledge, thyroid surgery, which could be classified as intermediate risk surgery, has been studied rarely [9]. This is why the aim of our study was to determine the incidence and predictors of IOVBP/CD in thyroid surgery patients.

METHODS

This prospective five-year study was conducted at the Center for Endocrine Surgery, University Clinical Center of Serbia, Belgrade, where most patients with thyroid pathology in Serbia are operated on. The study was institutionally approved; signed patient consent was waived as the treatment of patients did not differ from the usual one and no protected health information was collected. Eligible patients were those aged

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18 years and older referred to the University Clinical Center of Serbia for thyroid surgery. A total of 2,559 patients were included in the study. Because of the potential influence on the incidence of IOVBP/CD, we excluded seven patients with a diagnosis of hypothyroidism, 264 patients with hyperthyroidism, and 278 patients with autoimmune thyroid disease. We also excluded 758 patients with ASA 1 status because these were patients without comorbidities. A total of 1,252 euthyroid ASA 2 and ASA 3 patients were included. Our patients had the following admission diagnoses: 1) nodular goiter – 350 (28%); 2) multinodular goiter – 652 (52%); 3) thyroid gland cyst – 9 (0.7%); 4) struma recidivans – 69 (5.5%); 5) papillary carcinoma – 78 (6.2%); 6) medullary carcinoma – 69 (5.5%); 7) Hürthle cell carcinoma – 8 (0.6%); 8) follicular carcinoma – 5 (0.4%); 9) oxyphil lesion – 12 (0.9%).

We noted the incidence and risk factors of the following IOVBP/CD: hypertension, severe hypertension, hypotension, tachycardia, bradycardia, new onset atrial fibrillation/flutter and extrasystole, ventricular and supraventricular, which we define as follows: hypertension – an increase of systolic blood pressure ≥ 20% compared to baseline values within 15 minutes; severe hypertension – blood pressure ≥ 220/120 mmHg; hypotension – a decrease of systolic blood pressure ≥ 20% compared to baseline values within 15 minutes; tachycardia: heart rate ≥ 85 beats per minute for at least five minutes; bradycardia: heart rate ≤ 60 beats per minute for at least five minutes; frequent VES/SVES (premature ventricular and supraventricular contractions) > 6 per minute; new onset atrial fibrillation/flutter [9].

The observed values of blood pressure and heart rate were recorded at least every five minutes using noninvasive measurements and recorded in the list of anesthesia. The treating anesthesiologist was deciding on when to use a certain drug and in which dose, so that the occurrence of these events would not affect the outcome of the surgery. There was no mortality in our study, neither intraoperative nor postoperative. The patients were divided into two groups – the group with IOVBP/CD and the group without it.

The predictive power of 10 variables were studied: age (< or ≥ 50 years), sex, body mass index (BMI) (< or > 25 kg/m^2), ASA status (ASA 2 and ASA 3), admission diagnosis, type of operation (total thyroidectomy vs. others), difficult intubation of the trachea (defined as the inability to visualize the glottis during laryngoscopy, Cormack–Lehane grades 3 and 4), duration of surgery (minutes), time under general anesthesia (minutes) and coexisting diseases. The following coexisting diseases were observed: hypertension, cardiomyopathy (CMP), cardiac arrhythmias (tachycardia, bradycardia, atrial fibrillation/flutter and extrasystoles), angina pectoris, diabetes mellitus (DM) (and therapeutic regimen in patients with DM – insulin, oral hypoglycemic agents, diet), and kidney disease (chronic and terminal renal insufficiency).

The patients who were on chronic antihypertensive, antiarrhythmic therapy (especially on beta blockers) received their therapy preoperatively, including the day of surgery. All surgery was performed during general anesthesia. The patients were pre-medicated 20 minutes prior to surgery (midazolam 0.1 mg/kg and atropine 0.5 mg i.m.). During induction, all the patients received 0.05–0.1 mg of fentanyl and 1.5 mg/kg of propofol. To facilitate intubation, we used 1.1 mg/kg of succinylcholine, and maintained further relaxation with 0.5 mg/kg of rocuronium. Anesthesia was maintained with fentanyl (5 μg/kg) and a mixture of air gases (2 L/min.), oxygen (2 L/min.), and sevoflurane at an appropriate concentration.

For statistical analysis of data we used the statistical software package SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were described using measures of central tendency (mean) and measure of dispersion (standard deviation). We used percentage to describe categorical data. The normality of data distribution was checked by one-sample Kolmogorov–Smirnov test. For statistical analysis of continuous variables, Mann–Whitney U-test was used, depending on the nature of the data. Categorical data were compared using Pearson's χ^2 test. Logistic regression analysis was conducted to evaluate the differences between patients with and without IOVBP/CD in their observed risk factors. Odds ratios and their 95% confidence intervals represented relative risks for each independent risk factor associated with intraoperative incidents. All reported p-values were two-sided. The level of significance was set at 0.05.

RESULTS

Most of our patients were female (86.3%), mean age 56.7 ± 11.5 years. We also converted age into a categorical variable through the use of a receiver operating characteristic curve, and demonstrated the optimal balance of sensitivity and specificity at a cutoff age of ≥ 50 years. Nine hundred and nineteen patients (73.4%) were older than 50 years, most of them had at least one IOVBP/CD (77.9% vs. 22.1%), which was statistically significant (p = 0.000). The average duration of surgery was 69.5 ± 24.1 minutes and the mean time under general anesthesia was 79.4 ± 24.7 minutes. The distributions of other risk factors in our study are shown in Table 1. IOVBP/CDs were registered in 72.1% of the patients, whereas 27.9% of the patients were without IOVBP/CDs. The most common problem was hypertension (61.4%), while severe hypertension occurred in 3.1% and hypotension in 6.5% of the patients. In 27.9% of the patients, different intraoperative cardiac arrhythmias were registered, the most common being tachycardia (18.2%), followed by bradycardia (6.5%), frequent VES/SVES (2.4%), and the least common was atrial fibrillation/flutter (0.7%).

Patients with IOVBP/CD were significantly older, more often had a BMI > 25 kg/m^2 and were ASA 3. There was no statistically significant difference in frequency of IOVBP/CD between male and female patients. Significantly higher number of patients in the group with IOVBP/CD had a history of hypertension. There was no significant difference in the frequency of previous diagnosis of cardiac arrhythmias and angina pectoris between the two groups, while the CMP was more often recorded in the group with IOVBP/CD. There were no differences in relation to

Table 1. Distribution of risk factors

Risk factor	n (%)
Age (mean ± SD)	56.86 ± 11.42
Sex: male/female	171 (13.7%) / 1081 (86.3%)
BMI > 25 kg/m²	823 (65.7%)
ASA 2 / ASA 3	1004 80.2%) / 248 (19.8%)
Type of surgery: total thyroidectomy / others	959 (76.6%) / 293 (23.4%)
Difficult intubation	153 (12.2%)
Coexisting disease	
Hypertension	832 (66.5%)
Cardiac arrhythmias	85 (6.8%)
Bradycardia	2 (0.2%)
Tachycardia	24 (1.9%)
Atrial fibrillation / flutter	36 (2.9%)
Frequent VES/SVES*	23 (1.8%)
Angina pectoris	62 (5%)
Cardiomyopathy	98 (7.8%)
Diabetes mellitus / insulin dependent	149 (11.9%) / 44 (3.5%)
Kidney disease	22 (1.8%)

* > 6 premature ventricular or supraventricular contractions/minute;
BMI – body mass index; ASA – American Society of Anesthesiologists

admission diagnosis, type of surgery and the incidence of difficult intubation, while the duration of surgery and the time under general anesthesia were statistically significantly longer in patients with IOVBP/CD (Table 2).

To determine the effect of each variable on the occurrence of IOVBP/CD, the logistic regression model was used (Table 3). Univariate logistic regression analysis revealed a statistically significant difference between patients with and without IOVBP/CD in their age, ASA status, BMI, duration of surgery, and the time under general anesthesia, as well as previous hypertension and CMP. Multivariate analysis showed that independent predictors for IOVBP/CD were age, hypertension, and cardiomyopathy.

Table 2. Incidence of risk factors among patients with and without IOVBP/CD

Risk factor	IOVBP/CD		p
	Yes	No	
Sex (female)	780 (86.4%)	301 (86.2%)	0.951
BMI > 25 kg/m²	619 (68.5%)	204 (58.5%)	0.001*
ASA 2 ASA 3	708 (78.5%) 194 (21.5%)	296 (84.8%) 53 (15.2%)	0.012*
Age (mean ± SD)	58.3 ± 11.1	53.2 ± 11.4	0.000*
Admission diagnosis (multinodular goiter)	482 (53.4%)	152 (43.6%)	0.167
Hypertension	643 (71.2%)	189 (54.2%)	0.000*
Cardiac arrhythmias	63 (7.0%)	22 (6.3%)	0.671
Bradycardia Tachycardia Atrial fibrillation/flutter Frequent VES/SVES**	2 (3.2%) 14 (22.2%) 31 (49.2%) 16 (25.4%)	0 (0%) 10 (45.5%) 5 (22.7%) 7 (31.8%)	0.601
Angina pectoris	50 (5.5%)	12 (3.4%)	0.125
Cardiomyopathy	84 (9.3%)	14 (4.0%)	0.002*
Diabetes mellitus	117 (13%)	32 (9.2%)	0.064
Insulin-dependent diabetes mellitus	36 (30.8%)	8 (25%)	0.672
Kidney disease	16 (1.8%)	6 (1.7%)	0.949
Difficult intubation of trachea	119 (12.1%)	44 (12.6%)	0.297
Type of surgery (total thyroidectomy)	702 (77.7%)	257 (73.6%)	0.103
Duration of surgery (minutes)	70.4 ± 23.9	67 ± 24.4	0.008*
TUGA (minutes)	80.3 ± 24.3	76.9 ± 25.5	0.006*

BMI – body mass index; ASA – American Society of Anesthesiologists; CMP – Cardiomyopathy; DM – diabetes mellitus; TUGA – time under general anesthesia;
*statistically significant $p < 0.05$;
**> 6 premature ventricular or supraventricular contractions/minute

DISCUSSION

The results of our study indicate a high incidence of IOVBP/CD in euthyroid patients undergoing thyroid gland surgery (72.1%). Röhrig et al. [2] registered IOVBP/CD in 17.5% of patients, but they studied all types of non-cardiac surgery, including urgent surgery. It was shown that the occurrence of IOVBP/CD was affected by age, male gender, ASA status, previous cardiac disease and type of surgery. Sanborn et al. [4] found the incidence of IOVBP/CD in 6.5% of patients. The authors define intraoperative hypertension as systolic blood pressure of more than 195 mmHg, with the explanation that if they used lower values, almost two thirds of patients would have intraoperative hypertension. It was shown that independent predictors were urgent surgery, age over 70 years, and ASA 3. Both studies registered IOVBP/CD automatically by using computerized machine-readable record sheets, in contrast to our study where data were recorded manually.

To indicate the importance of methods of data recording, the study of Benson et al. [3] compared manual with automatic recording of blood pressure (BP). On a sample of 16,019 patients, it has been shown that much more adverse events were detected automatically than manually (18.7% vs. 5.7%). Both ways of recording data have their advantages and drawbacks. The main complaint to the automatically recorded values of blood pressure is the frequent occurrence of artifacts which significantly affect the validity of the data, while the manual mode is criticized for subjectivity.

The explanation for such a high incidence of IOVBP/CD in our study can be viewed from several aspects: selection of patients who were included in the study (excluded ASA 1, thyroid surgery only), institution where the study was carried out (university clinical center – tertiary institution), criteria for defining IOVBP/CD (significantly different among studies), and the method of recording data (in our study manual). Our study included only patients with ASA 2 and ASA 3 status, patients who had coexisting diseases and in which perioperative complications are most commonly reported.

Although preoperative cardiology management has significantly advanced in recent years, we are still not able to exactly predict the individual risk. One of the most commonly used models for cardiovascular risk prediction is Lee's Revised Cardiac Risk Index (RCRI); a patient is at risk if he/she has two or more risk factors (ischemic heart disease, congestive heart failure, cerebrovascular disease,

Table 3. Logistic regression for IOVBP/CD

Parameters	IOVBP/CD			
	Univariate		Multivariate	
	OR (95% CI OR)	p	OR (95% CI OR)	p
ASA	0.808 (0.684–0.955)	0.012*	1.026 (0.853–1.233)	0.788
Age≥ 50 yr	0.962 (0.951–0.972)	0.000	0.971 (0.959–0.983)	0.000*
Sex	0.989 (0.691–1.416)	0.951		
BMI	0.645 (0.500–0.833)	0.001*	0.945 (0.809–1.104)	0.475
Admission diagnosis	1.019 (0 992–1.046)	0.168		
Hypertension	0.478 (0.370–0.616)	0.000*	0.628 (0.474–0.832)	0.001*
Cardiac arrhythmias	0.897 (0.543–1.482)	0.671		
Type of cardiac arrhythmias	0.955 (0.809–1.127)	0.584		
Angina pectoris	0.607 (0.320–1.155)	0.128		
Cardiomyopathy	0.407 (0.228–0.728)	0.002*	0.529 (0.282–0.993)	0.047*
Diabetes mellitus	0.678 (0.449–1.024)	0.065		
Therapy for diabetes mellitus	1.197 (0.522–2.747)	0.671		
Kidney disease	0.970 (0.376–2.499)	0.949		
Type of kidney disease	0.975 (0.664–1.433)	0.899		
Type of surgery	1.033 (0.992–1.075)	0.113		
Difficult intubation	1.180 (0.864–1.611)	0.298		
Duration of surgery (min.)	0.994 (0.988–0.999)	0.027*	0.991 (0.966–1.017)	0.486
TUGA (min.)	0.810 (0.694–0.945)	0.007*	1.004 (0.979–1.029)	0.759

ASA – American Society of Anesthesiologists; BMI – body mass index; TUGA – time under general anesthesia;
*statistically significant $p < 0.05$

diabetes mellitus treated with insulin, renal failure, and high-risk surgery) [10]. Boersma et al. [11] demonstrated a substantial improvement of Lee's index predictive power by adding type of surgery, age, and ECG findings.

However, the most important reason for such large variations in the frequency of IOVBP/CD between different studies is the method of defining intraoperative problems, especially hypertension. Studies differ in the type of blood pressure which is observed, systolic or mean arterial BP; which change of value of BP is considered significant, relative to the patient's baseline blood pressure or below/above a certain absolute threshold. Minimum length of duration of the changes of BP, interval, and the method of measurement (invasive or noninvasive) also differ among studies [1, 2, 4, 7, 8, 12, 13, 14]. Our previous study showed that independent predictors for intraoperative hypertension were older age, BMI 25 kg/m^2, and hypertension as a coexisting disease [15]. Also, our recently published study that examined the prevalence of hypertension and risk factors for its occurrence in patients undergoing parathyroidectomy found intraoperative hypertension in 56.9% of patients and also showed that independent predictors were older age and history of hypertension [16].

More than two thirds of surgical patients and nearly 80% of cardiac patients have hypertension as a coexisting disease [12]. History of hypertension, especially nontreated, increases the risk for intraoperative complications [17]. In our study, 66.5% of patients had hypertension as a coexisting disease, while intraoperative hypertension was registered in 61.4% of patients. Most of the patients who had hypertension as a coexisting disease also had intraoperative hypertension (76.3%), which implies that if a patient had a previous history of hypertension, he or she has a greater likelihood of having intraoperative hypertension.

Demonstrating the effect of defining the value of BP, and having in mind the influence of intraoperative hypotension on the development of postoperative complications and the importance in predicting adverse outcome, one study found 140 different definitions of intraoperative hypotension, resulting that the incidence of intraoperative hypotension varies between 5% and 99% [18]. In our study, hypotension occurred in 6.5% of patients.

Also, there is little available data about the incidence and risk factors of IOVBP/CD in thyroid surgery. In our previous study [9], in which we examined the occurrence of IOVBP/CD in 200 patients who underwent thyroidectomy, IOVBP/CD was recorded in 38% of patients. IOVBP/CDs were defined in the same way as in this study, but the majority of patients (49%) had ASA 1 status (without comorbidity).

Our study showed that independent predictors for the occurrence of IOVBP/CD were age, previous hypertension, and cardiomyopathy. Some other studies have also confirmed the influence of older age on the occurrence of both intraoperative complications and postoperative morbidity and mortality [1, 2, 5, 19]. There is an increasing number of persons older than 65, and these are precisely the patients who most often require surgical treatment. It was shown that age, per se, did not affect the occurrence of postoperative complications, and that, complications in patients older than 70 years should not be expected unless there are comorbidities [20]. Similar results were found in studies which examined the impact of age on the occurrence of postoperative complications in thyroid surgery. Passler et al. [21] have shown no difference in morbidity or mortality between patients aged ≥ 75 years and younger patients, while Mekel et al. [22] demonstrated that the age of ≥ 80 years is associated with higher morbidity after

thyroid surgery, although not independently. Monk et al. [23] demonstrated higher one-year mortality in patients older than 65 years in contrast to younger populations (10.2% vs. 5.5%, respectively) and comorbidity as the most powerful predictive factor.

Our study showed that although the duration of surgery and time under general anesthesia were significantly longer in patients with intraoperative events, they were not selected as predictors. Reich et al. [13] also showed that intraoperative tachycardia and hypertension more often occured in operations of longer duration and that they were associated with negative postoperative outcomes. Other studies have also confirmed the influence of the duration of surgery on the occurrence of IOVBP/CD [5, 14]. It has also been shown that with every extension of the duration of anesthesia there is an increased risk of complications – for every 60 minutes of anesthesia, the risk of having a complication increases by 18% to 36% [20].

We were not able to confirm diabetes mellitus and renal failure as predictors for IOVBP/CD. The study by Kheterpal et al. [5] also found that diabetes mellitus and renal failure were not predictors for IOVBP/CD, with the explanation that the reason for such a result is probably better preoperative management, as well as standardization of treatment of these patients. Our previous studies confirmed the importance of adequate preoperative preparation of diabetic patients, for the prevention and reduction of intra and postoperative complications [24]. Accordingly, all our patients with diabetes mellitus were well prepared for surgery, they had serum glucose level and glycosylated hemoglobin in the range of normal values, which probably contributed to the fact that this comorbidity did not show up as an important risk factor for IOVBP/CD.

It is known that the incidence of difficult intubation of the trachea is higher in thyroid surgery compared to other types of surgery. The incidence of difficult intubation in our previous studies, which included more than 2,000 patients who underwent thyroid surgery, were 5.5% and 6.81%, respectively [25, 26], while Adnet et al. [27] and Amathieu et al. [28] reported even higher incidence (8% and 11.1%, respectively). In this study, difficult intubation was registered in 12.2% of patients. Difficult intubation, especially if it takes a long time, increases the risk of various complications, including cardiovascular. We expected that such a high incidence of difficult intubation would significantly contribute to occurrence of IOVBP/CD. However, difficult intubation was not a risk factor for IOVBP/CD. The reason for that is probably the good practice of the experienced anesthesiological team in our center, who successfully solve difficult intubations on a daily basis.

Although only 7.8% of our patients had cardiomyopathy, CMP was an independent predictor for IOVBP/CD. Other studies also showed similar results [1, 8].

A potential limitation of our study is that we have not examined the impact of these events on the postoperative outcome. However, since the aim of our study was to determine the incidence and risk factors of IOVBP/CD, and not their impact on postoperative outcome, we believe that this is a topic for a future study.

CONCLUSION

Because of the large number of patients with cardiovascular comorbidities, the incidence of intraoperative variations in blood pressure and/or occurrence of cardiac dysrhythmias is high, even in thyroid surgery – which is considered an intermediate-risk surgery. Our study showed that older age, hypertension, and cardiomyopathy as a coexisting disease are independent risk factors for IOVBP/CD. Patients with these risk factors constitute a group in which anesthesiologists should pay special attention to the manner of preparing and maintaining anesthesia, in order to minimize significant variations of intraoperative blood pressure values and/or the occurrence of cardiac dysrhythmias.

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REFERENCES

1. Forrest JB, Rehder K, Cahalan MK, Goldsmith CH. Multicenter study of general anesthesia III. Predictors of severe perioperative adverse outcomes. Anesthesiology. 1992; 76(1):3–15.
2. Röhrig R, Junger A, Hartmann B, Klasen J, Quinzio L, Jost A, et al. The incidence and prediction of automatically detected intraoperative cardiovascular events in noncardiac surgery. Anesth Analg. 2004; 98(3):569–77.
3. Benson M, Junger A, Michel A, Sciuk G, Quinzio L, Marquardt K, et al. Comparison of manual and automated documentation of adverse events with an Anesthesia Information Management System (AIMS). Stud Health Technol Inform. 2000; 77:925–9.
4. Sanborn KV, Castro J, Kuroda M, Thys DM. Detection of intraoperative incidents by electronic scanning of computerized anesthesia records: comparison with voluntary reporting. Anesthesiology. 1996; 85(5):977–87.
5. Kheterpal S, O'Reilly M, Englesbe MJ, Rosenberg AL, Shanks AM, Zhang L, et al. Preoperative and intraoperative predictors of cardiac adverse events after general, vascular, and urological surgery. Anesthesiology. 2009; 110(1):58–66.
6. Sabaté S, Mases A, Guilera N, Canet J, Castillo J, Orrego C, et al. Incidence and predictors of major perioperative adverse cardiac and cerebrovascular events in non-cardiac surgery. Br J Anaesth. 2011; 107(6):879–90.
7. Reich DL, Bodian CA, Krol M, Kuroda M, Osinski T, Thys DM. Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery. Anesth Analg. 1999; 89(4):814–22.
8. Seki M, Kashimoto S, Nagata O, Yoshioka H, Ishiguro T, Nishimura K, et al. Are the incidences of cardiac events during noncardiac surgery in Japan the same as in the United States and Europe? Anesth Analg. 2005; 100(5):1236–40.

9. Dimitrijevic N, Neskovic V, Obrenovic-Kircanski B, Gvozdenovic LJ, Diklic A, Pavlovic D, et al. Cardiovascular complications during anaesthesia in thyroid gland surgery. In: "Proceedings Eurosurgery 2000", Istanbul, Turkey; Bologna: Monduzzi Editore, International Proceeding Division; 2000. p. 127–30.
10. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999; 100(10):1043–9.
11. Boersma E, Kertai MD, Schouten O, Bax JJ, Noordzij P, Steyerberg EW, et al. Perioperative cardiovascular mortality in noncardiac surgery: Validation of the Lee cardiac risk index. Am J Med. 2005; 118(10):1134–41.
12. Aronson S, Stafford-Smith M, Phillips-Bute B, Shaw A, Gaca J, Newman M. Intraoperative systolic blood pressure variability predicts 30-day mortality in aortocoronary bypass surgery patients. Anesthesiology. 2010; 113(2):305–12.
13. Reich DL, Bennett-Guerrero E, Bodian CA, Hossain S, Winfree W, Krol M. Intraoperative tachycardia and hypertension are independently associated with adverse outcome in noncardiac surgery of long duration. Anesth Analg. 2002; 95(2):273–7.
14. Reich DL, Hossain S, Krol M, Baez B, Patel P, Bernstein A, et al. Predictors of hypotension after induction of general anesthesia. Anesth Analg. 2005; 101(3):622–8.
15. Kalezic N, Stojanovic M, Milicic B, Antonijevic V, Sabljak V, Markovic D, et al. The incidence of intraoperative hypertension and risk factors for its development during thyroid surgery. Clin Exp Hypertens. 2013; 35(7):523–7.
16. Sabljak VD, Zivaljevic VR, Milicic BR, Paunovic IR, Toskovic AR, Stevanovic KS, et al. Risk factors for intraoperative hypertension during the surgery of primary hyperparathyroidism. Med Princ Pract. 2017; 26(4):381–6.
17. Paix AD, Runciman WB, Horan BF, Currie MJ. Crisis management during anaesthesia: hypertension. Qual Saf Health Care. 2005; 14(3):e12.
18. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: Literature definitions applied to a retrospective cohort using automated data collection. Anesthesiology. 2007; 107(2):213–20.
19. Bijker JB, van Klei WA, Vergouwe Y, Eleveld DJ, van Wolfswinkel L, Moons KG, et al. Intraoperative hypotension and 1-year mortality after noncardiac surgery. Anesthesiology. 2009; 111(6):1217–26.
20. Boruk M, Chernobilsky B, Rosenfeld RM, Har-El G. Age as a prognostic factor for complications of major head and neck surgery. Arch Otolaryngol Head Neck Surg. 2005; 131(7):605–9.
21. Passler C, Avanessian R, Kaczirek K, Prager G, Scheuba C, Niederle B. Thyroid surgery in the geriatric patient. Arch Surg. 2002; 137(11):1243–8.
22. Mekel M, Stephen EA, Gaz DR, Perry HZ, Hodin AR, Parangi S. Thyroid surgery in octogenarians is associated with higher complication rates. Surgery. 2009; 146(5): 913–21.
23. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg. 2005; 100(1):4–10.
24. Kalezic N, Velickovic J, Jankovic R, Sabljak V, Zivaljevic V, Vucetic C. Preoperative preparation of patient with diabetes mellitus. Acta Chir Yugosl. 2011; 58(2):97–102.
25. Kalezić N, Milosavljević R, Paunović I, Živaljević V, Diklić A, Matić D, et al. The incidence of difficult intubation in 2000 patients undergoing thyroid surgery: single center experience. Vojnosanit Pregl. 2009; 66(5):377–82.
26. Kalezić N, Sabljak V, Stevanović K, Milicić B, Marković D, Tošković A, et al. Predictors of difficult airway management in thyroid surgery: a five-year observational single-center prospective study. Acta Clin Croat. 2016; 55 Suppl 1:9–18.
27. Adnet F, Racine SX, Borron SW, Clemessy JL, Fournier JL, Lapostolle F, et al. A survey of tracheal intubation difficulty in the operating room: a prospective observational study. Acta Anaesthesiol Scand. 2001; 45(3):327–32.
28. Amathieu R, Smail N, Catineau J, Poloujadoff MP, Samii K, Adnet F. Difficult intubation in thyroid surgery: Myth or reality? Anesth Analg. 2006; 103(4):965–8.

Фактори ризика за појаву интраоперативних варијација вредности крвног притиска и срчаних дисритмија током тиреоидне хирургије

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САЖЕТАК

Увод/Циљ Интраоперативне варијације крвног притиска и/или срчане дисритмије (ИВКП/СД) један су од најчешћих узрочника морбидитета и морталитета хируршких болесника. Циљ студије је био да испита учесталост и факторе ризика за појаву ИВКП/СД у тиреоидној хирургији код болесника са коморбидитетима.

Методе Испитивање је обухватило 1252 еутиреоидна болесника *ASA* 2 и *ASA* 3 статуса подвргнутих тиреоидној хирургији. Испитиван је утицај следећих фактора ризика: пол, старост, индекс телесне масе (ИТМ), *ASA* статус, пријемна дијагноза, тип операције, трајање операције, трајање анестезије, отежана интубација трахеје, као и коморбидитети: хипертензија, кардиомиопатија, срчане аритмије, ангина пекторис, дијабетес мелитус, болести бубрега. Регистровани су интраоперативно: хипертензија, хипертензивна криза, хипотензија и срчане аритмије. Коришћен је Пирсонов χ2-тест, униваријантна и мултиваријантна регресиона анализа за статистичку обраду података.

Резултати Већину болесника су чиниле жене (86,3%). ИВКП/СД су регистровани код 903 (72,1%) болесника. Најчешћи поремећај је била интраоперативна хипертензија – 61,4%. Униваријантном анализом је регистровано седам фактора ризика за појаву ИВКП/СД: године живота, *ASA* 3 статус, ИТМ > 25 kg/m^2, трајање хирургије, трајање анестезије, хипертензија и кардиомиопатија као коморбидитет. Мултиваријантном регресионом анализом издвојила су се три независна предиктора појаве ИВКП/СД: године старости, хипертензија и кардиомиопатија.

Закључак ИВКП/СД су честе у тиреоидној хирургији. Најчешћа је интраоперативна хипертензија. Старије животно доба, хипертензија и кардиомиопатија као коегзистирајуће болести су независни фактори ризика за појаву ИВКП/СД.

Кључне речи: тиреоидектомија; хипотензија; хипертензија; срчане аритмије

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Distal humerus nonunions after failed internal fixation – treatment with the Ilizarov external fixator

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SUMMARY

Introduction/Objective Nonunions of the distal humerus after unsuccessful surgical treatment represents a challenging surgical problem. The complexity of this condition is increased by bone atrophy, scar tissue, poorly vascularized bone fragment, limited elbow mobility, osteomyelitis, and local neurological damage. The advantages of using the Ilizarov external fixation method are stable fixation, adequate fracture reduction, and fragment compression accompanied by minimal soft tissue trauma, with the possibility of early elbow mobilization. This aim of this paper is to present the treatment results of 19 patients with nonunion of distal humerus after internal osteosynthesis managed by the Ilizarov external fixation method.

Methods Nineteen consecutive patients were treated with the Ilizarov external fixator. The study group includes 11 male and eight female patients with an average age of 42 years. Surgical technique consisted of approaching the nonunion, removing loose fixation material, making resection and debridement of bone fragments, after which the Ilizarov fixator was placed. Rehabilitation of the elbow started in the early postoperative period. The functional status of the arm was evaluated using the Disabilities of the Arm, Shoulder and Hand (DASH) score.

Results All the patients achieved solid bony union after an average of seven months from the application of the external fixator. In 17 patients radiographic analysis indicated the preservation of joint space, while two showed degenerative changes. All the patients showed improvement in elbow range of motion and significantly better DASH score with postoperative value of 21.

Conclusion As a treatment of distal humerus nonunion, the Ilizarov external fixation method provides successful healing and increased range of motion in the elbow.

Keywords: humerus; nonunion; Ilizarov technique

INTRODUCTION

Nonunions of the distal part of the humerus occurring after unsuccessful fracture treatment with open reduction and internal fixation (ORIF) represents a challenging surgical problem [1]. In most cases, this condition is characterized by instability, pain, weakness and reduced range of motion in the elbow joint, which all leads to a high degree of disability of the entire upper extremity [2]. The complex patterns of fracture, low osteogenic potential, damage of soft tissue, if combined with the wrong or inadequate initial fixation, are the main reasons for the development of pseudoarthrosis in this region of the humerus. Other predisposing factors include older age, alcoholism, smoking, obesity, presence of infection, as well as non-operative treatment [3]. The incidence of pseudoarthrosis after treatment of distal humerus fractures is 8–25%, and is most often encountered in the supracondylar region [4]. The complexity of this condition is increased by bone atrophy, scar tissue from previous interventions, small and poorly vascularized bone fragment, limited elbow mobility, and local neurological damage. Bone stock can be seriously compromised by bone absorption, further accelerated with loosening of osteo-fixation material. All this brings numerous obstacles to the successful healing of pseudoarthrosis and achieving good functional results [5].

The most commonly used treatment methods include internal osteosynthesis, the use of bone grafts, arthroplasty, but also elbow arthrodesis. The definitive treatment modality still remains controversial, initiating numerous discussions and disagreements in orthopedic circles [6]. The main reason for disagreement is the assertion of some experts that open surgery carries an increased risk of disrupting vascularity of fragments, as well as the risk of reducing elbow range of motion. Other studies point to satisfactory results after open intervention, which leads to many difficulties in setting operative indications and deciding on the most appropriate treatment option [2, 3]. The presence of infection and poor local soft tissues makes conventional methods of treatment profoundly difficult [7]. At the Banjica Institute for Orthopedic Surgery (Banjica IOS) these conditions are commonly treated by the Ilizarov method of external fixation. The advantages of using external fixation compared to other treatment methods are stable fixation, adequate fracture reduction, and fragment compression accompanied by minimal soft tissue trauma, with the possibility of early elbow mobilization. The basic principle of the Ilizarov method is stimulating ossification process using a compression force, which provides favorable environment for bone fragment healing and biosynthetic processes witch increase local resistance to infection occurrence [8].

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The aim of this paper is to present the treatment results of 19 patients with nonunion of the distal humerus after internal osteosynthesis managed at our hospital using the Ilizarov external fixation method.

METHODS

In this retrospective study, we analyzed the results of 19 patients treated from 1990 to 2000 at the Banjica IOS with the Ilizarov external fixator for distal humerus nonunion after failed ORIF. The study group includes 11 male and eight female patients with an average age of 42 years (range of 16 to 77 years). The mechanism of injury was fall, motor-vehicle or traffic accident. Five patients had nonunions complicated with osteomyelitis. One patient had ulnar, and one had radial nerve paresthesia, both as a result of an initial injury or previous treatment. Nonunions were diagnosed radiographically at least six months after the initial treatment in terms of failing to develop calluses with loosening of the fixation material. The nonunions were characterized according to Weber and Cech [9] criteria as reactive (present in 10 patients) and non-reactive (present in nine patients) (Table 1).

Pre- and postoperative assessment of the elbow range of motion, neurovascular status, evidence of infection and radiographic evaluation of distal humerus in two planes were carried out. The functional status of the arm was evaluated before and after treatment using the Disabilities of the Arm, Shoulder and Hand (DASH) scores [10, 11].

Surgical technique included the principles for open monolocal compression osteosynthesis using the Ilizarov external fixator. For every patient, surgical treatment was conducted in a single act. After the initial incision, approaching the nonunion was followed by the removal of loose fixation material and by taking of a microbiological swab. The bone ends were debrided and cleaned of all synovial and fibrous tissue with special attention on sparing soft tissue attachment, thus preserving the fragments vascularization. Avascular bone was resected until punctuate bleeding was seen at the bony ends, after which intramedullary canals were opened proximally and distally. The adapted fragments were provisionally reduced and fixed using Kirschner wires. After closing the surgical wound, the Ilizarov fixator was placed. Two transfixation wires were placed in the proximal third of the humerus and attached to the frame. After that, the humerus was fixed and connected to the frame using two wires 4–5 cm long above the nonunion. Three or four distal crossing wires were passed through the epiphyseal–metaphyseal region. The elbow is being extended when placing wires anteriorly and flexed during insertion of wires posteriorly in order to reduce tensions on the soft tissue. Frames were connected with distractors. Axial compression was established on the operating table in order to achieve stabile contact of bone fragments (Figure 1) [8, 12].

From the second postoperative day axial, compression was applied evenly, 0.5–1 mm per day for three to four weeks. After this, the compression was maintained at the rate of 0.5 mm per week until the removal of the fixator.

The physical rehabilitation of the elbow, in terms of active and passive motion exercises, was carried out in the early postoperative period. The patients were initially allowed to use the treated limb without the use of significant force. The control and dressing of the wound and skin around the wires was done once a day. Osseous healing was defined as the presence of crossing trabecular bone on the lateral and anteroposterior radiographs. Upon establishing the fusion of nonunion, the fixator was removed. Physical rehabilitation was resumed to preserve and increase the range of motion in the elbow, to establish the muscle tone, as well as to train the use of the extremity in everyday

Table 1. Preoperative parameters

Case	Age/ Sex	Injury	Type	Complication of fracture	Elbow ROM		Nonunion type	DASH score
					Flex./Ext.	Pro./Sup.		
1	41/M	MVA	open	infection	60/-30	50/40	non-reactive	81.7
2	35/M	MVA	open	infection	80/-30	60/40	reactive	76.7
3	41/F	Fall	closed	radial nerve paresis	50/-30	60/60	reactive	95.8
4	42/M	TA	open		70/-40	90/75	reactive	79.2
5	16/F	TA	open	ulnar nerve paresis	60/-30	90/90	non-reactive	84.2
6	20/M	TA	closed	infection	70/-20	90/90	non-reactive	79.3
7	41/M	Fall	open		60/-40	90/90	reactive	89.2
8	43/M	TA	closed		90/-20	90/90	non-reactive	95.0
9	33/M	TA	closed		60/-80	70/80	reactive	85.8
10	40/M	TA	closed		90/-10	90/90	reactive	89.2
11	33/F	Fall	closed		70/-40	90/90	reactive	83.3
12	25/M	TA	closed		60/-30	90/90	non-reactive	81.7
13	53/F	Fall	closed		90/-20	90/90	non-reactive	90.8
14	26/M	MVA	open	infection	70/-40	90/90	reactive	85.5
15	60/F	Fall	closed		60/-30	90/90	reactive	81.1
16	54/F	Fall	closed		100/-20	90/90	reactive	84.2
17	51/F	Fall	closed		70/-40	70/80	non-reactive	89.2
18	77/F	Fall	closed		40/-20	90/90	non-reactive	80.8
19	73/M	Fall	closed	infection	80/-30	90/90	non-reactive	95.8

MVA – motor vehicle accident; TA – traffic accident; ROM – range of motion; DASH – Disabilities of the Arm, Shoulder and Hand

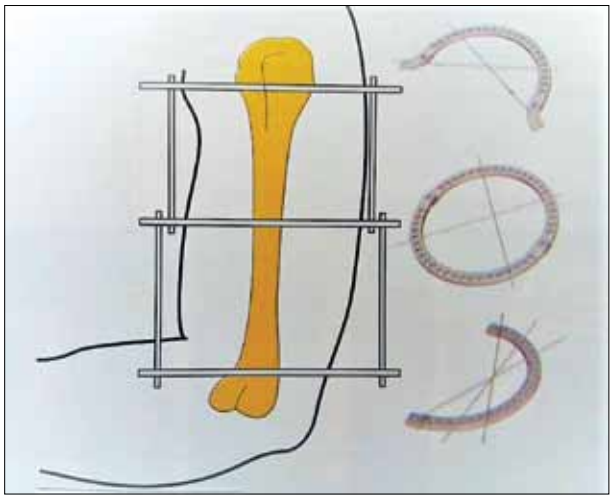

Figure 1. Schematic view of application of the Ilizarov external fixator on the humerus (taken from Tomić [8])

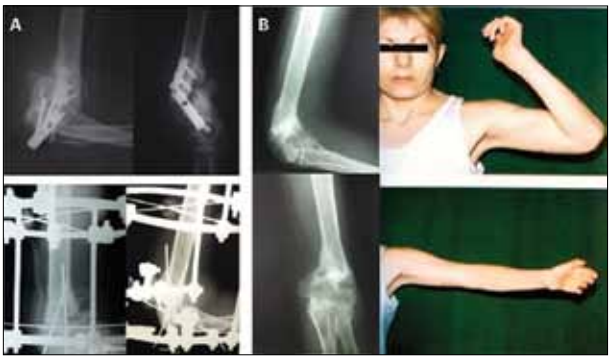

Figure 2. (A) Radiographs of a 33-year-old female patient treated with the Ilizarov method eight months after failed initial osteosynthesis; (B) radiographs and clinical photographs after the application of the Ilizarov fixator for nine months, showing complete union, with elbow motion restoration

activities. The mean follow-up period was 71 months postoperatively (range of 34 to 144 months) (Table 1).

RESULTS

All patients achieved solid bony union. The average time for application of external fixator was seven months (range of five to nine months).

At the last follow-up, the mean range of flexion/extension was 94° to -13°, and pronation/supination 89° to 87°. In all the cases, the elbow range of motion was increased after treatment without clinical signs of instability or significant deviation from the anatomical axis. Radiographic analysis indicated the preservation of joint space in 17 patients, while the other two showed degenerative changes. No elbow instability was encountered for any patient.

There were shortening of the arm, as a result of previous surgeries, bone resorption, debridement, and compression at the nonunion site. An average shortening measured at the last follow-up was 3 ± 1.5 cm, which did not affect the functionality of the limb and was well tolerated by the patients.

All the patients exhibited improvements in shoulder and elbow motion after treatment. The mean value of the DASH score before surgery was 86, whereas the mean score after complete recovery was 21. This showed a significant recovery in the function of the entire upper extremity (Figure 2). Postoperatively, nine patients had no pain in the elbow, eight had moderate pain, while the two had severe pain. Ten patients showed almost complete recovery with minimal disability, while seven had moderate residual disability, and two had severe elbow function impairment. Complete soft-tissue recovery was achieved in all the patients.

There were eight postoperative infections. Five patients had superficial pin-tract infection, successfully treated with oral antibiotics and antiseptic solutions applied locally. The other three had infections of deep structures resolved with debridement, irrigation, intravenous administration of antibiotic and reassembly of external fixator. Two patients had ulnar nerve paresthesia and were treated conservatively, with complete recovery after two mounts. All postoperative parameters are shown in Table 2.

DISCUSSION

Nonunions of the distal humerus are uncommon and are usually associated with instability, reduced elbow mobility, strength loss, pain, and functional loss [3].

An important factor in the development of nonunion of the distal humerus is inadequate choice of surgical techniques or implants during the primary fracture operation [13]. The treatment of nonunions of this region, after previously unsuccessful surgeries is very difficult and complex [14]. Repeated procedures in the area above the elbow usually result in elbow contractures, articular cartilage deterioration, and, in most cases, ulnar nerve lesions [15]. Each of these conditions should be taken into consideration during preoperative evaluation and treatment selection. Although such operations are difficult and complicated, detailed preoperative planning with adequate fixation methods and early postoperative rehabilitation ensures healing and good functional results [6]. These nonunions present with wide range of different characteristics, consequently surgical treatment must be individualized for each patient [3].

Because of the complexity of this problem, decision making in the management of these nonunions is difficult and not well clarified in the literature [6]. The type of treatment depends on several factors, including functional requirements of the patient, the condition of soft tissues and articular cartilage, the range of motion in the elbow, and bone quality [16]. Many treatment options have been described, including open reduction – internal fixation with plates and screws, intramedullary nailing with interfragmentary wiring, elbow arthroplasty, and free vascularized bone grafting [17–20].

This paper describes treatment of patients with nonunion of the distal part of the humerus with the Ilizarov external fixator. The advantages of this method are the ability to achieve adequate fracture reduction and stable fixation, to provide a gradual or intermittent compression of fragments, and to allow early rehabilitation, as well as the opportunity to treat transitional infected nonunions [8].

Table 2. Postoperative parameters

Case	Follow-up (months)	EFT (months)	Pain	Disability	Elbow ROM		Compl.	Shortening (cm)	DASH score
					Flex./Ext.	Pro./Sup.			
1	96	9	none	minimal	80/-20	90/50	DI	2.0	25.0
2	116	9	none	moderate	100/-10	90/90	DI	4.5	20.0
3	84	6	none	moderate	100/-20	90/90	PTI	3.5	24.2
4	36	7	none	moderate	110/-10	80/90		4.0	14.2
5	38	6	none	minimal	90/-10	90/90		3.0	25.0
6	112	9	moderate	moderate	90/-20	90/90	PTI	2.0	15.8
7	96	8	moderate	minimal	90/-30	90/90		1.5	20.0
8	100	8	moderate	moderate	110/-10	90/90		2.0	27.5
9	144	7	moderate	minimal	90/-10	90/90	PTI	2.0	20.5
10	120	6	moderate	moderate	110/-0	90/90		4.0	20.8
11	60	5	none	minimal	90/-20	90/90		2.0	14.2
12	37	8	none	minimal	90/-10	90/90	UNP	4.0	20.0
13	39	9	moderate	moderate	110/-10	90/90	UNP	2.0	24.2
14	94	8	moderate	minimal	90/-10	90/90	PTI	3.0	20.8
15	36	7	none	minimal	80/-10	90/90		2.0	17.5
16	34	6	none	minimal	110/-10	90/90		3.5	14.2
17	39	6	moderate	minimal	90/-20	80/80		4.0	18.3
18	36	9	severe	severe	60/-10	90/90	PTI	3.5	29.2
19	34	8	severe	severe	90/-10	90/90	DI	2.5	27.5

EFT – external fixator time; PTI – pin-track infection; DI – deep infection; UNP – ulnar nerve paraesthesia; Compl. – complications; ROM – range of motion; DASH – Disabilities of the Arm, Shoulder and Hand

The clinical and radiographic results of this study correlate with the findings of Brinker et al. [15] by the range of motion and the rate of healing nonunions this part of the humerus. We consider that the success of the procedure is determined by standardizing surgical techniques in terms of complete and thorough debridement of nonunions exposing fresh bleeding bone ends; adjustment of fragments for appropriate contact; application of the adequate structure of the fixator; direct and intermittent compression; implementation of early physical rehabilitation and removal of the fixator only after verification of complete healing.

Infected nonunions are associated with marked osteopenia, a significant articular contracture, focal bone defects, and avascular or necrotic parts of bones that make reconstruction even more challenging. Studies show significantly worse results than those obtained in aseptic nonunions [7]. Success of this method in septic pseudoarthrosis is confirmed by the results of Brinker et al. [15], who applied on their patients a surgical technique similar to the one used in this study.

In a study conducted by Mitsunaga et al. [21], priority was given to achieving osseous healing over mobility, as the secondary objective. Their results showed union in 80% of patients with only 9° improvement in the elbow range of motion. Capsular release and arthrolysis in patients with distal humerus nonunion and motion limitation due to articular causes improve elbow mobility and reduce stress on the healing site during postoperative mobilization [3]. Many of the patients in the published ORIF studies underwent multiple contracture releases, sometimes in staged procedures, to attain their final range of motion [15]. In our series of patients, there was no need for subsequent loosening of soft tissue to improve the range of motion in the elbow. We believe that a stable fixation and early mobilization are equally important factors in the treatment of these conditions.

Significant DASH score improvement is consistent with other studies that analyzed the results of the Ilizarov method treatment [15]. Although it is uncomfortable for some patients, an external fixator provides stabile fixation of the nonunion site which allows greater freedom of movement in the shoulder and elbow, by which the whole arm becomes more functional [22]. The relatively small amount of shortening in our series was well tolerated by the patients and did not affect their functional outcome.

In our research, the ulnar neuropathy occurred in two patients, which were successfully treated non-operatively. Some authors state that anterior transposition of the ulnar nerve should be a routine part of the surgical procedure in the treatment of such nonunions [3].

ORIF is generally a recommended type of treatment of uninfected nonunions in younger, more active patients who have good bone stock at the injury site [16]. Ring et al. [2] treated 15 unstable nonunion of the distal humerus with contracture release, ORIF, and bone grafting. The functional results in their study were excellent in two patients, good in nine, and fair in one case.

Total elbow arthroplasty can be useful in older patients with osteoarthritis, but its application in younger patients remains controversial [19]. It is considered to be a technically demanding salvage procedure and should be done only when other operative procedures are unsatisfactory [23].

Elbow arthrodesis is reserved only for patients with infected nonunion. The procedure does not provide good results, since it affects the essential function of the elbow, thus limiting the movement in the joint. Resection or distraction arthroplasty and the use of joint allograft have yielded disappointing results [24].

CONCLUSION

Treatment of distal humerus nonunions with the Ilizarov external fixator after failed internal osteosynthesis provides successful healing and increased range of motion in the elbow. This method should be considered as the primary choice of treatment of distal humerus nonunion.

REFERENCES

1. Helfet DL, Kloen P, Anand N, Rosen HS. Open reduction and internal fixation of delayed unions and nonunions of fractures of the distal part of the humerus. J Bone Joint Surg Am. 2003; 85-A(1):33–40.
2. Ring D, Gulotta L, Jupiter JB. Unstable nonunions of the distal part of the humerus. J Bone Joint Surg Am. 2003; 85-A:1040–6.
3. Allende C, Allende BT. Post-traumatic distal humerus non-union: Open reduction and internal fixation: long-term results. Int Orthop. 2009; 33(5):1289–94.
4. Sanchez-Sotelo J, Torchia ME, O'Driscoll SW. Complex distal humeral fractures: Internal fixation with a principle-based parallel-plate technique. J Bone Joint Surg Am. 2007; 89(5):961–9.
5. Gallay SH, McKee MD. Operative treatment of nonunions about the elbow. Clin Orthop Relat Res. 2000; 370:87–101.
6. Patel VR, Menon K, Pool RD, Simonis RB. Nonunion of the humerus after failure of surgical treatment. Management using the Ilizarov circular fixator. J Bone Joint Surg Br. 2000; 82(7):977–83.
7. Haidukewych GJ, Sperling JW. Results of treatment of infected humeral nonunions: the Mayo Clinic experience. Clin Orthop Relat Res. 2003; 414:25–30.
8. Tomić S. Pseudoartroze i defekti kostiju, Metod Ilizarova. Beograd: Želnid; 2001. p. 121–48.
9. Weber BG, Cech O. Pseudoarthrosis: Pathology, Biomechanics, Therapy, Results. Berne, Switzerland: Hans Huber Medical Publisher; 1976. p. 181–4.
10. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med. 1996; 29(6):602–8.
11. Beaton DE, Katz JN, Fossel AH, Wright JG, Tarasuk V, Bombardier C. Measuring the whole or the parts? Validity, reliability, and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. J Hand Ther. 2001; 14(2):128–46.
12. Tomić S, Bumbaširević M, Lešić A, Mitković M, Atkinson HD. Ilizarov frame fixation without bone graft for atrophic humeral shaft nonunion: 28 patients with a minimum 2-year follow-up. J Orthop Trauma. 2007; 21(8):549–56.
13. Ali A, Douglas H, Stanley D. Revision surgery for nonunion after early failure of fixation of fractures of the distal humerus. J Bone Joint Surg Br. 2005; 87(8):1107–10.
14. Pugh DM, McKee MD. Advances in the management of humeral nonunion. J Am Acad Orthop Surg. 2003; 11(1):48–59.
15. Brinker MR, O'Conner DP, Crouch CC, Mehlhoff TL, Bennett JB. Ilizarov treatment of infected nonunions of the distal humerus after failure of internal fixation: an outcomes study. J Orthop Trauma. 2007; 21(3):178–84.
16. Ackerman G, Jupiter JB. Non-union of fractures of the distal end of the humerus. J Bone Joint Surg Am. 1988; 70(1):75–83.
17. Galatz LM, Williams GR Jr, Fenlin JM Jr, Ramsey ML, Iannotti JP. Outcome of open reduction and internal fixation of surgical neck nonunions of the humerus. J Orthop Trauma. 2004; 18(2):63–7.
18. Lin J, Chiang H, Chang DS. Locked nailing with interfragmentary wiring for humeral nonunion. J Trauma. 2002; 52(4):733–8.
19. Morrey BF, Adams RA. Semiconstrained elbow replacement for distal humeral nonunion. J Bone Joint Surg Br. 1995; 77(1):67–72.
20. Beredjiklian PK, Hotchkiss RN, Athanasian EA, Ramsey ML, Katz MA. Recalcitrant nonunion of the distal humerus: treatment with free vascularized bone grafting. Clin Orthop Relat Res. 2005; (435):134–9.
21. Mitsunaga MM, Bryan RS, Linscheid RL. Condylar nonunions of the elbow. J Trauma. 1982; 22(9):787–91.
22. Safoury YA, Atteya MR. Treatment of post-infection nonunion of the supracondylar humerus with Ilizarov external fixator. J Shoulder Elbow Surg. 2011; 20(6):873–9.
23. Sanchez-Sotelo J, Morrey BF. Linked elbow replacement: a salvage procedure for distal humeral nonunion. Surgical technique. J Bone Joint Surg Am. 2009; 91 Suppl 2:200–12.
24. Allieu Y, Marck G, Chammas M, Desbonnet P, Raynaud JP. Total elbow joint allograft for long term posttraumatic osteoarticular loss. Follow-up results at twelve years. Rev Chir Orthop Reparatrice Appar Mot. 2004; 90(4):319–28.

Псеудоартрозе дисталног хумеруса после неуспеле унутрашње остеосинтезе – лечење методом Илизарова

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САЖЕТАК

Увод/Циљ Псеудоартрозе дисталног дела хумеруса после неуспелог оперативног лечења су изазован хируршки проблем. Комплексности стања доприносе коштана атрфија, ожиљно ткиво, инсуфицијентна васкуларизација фрагмената, контрактура лакта, остеомијелитис и неуролошке лезије. Предности коришћења спољашњег фиксатора огледају се у могућности стабилне фиксације, адекватне репозиције и компресије праћене минималном траумом меких ткива уз могућност ране мобилизације лакта.

Циљ овог рада је био анализа резултата код 19 болесника са псеудоартрозом дисталног дела хумеруса лечених методом Илизарова после неуспеле унутрашње остеосинтезе.

Материјал Методом Илизарова лечено је 19 болесника – 11 мушкараца и 8 жена просечне старости 42 године. Хируршка техника састојала се у отварању псеудоартрозе, уклањању остеофиксационог материјала, ресекцији и дебридману коштаних фрагмената и постављању Илизаровљевог апарата. Непосредно после операције започета је физикална рехабилитација покрета у лакту. Функционални статус руке евалуиран је помоћу *DASH* скора.

Резултати Код свих испитиваних констатовано је потпуно коштано зарастање псеудоартрозе после просечног ношења апарата од седам месеци. Код 17 болесника радиографски је потврђен очуван зглобни простор, док су се код два развили знаци дегенеративног обољења лакта. Код свих је повећан обим покрета у лакту уз значајно бољи *DASH* скор после операције (просечно 21).

Закључак Лечење псеудоартроза дисталног хумеруса методом Илизарова обезбеђује успешно зарастање и повећање обима покрета у лакту.

Кључне речи: хумерус; псеудоартроза; метод Илизарова

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Effect of anterior cruciate ligament reconstruction with hamstring tendons on Insall–Salvati index and anterior knee pain

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SUMMARY
Introduction/Objective The relationship between anterior knee pain and the Insall–Salvati ratio after anterior cruciate ligament (ACL) reconstruction with hamstring tendon were evaluated in this study.
Methods We evaluated 39 patients that had an ACL reconstruction surgery with hamstring tendon. All the patients were evaluated for the Insall–Salvati ratio preoperatively and postoperatively. Fourteen patients had anterior knee pain at the end of the first year after the surgery. The patients were evaluated at the end of the first year after the surgery with the Lysholm score and the Tegner activity scale. The patients' preoperative and postoperative measurements were analyzed by using the Wilcoxon test, and the differences between the patients with anterior knee pain and those without it were analyzed by the Mann–Whitney U test.
Results Preoperatively, mean Insall–Salvati ratio was found to be 0.91 ± 0.1, whereas postoperative ratio was 0.85 ± 0.09 ($p \leq 0.05$). In the group without anterior knee pain, the mean Tegner activity score was 8.56 ± 1.04, and the mean Lysholm score was 87.36 ± 9.42. The mean Tegner activity score was 7.21 ± 0.97 and the mean Lysholm score was 74.43 ± 9.94 in the group with anterior pain. There was a decrease in the Insall–Salvati ratio as a result of the surgery, but patients with anterior knee pain had lower values of the Insall–Salvati ratio preoperatively.
Conclusion Low preoperative Insall–Salvati ratio can be an indicator of anterior knee pain in the early period after ACL reconstruction with hamstring tendons. The mean Tegner activity score and the mean Lysholm score have higher values in the group without anterior pain postoperatively.
Keywords: anterior cruciate ligament, reconstruction; Insall–Salvati index; hamstring tendons

INTRODUCTION

Anterior cruciate ligament (ACL) injuries are commonly seen injuries among knee joint especially in young population [1]. Reconstruction of the ACL is a well-established procedure with hamstring tendons. Approximately 200,000 ACL reconstructions are performed annually in the United States. ACL injury incidence is one in 3,000 per year [2]. There are two main goals of ACL reconstruction. The first one is the restoration of functional stability without pain. The second one is to prevent degenerative changes of the knee joint. There are several defined surgical techniques for the reconstruction of an ACL tear. As a result of these reconstruction techniques, several complications can be seen. Anterior knee pain is an important complication that can be seen after ACL reconstruction. Etiology of anterior knee pain includes chondromalacia of the patella, patellar tendinitis, lateral compression syndrome, quadriceps tendinitis, and patella maltracking. It can especially be seen after the reconstruction done with patellar tendon.

The Insall–Salvati ratio is used for determining the patellar position with patellar tendon and patellar length ratio. There is a relation between patella position and anterior knee pain. Shortening of the patellar tendon can be the reason for patellofemoral pain. As a result of the patellar tendon, shortening flexion contracture can occur. This may explain the relation between the patella baja and patellofemoral pain [3]. Another theory for the etiology of patellofemoral pain or anterior knee pain is the quadriceps inhibition. According to this theory, there is an alteration of patellar tracking when quadriceps contract in the ACL-deficient knee near the extension. Anterior translation of the tibia can push the patella laterally and this force changes patellar contact areas and anterior knee pain can occur as a result of these contact area differences. The third reason is the general inflammation of the joint, which can be the reason for decreased patellar mobility and increased patellar compression forces[4].

There have been technical changes and advances during recent years for the treatment of ACL tear and many studies showed successful results of arthroscopic ACL reconstruction [5]. Hamstring tendons as autografts are a popular treatment modality for ACL reconstruction nowadays. Anterior knee pain is an important problem that can also be faced after ACL reconstruction with a hamstring tendon.

The primary goal of this retrospective study is to compare the Insall–Salvati ratio of the ACL reconstructed knee preoperatively and

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postoperatively. The secondary goal is to investigate the relationship between the anterior knee pain and the Insall–Salvati ratio.

METHODS

Study design

This study was conducted in accordance with the ethical standards of the institutional committee and with the Helsinki Declaration of 1975, as revised in 2013, following the institutional review board approval No. 10840098- 604.01.01-E.22402. We retrospectively evaluated 39 patients who underwent ACL reconstruction surgery with the hamstring tendon graft between January 2014 and January 2015. There were three female and 36 male patients. The mean age of the patients was 27.8 years (the range being 18–47 years) at the time of surgery. We evaluated 39 patients as two groups – the first one comprised patients with anterior knee pain, and the second one those without it. Fourteen patients had persistent anterior knee pain one year after the surgery. Preoperative and postoperative Insall–Salvati ratio was determined by lateral X-ray imaging. Postoperative Lysholm and Tegner activity scale scores of the patients were collected.

Radiological measurements

The measurement of the patellar height was based on the Insall–Salvati method and was determined by the ratio of the patellar tendon length over the diagonal distance of the patella bone on a lateral view radiograph with the knee at 20–30° of flexion. The normal value of the patellar height was 1.0 ± 0.2 SD. Patella alta is defined as the ratio greater than 1.2, and patella baja as the ratio of 0.8 or less [6].

Clinical outcome measurements

The patients were evaluated at the end of the first year after the surgery with the Lysholm score and the Tegner activity scale. The Tegner activity scale is used to measure the outcome of knee ligament injuries [7]. The Lysholm score determines the functional status of the patient [8]. The Tegner activity scale is an extension of the Lysholm score that gives information about activity level [8].

Surgical technique

All the ACL reconstructions were performed by using hamstring tendon as autograft. The hamstring tendons (semitendinosus and gracilis tendons) were harvested. Double-loop (four-stranded) grafts of the hamstring tendons were prepared. Femoral tunnel is prepared through the anteromedial arthroscopic portal. We prefer the transportal technique because it provides an improved position of tibial and femoral tunnels when compared with the trans-tibial technique [9]. Femoral side fixation was provided with an endobutton, while tibial side fixation was provided with bio-screws and staples.

Postoperative treatment and evaluation

All the patients used knee braces in full extensions for the treated knee after the surgery. Early range of motion exercise and quadriceps muscle strengthening was encouraged in all the patients. All the patients were included in the same physiotherapy program.

Statistical analysis

Compliance with the normal distribution of the data has been tested and non-parametric methods were used because they are not normally distributed. The patients' preoperative and postoperative Insall–Salvati values and clinical outcome measurements were analyzed by the Wilcoxon test, and the differences between patients with anterior knee pain and those without it were analyzed by the Mann–Whitney U-test; 95% confidence interval was used and $p < 0.05$ was considered statistically significant.

RESULTS

Radiological results

Preoperative mean Insall–Salvati ratio was found to be 0.91 ± 0.1. Postoperative mean Insall–Salvati ratio was 0.85 ± 0.09 ($p \leq 0.05$) There was a statistically significant difference between the preoperative and postoperative Insall–Salvati ratio. The mean Insall–Salvati ratio was found to be 0.93 ± 0.1 in the group without anterior pain preoperatively. The mean Insall–Salvati ratio was 0.86 ± 0.09 in the group with anterior knee pain preoperatively. Postoperatively, the mean Insall–Salvati ratio was 0.89 ± 0.8 in the group without anterior knee pain, while the mean Insall–Salvati ratio was 0.79 ± 0.7 in the group with anterior knee pain. There was also a statistically significant difference between the preoperative and postoperative Insall–Salvati ratio between the groups (pre: $p = 0.025$; post: $p = 0.002$). There was a decrease in the Insall–Salvati ratio as a result of the surgery, but patients with anterior pain had lower values of the Insall–Salvati ratio preoperatively. Low preoperative Insall–Salvati ratio can be an indicator of anterior knee pain after ACL reconstruction with hamstring tendons. Among these 39 patients, 11 had the Insall–Salvati ratio less than 0.8. However, these 11 patients also had the Insall–Salvati ratio less than 0.8 preoperatively.

Clinical outcome measurements

The mean Tegner activity score was 8.08 ± 1.2 and the mean Lysholm score was 82.72 ± 11.37 postoperatively. The mean Tegner activity score was 8.56 ± 1.04 and the mean Lysholm score was 87.36 ± 9.42 in the group without anterior knee pain. The mean Tegner activity score was 7.21 ± 0.97 and the mean Lysholm score was 74.43 ± 9.94 in the group with anterior pain. The mean Tegner activity score and the mean Lysholm score had higher values in

the group without anterior pain. There was a statistically significant difference in the postoperative mean Tegner activity score and the mean Lysholm score between the two groups ($p \leq 0.001$).

DISCUSSION

According to the study done by Hantes et al. [10], patellar tendon shortening can be seen after harvesting the patellar tendon for anterior cruciate ligament reconstruction. However, there is no shortening of the patellar tendon after harvesting the hamstring tendons for anterior cruciate ligament reconstruction. Authors stated that there was no significant difference between functional outcome and incidence of patella baja between the two groups [10]. Our results, on the other hand, indicate a decrease in the Insall–Salvati ratio between preoperative and postoperative values in the ACL deficient knees treated with hamstring tendons.

After an ACL injury, patellar tendon length elongation can be seen. This elongation increases the Insall–Salvati ratio. Increased patellar tendon length can be the reason for quadriceps muscle weakness after an ACL injury. The patellar tendon length has an effect on biomechanical properties of the patellar articulation [11]. An increased length of the patellar tendon can cause an increase in quadriceps slack length, which reduces quadriceps mechanical advantage [12]. Our results show patellar tendon shortening after ACL reconstruction because of the decrease in the Insall–Salvati ratio between preoperative and postoperative values. After the ACL reconstruction and quadriceps muscle strengthening physiotherapy program there can be shortening of patellar tendon length. It can be the reason why we have detected patellar tendon shortening between preoperative and postoperative values.

The Insall–Salvati ratio is low for patella baja, which is noted as a risk factor for ACL injury in adults [13]. As a result of another study that evaluated ACL injuries in children, there is a significant association between an ACL tear and the increased patellar tendon length with a greater Insall–Salvati ratio. For this reason, patella alta can be a risk factor for ACL injuries in pediatric patients [14]. Mean preoperative value of the Insall–Salvati ratio is 0.91 ± 0.1 according to our study.

Patients with higher body mass index, low physical performance, low quality of life, kinesiophobia, and late return to sportive activities have patello femoral pain after ACL reconstruction. Older age at the time of ACL reconstruction was only predictor for patellofemoral pain [15]. Preoperative quadriceps strength, age, sex, and knee pain are important factors to achieve sufficient quadriceps strength recovery at the time of returning to sports activities [16]. In our study, there is no statistical evaluation of the relationship between the age at the time of the surgery and anterior knee pain after ACL reconstruction. But in general terms, we detected anterior knee pain in all age groups.

Patellofemoral osteoarthritis is another important factor for anterior knee pain after ACL reconstruction and it is associated with decreased functional performance [17]. Patellofemoral osteoarthritis was detected in 26% of patients 12 years after ACL reconstruction. Increased age and tibiofemoral osteoarthritis are predisposing factors for patellofemoral osteoarthritis after ACL reconstruction [18]. Excessive lateral pressure syndrome and patellar lateralization are strongly correlated with anterior knee pain after ACL reconstruction [19]. Abnormal orientation in the coronal plane and twist of the patellar tendon can be the reason for patellar rotation. As a result of this rotation, the contact pressure of the lateral patellofemoral joint increases, which may predispose degenerative changes and anterior knee pain after ACL reconstruction [20]. After excision of the ACL in cadaveric knees, lateral shift and tilt of the patella increases as a result of these biomechanical changes, contact area and pressure on the patellofemoral joint decreases [21, 22]. We did not evaluate the relationships of patellofemoral osteoarthritis in our patients with anterior knee pain. Also, our follow-up period was too short to make such inferences.

Increased blood flow in the infrapatellar fat pad is an important factor for anterior knee pain after ACL reconstruction with hamstring tendon autografts, and ultrasound evaluation can be useful for determining the etiology of the anterior knee pain [23]. However, we did not perform ultrasound evaluation of our patients with anterior knee pain after ACL reconstruction.

According to the study by Chase et al. [24], patella baja has no effect on postoperative anterior knee pain. But the loss of knee extension greater than 5° correlates with anterior knee pain [24]. There is a statistically significant difference in the results of the Lysholm score and the Tegner activity scale in bwtween the group with anterior pain and the one without it. Also, we have found statistically significant difference between patella baja and anterior knee pain after ACL reconstruction with hamstring tendons.

There are numerous studies which compare graft selection and anterior knee pain after ACL reconstruction. Increased anterior knee pain and kneeling pain have been reported after ACL reconstruction with bone – patellar tendon – bone autografts when compared with hamstring tendon autografts [25]. But some study results show that there were no significant differences in terms of anterior knee pain after ACL reconstruction with bone – patellar tendon – bone autografts or hamstring tendon autografts [26]. In a study by Shi and Yao [27] there is greater pain upon kneeling in the group with hamstring tendon grafts than in the one with patellar tendon grafts. In our series there were 14 patients with anterior knee pain that had ACL reconstruction with hamstring tendons. There was no group that was treated with bone – patellar tendon – bone autografts in our study. In our study there is a restriction for the relationship between anterior knee pain and graft selection for ACL reconstruction.

Hantes et al. [10] compared the patellar tendon length in two groups after ACL reconstruction. The first group included patients that were treated with patellar tendons; the second group included patients treated with hamstring tendons. Operated knee values were compared to the non-operated side. They detected a significant 4.2 mm (9.7%)

patellar tendon shortening in the patellar tendon group and a non-significant 1.14 mm (2.6%) shortening in the hamstring tendon group and as a result of the study incidence of patella baja and overall functional outcome was not significantly different between the two groups [10]. We also detected patellar tendon shortening after ACL reconstruction with the hamstring tendon, but we evaluated the operated knees. We did not compare the operated side to the healthy side. This is an important restriction of our study.

CONCLUSION

There is a decrease in the Insall–Salvati ratio as a result of the surgery. However, patients with anterior knee pain had lower values of the Insall–Salvati ratio preoperatively. Preoperatively low Insall–Salvati ratio can be an indicator of anterior knee pain in the early period after ACL reconstruction with hamstring tendons. The mean Tegner activity score and the mean Lysholm score have higher values in the group without anterior pain postoperatively.

REFERENCES

1. Gianotti SM, Marshall SW, Hume PA, Bunt L. Incidence of anterior cruciate ligament injury and other knee ligament injuries: a national population-based study. J Sci Med Sport. 2009; 12(6):622–7.
2. National Institutes of Health (NIH) (2007). Prognosis and predictors of ACL reconstruction – a multicenter cohort study. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), Vanderbilt University, United States. (Accessed March 1, 2011). Available at: http://clinicaltrials.gov/ct2/show/NCT00463099.
3. Sachs RA, Daniel DM, Stone ML, Garfein RF. Patellofemoral problems after anterior cruciate ligament reconstruction. Am J Sports Med. 1989; 17(6):760–5.
4. Steiner ME. Surgical management of anterior cruciate ligament injuries. In: McKeon BP, Bono JV, Richmond JC, eds. Knee Arhroscopy: Springer; 2009. p. 128–52.
5. Prodromos CC, Han YS, Keller BL, Bolyard RJ. Stability results of hamstring anterior cruciate ligament reconstruction at 2- to 8-year follow-up. Arthroscopy. 2005; 21(2):138–46.
6. Insall J, Salvati E. Patella position in the normal knee joint. Radiology. 1971; 101:101–4.
7. Briggs KK, Lysholm J, Tegner Y, Rodkey WG, Kocher MS, Steadman JR. The reliability, validity, and responsiveness of the Lysholm score and Tegner activity scale for anterior cruciate ligament injuries of the knee: 25 years later. Am J Sports Med. 2009; 37(5):890–7.
8. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. Clin Orthop Relat Res. 1985; 198:43–9.
9. Yau WP, Fok AW, Yee DK. Tunnel positions in transportal versus transtibial anterior cruciate ligament reconstruction: a case-control magnetic resonance imaging study. Arthroscopy. 2013; 29(6):1047–52.
10. Hantes ME, Zachos VC, Bargiotas KA, Basdekis GK, Karantanas AH, Malizos KN. Patellar tendon length after anterior cruciate ligament reconstruction: a comparative magnetic resonance imaging study between patellar and hamstring tendon autografts. Knee Surg Sports Traumatol Arthrosc. 2007; 15(6):712–9.
11. van Eijden TM, Kouwenhoven E, Weijs WA. Mechanics of the patellar articulation: effects of patellar ligament length studied with a mathematical model. Acta Orthop Scand. 1987; 58(5):560– 6.
12. Draganich LF, Andriacchi TP, Andersson GB. Interaction between intrinsic knee mechanics and the knee extensor mechanism. J Orthop Res. 1987; 5(4):539–47.
13. Lin CF, Wu JJ, Chen TS, Huang TF. Comparison of the Insall–Salvati ratio of the patella in patients with and without an ACL tear. Knee Surg Sports Traumatol Arthrosc. 2005; 13(1):8–11.
14. Degnan AJ, Maldjian C, Adam RJ, Fu FH, Didomenico M. Comparison of Insall–Salvati ratios in children with an acute anterior cruciate ligament tear and a matched control population. AJR Am J Roentgenol. 2015; 204(1):161–6.
15. Culvenor AG, Collins NJ, Vicenzino B, Cook JL, Whitehead TS, Morris HG, et al. Predictors and effects of patellofemoral pain following hamstring-tendon ACL reconstruction. J Sci Med Sport. 2016; 19(7):518–23.
16. Ueda Y, Matsushita T, Araki D, Kida A, Takiguchi K, Shibata Y, et al. Factors affecting quadriceps strength recovery after anterior cruciate ligament reconstruction with hamstring autografts in athletes. Knee Surg Sports Traumatol Arthrosc. 2017; 25(10):3213–9.
17. Culvenor AG, Lai CC, Gabbe BJ, Makdissi M, Collins NJ, Vicenzino B, et al. Patellofemoral osteoarthritis is prevalent and associated with worse symptoms and function after hamstring tendon autograft ACL reconstruction. Br J Sports Med. 2014; 48(6):435–9.
18. Øiestad BE, Holm I, Engebretsen L, Aune AK, Gunderson R, Risberg MA. The prevalence of patellofemoral osteoarthritis 12 years after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc. 2013; 21(4):942–9.
19. Osowska K, Fabiś J, Fabiś A, Grodzka M, Zwierzchowski JT. The evaluation of the influence of selected patellofemoral joint geometry indicators observed in magnetic resonance imaging on the incidence of anterior knee pain in patients after anterior cruciate ligament reconstruction using hamstrings. Pol Orthop Traumatol. 2013; 78:247–50.
20. van de Velde SK, Gill TJ, DeFrate LE, Papannagari R, Li G. The effect of anterior cruciate ligament deficiency and reconstruction on the patellofemoral joint. Am J Sports Med. 2008; 36(6):1150–9.
21. Hsieh YF, Draganich LF, Ho SH, Reider B. The effects of removal and reconstruction of the anterior cruciate ligament on patellofemoral kinematics. Am J Sports Med. 1998; 26(2):201–9.
22. Hsieh YF, Draganich LF, Ho SH, Reider B. The effects of removal and reconstruction of the anterior cruciate ligament on the contact characteristics of the patellofemoral joint. Am J Sports Med. 2002; 30(1):121–7.
23. Kanamoto T, Tanaka Y, Yonetani Y, Kita K, Amano H, Kusano M, et al. Anterior knee symptoms after double-bundle ACL reconstruction with hamstring tendon autografts: an ultrasonographic and power Doppler investigation. Knee Surg Sports Traumatol Arthrosc. 2015; 23(11):3324–9.
24. Chase JM, Hennrikus WL, Cullison TR. Patella infera following arthroscopic anterior cruciate ligament reconstruction. Contemp Orthop. 1994; 28(6):487–93.
25. Xie X, Xiao Z, Li Q, Zhu B, Chen J, Chen H, et al. Increased incidence of osteoarthritis of knee joint after ACL reconstruction with bone – patellar tendon – bone autografts than hamstring autografts: a meta-analysis of 1,443 patients at a minimum of 5 years. Eur J Orthop Surg Traumatol. 2015; 25(1):149–59.
26. Heijne A, Hagströmer M, Werner S. A two- and five-year follow-up of clinical outcome after ACL reconstruction using BPTB or hamstring tendon grafts: a prospective intervention outcome study. Knee Surg Sports Traumatol Arthrosc. 2015; 23(3):799–807.
27. Shi DL, Yao ZJ. Knee function after anterior cruciate ligament reconstruction with patellar or hamstring tendon: a meta-analysis. Chin Med J (Engl). 2011; 124(23):4056–62.

Ефекти реконструкције предње унакрсне везе затколеним тетивама на Инсол–Салватијев индекс и бол у колену

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САЖЕТАК

Увод/Циљ Циљ овог рада је био процена односа бола у колену и Инсол–Салватијевог односа после реконструкције предње унакрсне везе (ПУВ) затколеним тетивама.

Методе Анализирали смо 39 испитаника са реконструкцијом ПУВ. Код свих испитаника одређени су Инсол–Салватијев индекс пре и постоперативно, а годину дана после операције Лисхолмов скор и Тегнерова скала активности. Бол у колену је имало њих 14 у години после операције. Пре и постоперативне вредности анализиране су Вилкоксоновим тестом, а Ман–Витнијевим У тестом разлике код испитаника са боловима и без њих.

Резултати Инсол–Салватијев индекс је преоперативно био 0,91 ± 0,1, а постоперативно 0,85 ± 0,09 ($p \leq 0,05$). У групи без болова у колену вредност Тегнерове скале била је 8,56 ± 1,04, а Лисхолмовог скора 87,36 ± 9,42. У групи са болом у колену вредност Тегнерове скале била је 7,21 ± 0,97, а Лисхолмовог скора 74,43 ± 9,94. Постоји смањење Инсол–Салватијевог индекса као резултат операције, али болесници са боловима у колену су преоперативно имали ниже вредности овог индекса.

Закључак Преоперативно низак Инсал–Салватијев индекс може бити значајан индикатор бола у колену у раном периоду после реконструкције ПУВ са затколеним тетивама. Вредности Тегнерове скале активности и Лисхолмовог скора биле су веће у групи без бола после операције.

Кључне речи: предња унакрсна веза, реконструкција; Инсол–Салвати индекс; затколене тетиве

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Angiogenic capabilities of omentomyelopexy for injured spinal cord revascularization

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SUMMARY

Introduction/Objective Increasing incidence of spinal cord injuries presents a very important issue. These patients are usually very young, treatment is very difficult, long, expensive, and, in general, of little success. The aim of this study was to evaluate the angiogenic potential of the omental graft in spinal cord revascularization after the injury.

Methods The study included 19 patients, who underwent a recurrent surgical procedure for pain syndrome or surgical complication, and one patient in whom angiography revealed no flow in the distal part of an omental graft.

Results Our study confirmed angiogenic capabilities of the omental graft placed in the course of omentomyelopexy, for the injured spinal cord revascularization, macroscopically and histopathologically. Study results are limited due to including patients only when the postoperative period was complicated.

Conclusion Our study provides some invasive insight into the angiogenic capabilities, although further (likely less invasive) studies are needed to elucidate more clearly omental angiogenesis in spinal cord injury, and to include patients in whom the procedure went well.

Keywords: omentum; omentomyelopexy; spinal cord injury; angiogenesis; revascularization

INTRODUCTION

Injuries of the vertebral column, spinal cord, and cauda equina are present in 0.7–4% of all traumatic injuries, and 6.3% of traumatic injuries of the skeletal system, and their frequency increases mainly due to traffic accidents [1]. According to the data from Vietnam, missile-caused injuries of these structures were considered to appear in only 1%, although more current results suggest a far more frequent incidence of about 17% of missile injuries during the global war on terrorism [2, 3]. Although increasing incidence of spinal cord injuries (SCI) presents a very important issue, the most important one is the very nature of the injury. These patients are usually very young (approximately 20 years old), treatment is very difficult, long, expensive and, in general, of little success [4, 5].

Development of spinal fusion enabled the vertebral column to be stabilized after the injury, but very little to no improvement was achieved in SCI treatment [6]. Recently, the debate was re-sparked once again, as numerous treatment options have been developed recently, although their impact on spinal cord recovery after injury remained questionable [7].

The role of omental transposition for the brain and spinal cord vascularization was first mentioned in the mid-70s, by Goldsmith et al. [8, 9], and, since then, many authors have suggested various implementations of the omentum in both SCI and degenerative disease of the spine [10, 11, 12].

Due to omental richness in blood and lymphatic vessels and the ability to coalesce the injured area with capillary ingrowth during the first four to six hours, the omentum presents theoretically ideal tissue to revascularize the damaged spinal cord [13]. Omentopexy is a surgical procedure to connect the great omentum with a nearby organ, which induces the arterial circulation in the omental graft, thus causing the arterial circulation improvement in the target organ [14, 15]. Herewith, we have tried to encourage omental transposition for SCI through omentomyelopexy, by evaluating the angiogenic potential of the omental graft in spinal cord revascularization after the injury.

METHODS

Study group and inclusion criteria

The study included 19 patients who underwent a recurrent surgical procedure for pain syndrome or surgical complication [infection, meningoomentocele or cerebrospinal fluid (CSF) fistula], and one patient in whom angiography

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revealed no flow in the distal part of the omental graft. The initial group of patients consisted of 100 patients (89 male and 11 female), treated with omentomyelopexy due to the missile-caused SCI neurological deficit at the Department of Neurosurgery of the Military Medical Academy in Belgrade, Serbia, during a five-year period (1993–1997).

Patients included in the study fulfilled all the criteria: decompressive surgery performed for missile-caused spinal cord injury; omentomyelopexy performed for stabile neurological deficit, after initial decompressive surgery; recurrent surgery for pain syndrome or complication of omentomyelopexy.

The purpose of omentomyelopexy is angiogenesis of the damaged spinal cord, using the multipotent organ of the abdominal cavity, to provide revascularization, and to create adequate conditions for damaged spinal cord remyelization. This would all lead to nerve impulse propagation reestablishment, and consequent neurological improvement [16].

Postoperative pain syndrome was present in seven patients, and it appeared two to five years after the surgery. All the patients suffered from missile injuries of the spinal cord ranging between the T10 and the L2 spinal levels. After the injury, initial treatment included decompressive laminectomy and evacuation of bony fragments from the spinal canal, which was followed by omentomyelopexy 4–17 months after the initial surgery. The treatment option for these patients was microsurgical approach to the dorsal root entry zone (DREZ-otomy) [17].

Meningoomentocele developed in five patients, CSF fistula developed in three, and an infection of the neurosurgical site occurred in three patients. Reoperation was indicated to resolve these complications [18].

RESULTS

Direct intraoperative observation

Surgical treatment of complications also allowed a look into the surgical site to observe and evaluate the omentomyelopexy angiogenesis in vivo. Macroscopic photos were taken, while the small part of the grafted omentum was excised and referred to histopathological analysis to assess the viability and vasculature of the grafted omentum [19].

Splenic artery angiography

Selective angiography of the splenic artery was performed during the early postoperative period (on the 10th day after the surgery) in three patients to determine the vascular competency and to evaluate early angiogenic capabilities of the omental graft. Anastomosis between the omental flap arteries and the vertebral and spinal artery was corroborated in one patient, which confirmed angiogenic capabilities of the transposed omentum [16]. One patient's angiography revealed only abdominal blood vessels, although no signs of graft necrosis were present; a revision was performed only to confirm the graft vitality and blood flow persistence.

Macroscopic appearance

In patients who were re-operated on due to infection, the omental graft appeared pale, volume was reduced to about 50% of the initial value (mainly due to fatty tissue reduction, while the vascular structures were not significantly changed), and active bleeding from the graft surface was noted. On the other hand, re-operation revealed that CSF fistula or meningoomentocele induced no significant changes in the graft macroscopic appearance.

The omental graft in patients who underwent DREZ-otomy due to painful syndrome was also evaluated, and the results are presented in Table 1.

Histopathologic changes in the omental graft

Myxoid changes were present in the omental graft adipose tissue, the connective tissue in the mature lobular adipose tissue, the merging of the fiber striated musculature, the isles of lymphocytic infiltration due to inflammation, as well as histological changes of vascular structures. Newly formed, thin-walled blood vessels of irregular diameter and proliferation of the intima were present Perivascular connective tissue expansion was also present [19].

DISCUSSION

There is no definitive treatment for SCI. None of the treatment options have shown any significant influence to the functional outcome of these patients. Numerous

Table 1. Characteristics of patients in whom a DREZ-otomy was performed for pain syndrome after omentomyelopexy for SCI [17]

Age	Sex	ASIA assessment result	Time from injury to omentomyelopexy (months)	Time to DREZ-otomy after omentomyelopexy (months)	Omental graft vitality
35	M	(C) sensory level T12	4	30	vital
35	M	(B) sensory level T12	9	26	atrophic
27	M	(D) sensory level T12	10	33	vital
25	M	(A) sensory level T12	14	60	disintegrated
29	M	(C) sensory level T12	14	34	vital
31	M	(B) sensory level L2	17	36	atrophic
41	M	(B) sensory level T12	14	42	disintegrated

techniques, including stem cells, collagen implants, and electric devices have been proposed by authors, although not many studies have been performed in human population [20, 21, 22].

Functional outcome is the only parameter significant for the patient, but scientific interest is broader, and any indication of notable positive effect on the spinal cord repair and regeneration is considered to be of the greatest importance.

Our study is unique for its two-way confirmation of the successful implantation of transposed omentum, the angiographic, and direct intraoperative observation [16, 17, 19].

An MRI study by Goldsmith et al. [23] was performed on cats, but also in a patient suffering from SCI, who had omental–collagen bridge reconstruction that connects the proximal and distal ends of the transected spinal cord. The patient in this paper has clinically progressed to the point where she can ambulate with the use of a walker. A spinal cord defect of 4 cm in length showed MRI signs of development of a longitudinal spinal cord connection in the area of the omental–collagen bridge.

This study provides some insight into the interaction of the transposed omentum and the injured spinal cord. Although functional recovery is not exclusively related to the observed and noted changes, the histopathologic and angiogenic capabilities are the basis of the recovery development.

CONCLUSION

Our intraoperative study confirmed angiogenic capabilities of the omental graft placed in the course of omentomyelopexy, for the injured spinal cord revascularization, although study results are definitely diminished due to including only patients in whom there were complications or pain syndrome.

Further (likely less invasive) studies, which would include patients in whom the procedure went well, are needed to provide more insight into omental angiogenesis in SCI.

NOTE

The paper is a part of Dr. Ljubodrag Minić's PhD thesis.

REFERENCES

1. Livshits AV. Surgery of the spinal cord. First American ed. Madison: International Universities Press; 1991.
2. Hardaway RM 3rd. Viet Nam wound analysis. J Trauma. 1978; 18(9):635–43.
3. Blair JA, Patzkowski JC, Schoenfeld AJ, Cross Rivera JD, Grenier ES, Lehman RA Jr., et al. Spinal column injuries among Americans in the global war on terrorism. J Bone Joint Surg Am. 2012; 94(18):e135(1–9).
4. Ignjatović M, Minić L, Cerović S, Ćuk V. [Injuries of the spinal cord]. Vojnosanit Pregl. 1997; 54(6):581–7.
5. Kalsi-Ryan S, Beaton D, Curt A, Popovic MR, Verrier MC, Fehlings MG. Outcome of the upper limb in cervical spinal cord injury: Profiles of recovery and insights for clinical studies. J Spinal Cord Med. 2014; 37(5):503–10.
6. Goldsmith HS. Treatment of acute spinal cord injury by omental transposition: a new approach. J Am Coll Surg. 2009; 208(2):289–92.
7. Heimburger RF. Is there hope for return of function in lower extremities paralyzed by spinal cord injury? J Am Coll Surg. 2006; 202(6):1001–4; discussion 4.
8. Goldsmith HS, Duckett S, Chen WF. Spinal cord vascularization by intact omentum. Am J Surg. 1975; 129(3):262–5.
9. Goldsmith HS, Chen WF, Duckett SW. Brain vascularization by intact omentum. Arch Surg. 1973; 106(5):695–8.
10. Goldsmith HS, Neil-Dwyer G, Barsoum L. Omental transposition to the chronically injured human spinal cord. Paraplegia. 1986; 24(3):173–4.
11. Zheng WJ. [Experimental study on the treatment of spinal cord injury with transplantation of the greater omentum]. Zhonghua wai ke za zhi [Chinese journal of surgery]. 1989; 27(2):93–5, 125.
12. Rafael H. Omental transplantation for cervical degenerative disease. J neurosurgery Spine. 2010; 13(1):139–40.
13. Khosla A, Bowen BC, Falcone S, Quencer RM, Green B. MR of omental myelosynangiosis. Am J Neuroradiol. 1995; 16(2):275–9.
14. Kohiyama R, Yamashita R, Okano R, Kai T, Kuratomi Y, Miyata M. [A successful case of omentopexy for bronchopleural fistula and empyema after right pneumonectomy]. Kyobu Geka. 1994; 47(3):252–5.
15. Ignjatović M, Ćuk V, Minić L, Kostić Z. [History of the development of surgery of the greater omentum]. Vojnosanit Pregl. 1996; 53(5):415–22.
16. Ignjatović M, Pervulov S, Ćuk V, Kostić Z, Minić L. Early angiogenic capabilities of the transposed omental flap after omentomyelopexy. Acta Chir Iugosl. 2001; 48(2):41–3.
17. Spaić M, Minić L, Ćitić R, Lukić Z, Tadić R. [Omentomyelosynangiosis – a direct intraoperative observation]. Vojnosanit Pregl. 2001; 58(3):249–54.
18. Ignjatović M, Ćuk V, Bjelović M, Minić L. [Complications in omentopexy and personal experience with 100 omentomyelopexies]. Vojnosanit Pregl. 2001; 58(6):585–93.
19. Ignjatović M, Cerović S, Ćuk V, Kostić Z, Minić L, Spaić M. Late histological changes in the transposed omental flap. Acta Chir Iugosl. 2001; 48(3):35–8.
20. Minev IR, Musienko P, Hirsch A, Barraud Q, Wenger N, Moraud EM, et al. Biomaterials. Electronic dura mater for long-term multimodal neural interfaces. Science (New York, NY). 2015; 347(6218):159–63.
21. Capogrosso M, Milekovic T, Borton D, Wagner F, Moraud EM, Mignardot JB, et al. A brain-spine interface alleviating gait deficits after spinal cord injury in primates. Nature. 2016; 539(7628):284–8.
22. Fan X, Wang JZ, Lin XM, Zhang L. Stem cell transplantation for spinal cord injury: a meta-analysis of treatment effectiveness and safety. Neural regeneration research. 2017; 12(5):815–25.
23. Goldsmith HS, Fonseca A Jr., Porter J. Spinal cord separation: MRI evidence of healing after omentum-collagen reconstruction. Neurol Res. 2005; 27(2):115–23.

Ангиогенетски потенцијал оментомијелопексије у реваскуларизацији повређене кичмене мождине

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САЖЕТАК

Увод/Циљ Учестале повреде кичмене мождине су велики проблем. Повређени су обично врло млади, лечење је врло тешко, дуго, скупо и генерално безуспешно.

Циљ овог рада је био да процени ангиогенетски потенцијал транспонираног оментума у реваскуларизацији кичмене мождине после повреде.

Методе Истраживање је обухватило 19 болесника, који су подвргнути поновном хируршком захвату због болног синдрома, хируршке компликације и једног болесника код којег ангиографија није показала проток у дисталном делу режња оментума.

Резултати Студија је потврдила ангиогенетске способности оменталног трансплантата за реваскуларизацију повређене кичмене мождине, макроскопски и хистопатолошки. Резултати студије су ограничени укључивањем само болесника са компликованим постоперативним током и реоперацијом.

Закључак Наша студија пружа одређени увид у ангиогенетске способности оментума, иако су потребне даље мање инвазивне студије како би се пружио бољи увид у оменталну ангиогенезу и укључили испитаници код којих је цео поступак прошао без компликација.

Кључне речи: оментум; оментомијелопексија; повреда кичмене мождине; ангиогенеза; реваскуларизација

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Modified orthotopic ileal neobladder – surgical technique and initial results

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SUMMARY

Introduction/Objective *Vesica ileale Padovana* is the surgical technique for reconstruction of lower urinary tract following radical cystectomy using isolated ileal segment. This operative technique requires dissection of both ureters in full length that cannot be possible in some cases. The paper is aimed to present our experience with modified surgical technique of *vesica ileale Padovana* using 40 cm of an isolated ileal segment.

Methods Ten male patients received modified ileal neobladder following radical cystectomy at our institution during the period from 2008 to 2011. The mean age of patients was 59 years (range 45–70). Median follow-up was 76 months (range 62–93). Patients were monitored cautiously for functional outcome, local recurrence, and distant progression.

Results Perioperative, early, and late postoperative mortality have not been noticed. There were only two major complications: prolonged postoperative ileus and prolonged urinary leakage requiring percutaneous nephrostomy and subsequent ureteral reimplantation due to stenosis of ureterovesical anastomosis in one patient (10%).

Average ileal neobladder capacity was 450 ml. Daytime and night continence were achieved in nine (90%) and seven (70%) patients, respectively.

Conclusion This modification of orthotopic ileal neobladder has not been difficult to perform in our hands. Modified technique provides a clear advantage in easier ureteral implantation more proximally than in the original technique, requiring less length of ureters. Initial encouraging results should be confirmed in further clinical practice.

Keywords: adult; male; urinary bladder neoplasms; cystectomy; urinary diversion; reconstructive surgery

INTRODUCTION

Radical cystectomy with urinary diversion is the gold standard in the treatment of patients having non-metastatic muscle invasive bladder cancer (T2-4a, N0-x, M0). Radical cystectomy is also indicated in patients with recurrent, BCG-refractory, high-risk superficial tumors, as well as in those with primary unresectable superficial tumors [1]. Urinary diversions can be classified as heterotopic and orthotopic. In heterotopic urinary diversions, urine is derived through urostomy, which can be incontinent, such as ureterocutaneostomy and ileal conduit, or continent, such as Indiana pouch and Kock pouch. In orthotopic urinary diversions, urine is derived through the urethra. A plentitude of orthotopic bladder substitutes following radical cystectomy have been reported in the literature [2, 3]. These procedures are attractive for patients requiring radical cystectomy because an avoidance of abdominal urostomy improves the patient's satisfaction with preserved body image.

Surgical technique of vesica ileale Padovana was originally reported by Pagano et al. [4].

This technique was created to imitate the natural bladder with implantation of the ureter in an antireflux manner. However, this technique requires careful preparation of ureters in full length because insufficient length of ureters can pose a real obstacle to the accomplishment of this procedure. Our modification of ileal folding after funnel creation enables more proximal implantation of ureters into the neobladder.

The aim of this paper is to present our modification of this surgical technique, as well as the initial results.

METHODS

During the period from January 2001 to November 2016, 420 patients underwent radical cystectomy at our institution. Out of them, 135 patients received ileal orthotopic bladder substitution.

During the 2008–2011 period, 10 male patients with muscle-invasive bladder cancer or BCG-refractory, T1G3 recurrent bladder cancer underwent radical cystectomy with modified vesica ileale Padovana orthotopic bladder replacement. The patients were selected for this procedure using the following criteria: (1) preoperative pathological stage ≤ pT2b; (2) absence of tumor in the prostatic urethra; (3) preserved morphology of the upper urinary tract; (4) American Society of Anesthesiologists (ASA) score ≤ 3; (5) no preoperative chemotherapy nor radiotherapy.

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Surgical technique

After pelvic lymphadenectomy and cystectomy with prostatectomy, the procedure is continued with reconstructive surgery. A 40-cm segment of ileum is isolated and detubularized (Figure 1) to create the orthotopic reservoir. The continuity of intestinal tract is re-established with a two-layer end-to-end ileal anastomosis. Only 10 cm of the distal end of the isolated ileum is used for the creation of the funnel for anastomosis with the urethra (Figure 2). The funnel is sewn by two running polyglactin 3-0 sutures as described in the original technique [4].

Further steps represent a modification of the original technique. The rest of the isolated ileal segment is folded in the form of the letter M (Figure 3). Lateral arms of the letter M serve for the creation of an extraluminal serosa-lined tunnel for the insertion of the ipsilateral ureter (Figure 4). The left ureter has to be carefully pulled through the mesenterium of the neobladder, taking care to avoid injury to mesenteric vessels. Both ureters are spatulated on the anterior side in the length of 12–15 mm and sutured in the lateral serosal tunnel by six to eight interrupted polyglactin 3-0 stitches. Both ureteral anastomoses are protected by ureteral catheter 6 to 8 Fr. Migration of the ureteral catheters is prevented by fixation to the ureteral wall with rapidly absorbable 4-0 polyglactin suture, taking care not to damage ureteral blood supply. Following anastomosis of the ureter with the neobladder, the serosal tunnel is closed over ureter using polyglactin 3-0 running suture (Figure 4).

Finally, the "M" plane is folded anteriorly to create an anterior wall of the neobladder and sutured to the anterior side of the previously formed funnel using seromuscular running suture with polyglactin 3-0 (Figure 5). Before

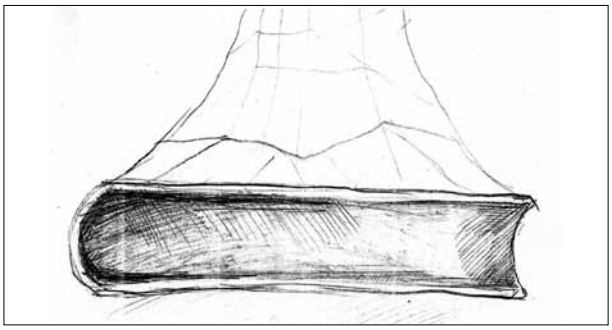

Figure 1. Detubularized isolated ileal segment in the full length

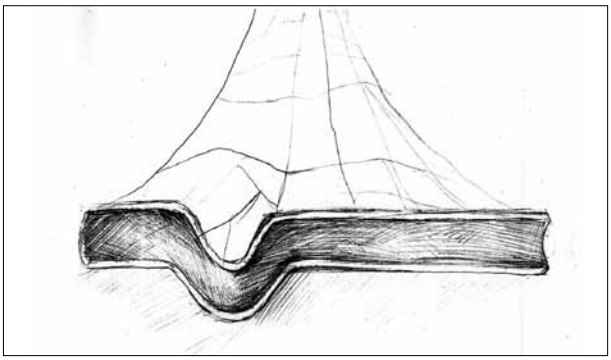

Figure 2. Preparation for the creation of the funnel outlet

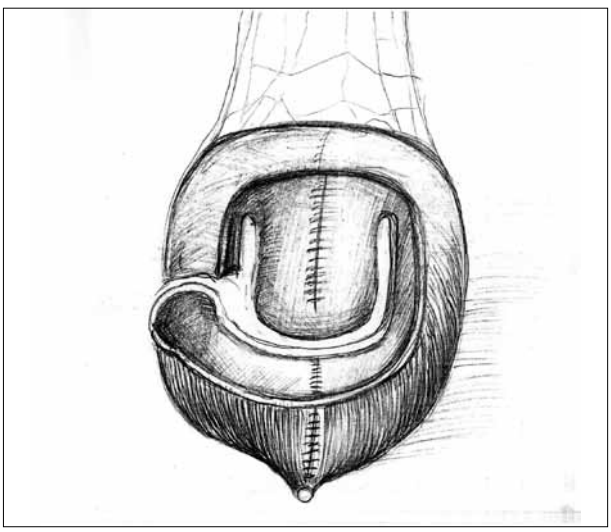

Figure 3. Creation of the "M" plane

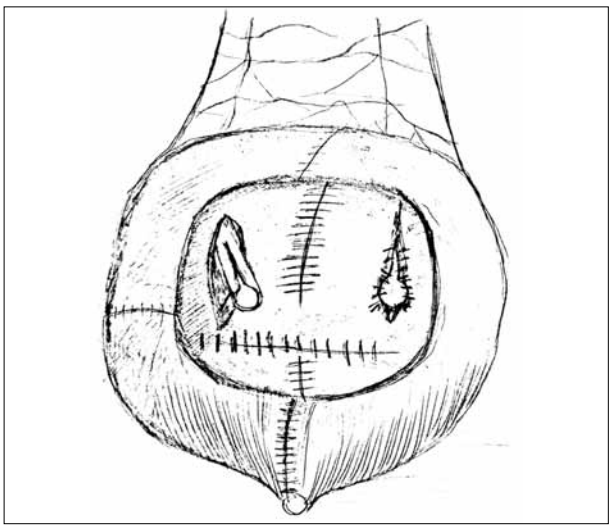

Figure 4. The posterior wall is created with serous-lined extramural tunnels and both ureters are indwelled into the neobladder; in the next step, the ureters have to be spatulated on the anterior side, splinted, and anastomosed to the neobladder; thereafter, serous-lined tunnels are closed over the ureters

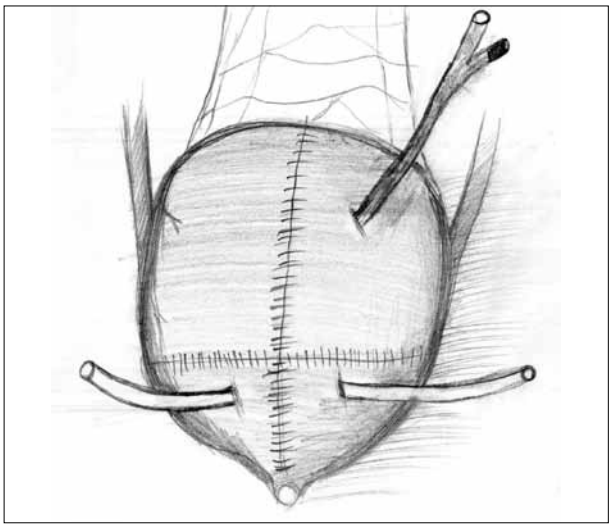

Figure 5. The final aspect of the neobladder following the closure of the anterior wall with cystostomy catheter and ureteral splints

completing reservoir closure, ureteral catheters are passed through the anterior wall of neobladder. In addition, 12 Fr two-way Foley catheter is placed for suprapubic cystostomy. Neobladder-urethral anastomosis is created with six interrupted polyglactin stitches over 18 Fr three channel Foley catheter.

Follow-up

In all the patients, scheduled follow-up visits were performed every three months during the first year, every four months during the second year, twice per year until the fifth year, and thereafter once per year. Upper urinary tract status was assessed using intravenous pyelogram or computed tomography urography six months and two years after surgery. Routine laboratory analyses including sedimentation rate, white blood cell count, red blood cell count, blood urea nitrogen, creatinine, liver function tests and urine were performed for each patient on every visit. In addition, ultrasound of the upper abdomen and chest X-ray were performed on all the patients on every visit. Uroflowmetry was performed at their six months visit, and urodynamic study at 12 months after the surgery. Daytime and nighttime continence were assessed by interviewing each patient during the follow-up visits.

RESULTS

Seven male patients with muscle invasive bladder cancer and three male patients with recurrent BCG-refractory T1G3 bladder cancer underwent radical cystectomy and orthotopic ileal neobladder using described modified technique. The patients were aged 59 years on average, the age range being 45–70 years. Bladder-confined disease (< pT3a) without lymph node metastases (pN0) was confirmed in all the patients by histopathological examination of the surgical specimen. There was no perioperative, early, or late postoperative mortality.

There were only two major complications: prolonged postoperative ileus and prolonged urinary leakage requiring percutaneous nephrostomy and subsequent ureteral reimplantation due to stenosis of uretero-neobladder anastomosis in one patient. There were no significant metabolic disorders.

Uroflowmetry at the six-month follow-up visit has shown Q_{max} = 20.3 ml/s on average, ranging 10–31 ml/s. Observed curves have not been interrupted, although they were more or less undulated. Postvoiding residual urine was 13 ml on average, ranging 0–90 ml. The mean capacity of the neobladder is 450 ml, ranging 350–600 ml. All the patients had satisfying bladder compliance and no patient had spontaneous neobladder contractions or pressure over 15 cmH_2O during the filling phase.

Daytime and nighttime continence were achieved in nine (90%) and seven (70%) patients, respectively.

DISCUSSION

Orthotopic bladder substitution is probably the most complex reconstructive procedure in uro-oncological surgery. The original technique of vesica ileale Padovana was described in 1990 [4]. This neobladder seems to resemble the natural bladder the most. Unfortunately, the technique has not become widely popular among the urologists due to several reasons. First, a preparation of full length of both ureters is required to perform their implantation correctly. Second, some authors have reported that funnel-shaped neobladders were disposed to emptying difficulties [5]. Finally, creating vesica ileale Padovana seems to be complicated for the majority of urologists.

On the other hand, widely accepted neobladders, such as Studer or Hautmann, require approximately 60 cm of ileum for the creation of the reservoir. Aleksić et al. [6] found that higher capacity neobladders were associated with higher postvoiding residual volume as well as higher reabsorption of urine. In addition, these orthotopic bladder substitutes are associated with a higher probability of malabsorption syndrome due to the use of the longer segment of terminal ileum.

Vesica ileale Padovana is a spheroidal reservoir that ensures optimal volume-to-surface ratio. In addition, this type of neobladder provides low end-filling pressure. Implantation of ureters using serous-lined extramural tunnel technique originally described by Abol-Enein and Ghoneim [7] provides excellent antireflux mechanism. However, ureters sometimes do not have sufficient length for the creation of tension-free uretero-neobladder anastomosis. Therefore, we suggest this modification, using different ileal folding to achieve serous-lined extramural tunnel more proximally than in the original technique. This modification also enables the creation of a shorter funnel-shaped outlet of the neobladder, diminishing long-term problems with bladder emptying.

Average neobladder capacity in the study was 450 ml at 12 months after surgery. Yadav et al. [8] reported an increase of the neobladder capacity up to three years after surgery. They created modified ileal neobladder using 45 centimeters of ileum and reported bladder capacity of 410 ml, 502 ml, and 588 ml at one, two, and three years after surgery, respectively.

The average Q_{max} was 20.3 ml/s with a range of 10–31 ml/s. The vast majority of studies have similar flow rates. However, the neobladder does not have significant contractions. Urinary flow rate depends on the driving force (straining of abdominal muscles or Crede's maneuver), as well as on the relaxation of the urethral sphincter. Therefore, patients with neobladder usually have undulated shapes on the uroflowmetric curve.

One patient with advanced age in the study lost daytime continence three years after surgery probably due to decreased tonus of the urethral sphincter. The nighttime leakage of urine was persistent during the follow-up period in three (30%) patients. However, an expert panel at the consensus conference, convened by the World Health Organization and the Société Internationale d'Urologie,

has found a 20–30% prevalence of nighttime incontinence in most of the reported series [9]. Detubularization of the isolated ileal segment is the key maneuver leading to the low-pressure reservoir. All neobladders have a good compliance due to characteristics of the bowel, and pressures over 15 cmH_2O have not been recorded during the filling phase of cystometry.

CONCLUSION

In our experience, this modification of vesica ileale Padovana neobladder is not difficult to perform. In our opinion, this technique provides a clear advantage in easier ureteral implantation, more proximally than in the original technique, requiring less length of the ureter. Initial encouraging results should be confirmed in further clinical practice.

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REFERENCES

1. Witjes AJ, Lebret T, Compérat EM, Cowan NC, De Santis M, Bruins HM, et al. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Urol. 2017; 71(3):462–75.
2. Hautmann RE, Abol-Enein H, Lee CT, Mansson W, Mills RD, Penson DF, et al. Urinary diversion: how experts divert. Urology. 2015; 85(1):233–8.
3. Nagele U, Sievert KD, Merseburger AS, Anastasiadis AG, Stenzl A. Urinary diversion following cystectomy. European Association of Urology Update Series 3. 2005; 129–37.
4. Pagano F, Artibani W, Ligato P, Piazza R, Garbeglio A, Passerini G. Vescica Ileale Padovana: a technique for total bladder replacement. Eur Urol. 1990; 17(2):149–54.
5. Studer UE, Burkhard FC, Schumacher M, Kessler TM, Thoeny H, Fleischmann A, et al. Twenty years experience with an ileal orthotopic low pressure bladder substitute – lessons to be learned. J Urol. 2006; 176(1):161–6.
6. Aleksic P, Bancevic V, Milovic N, Kosevic B, Stamenkovic DM, Karanikolas M, et al. Short ileal segment for orthotopic neobladder: a feasibility study. Int J Urol. 2010; 17(19):768–73.
7. Abol-Enein H, Ghoneim MA. Functional results of orthotopic ileal neobladder with serous-lined extramural ureteral reimplantation: experience with 450 patients. J Urol. 2001; 165(5):1427–32.
8. Yadav SS, Gangkak G, Mathur R, Yadav RG, Tomar V. Long-Term Functional, Urodynamic, And Metabolic Outcome Of A Modified Orthotopic Neobladder Created With A Short Ileal Segment: Our 5-Year Experience. Urology. 2016; 94:167–72.
9. World Health Organization (WHO) Consensus Conference on Bladder Cancer, Hautmann RE, Abol-Enein H, Hafez K, Haro I, Mansson W, Mills RD, et al . Urinary Diversion. Urology. 2007; 69(Suppl 1):17–49.

Модификована ортотопска илеална необешика – хируршка техника и почетни резултати

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САЖЕТАК

Увод/Циљ *Vesica ileale Padovana* је један од начина реконструкције доњег уринарног тракта после радикалне цистектомије коришћењем изолованог сегмента илеума. Оперативна техника захтева препарацију оба уретера читавом дужином, што није могуће код свих болесника.

Циљ рада је да се прикажу наша модификација оперативне технике *Vesica ileale Padovana* употребом изолованог сегмента илеума дужине 40 *cm* и иницијални резултати њене примене.

Материјал и методе У периоду 2008–2011. године код 10 болесника је урађена радикална цистектомија са деривацијом урина модификованом техником *Vesica ileale Padovana*. Просечна старост болесника била је 59 година (45–70). Просечно време праћења било је 76 месеци (62–93), а посматрани су функционални и онколошки резултати.

Резултати Периоперативни, рани и касни постоперативни морталитет нису забележени. Биле су само две компликације: протраховани динамски илеус и цурење урина на уретеронеобешичној анастомози која је захтевала перкутану нефростому са накнадном реимплантацијом уретера ради стенозе, код једног болесника. Просечан капацитет необешике био је 450 *ml*. Дневна и ноћна континенција су постигнуте код 9 (90%), тј. 7 (70%) болесника.

Закључак Модификовану технику илеумске необешике није тешко извести, а пружа значајну предност због једноставније анастомозе уретера и необешике која се налази нешто проксималније у односу на оригиналну технику. Охрабрујући иницијални резултати треба даље да се потврде у клиничкој пракси.

Кључне речи: неоплазме мокраћне бешике; цистектомија; деривације урина; реконструктивна хирургија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The stigma of obesity in adolescence

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SUMMARY

Introduction/Objective Obese children and adolescents are exposed to stigma and discrimination from peers, teachers, and family, which can lead to numerous health problems, including psychosocial ones. The aim of this study is to determine whether obese adolescents in Serbia are exposed to stigmatization and which are the most common forms of stigmatization they face.

Methods The study included 335 adolescents hospitalized for the treatment of obesity. During hospitalization, weight and height were measured, and body mass index was calculated. Participants independently completed the Questionnaire about Weight-based Stigmatization made for the purposes of this research. The Questionnaire also included questions about the gender and age of the respondents, as well as questions about obesity of their family members.

Results Fifty-nine percent of the participants experienced offence, 19% were teased, 47.5% were the subject of gossip, and 25% were excluded from their peer group; 45% reported that people had prejudice against them. Male adolescents faced overt forms of stigmatization/discrimination significantly more often than female adolescents. Nineteen percent of participants were stigmatized by healthcare workers, and 6% stated that their family was ashamed of their obesity.

Conclusion A significant percent of obese adolescents in Serbia is exposed to a stigma due to their weight, most often to insults, gossip, and social exclusion. Obese adolescents are most often exposed to stigmatization by peers, but there are a significant proportion of adolescents who are exposed to stigma from healthcare workers. It is necessary to educate healthcare workers about the stigma of body weight and its harmful effects and to implement measures to mitigate consequences of stigmatization of obese adolescents, as well as to prevent it.

Keywords: adolescent, obese; obesity, stigma; body weight

INTRODUCTION

Adolescence is the period of transition from childhood to adulthood marked with significant and turbulent changes regarding growth and development, psychological and social development. It is defined arbitrarily as the period from 10 to 19 years of age, and is divided into early adolescence (10 to 13 years), middle (14 to 16 years), and late adolescence (17 to 19 years).

According to the WHO Child Growth Reference Data, children and adolescents who have the body mass index (BMI) z-score between +2 and +3 are overweight, and children who have the BMI z-score of over +3 are obese [1]. The prevalence of obesity is increasing in all age groups, but especially worrisome is the dramatic increase of prevalence of obesity in children and adolescents. Between 1970s and 2012, the prevalence of child obesity tripled in the USA and in Canada it increased by 2.5 times [2]. In Serbia, the percentage of overweight children went up from 8.2% to 10.1% in the period between 2000 and 2013, and the percentage of obese children increased by 1.88 times (from 2.6% to 4.9%) [3].

Stigmatized persons are seen as inferior, evil or with serious flaws because of some of their characteristics or because of being members of a particular group. Stigmatization based on body weight includes negative attitudes, beliefs that are manifested through stereotypes, prejudice and rejection of overweight or obese persons [4]. Stigmatization often results in discrimination that includes unfair treatment or acting based on prejudice towards stigmatized persons.

Pediatricians in Serbia are well aware of and successfully resolve somatic problems that are consequences of obesity for many years. In many countries, in addition to the physical problems associated with obesity, considerable attention is paid to stigma and discrimination against obese children and adolescents. There are numerous studies about the stigma and discrimination of obese adults in multiple domains of living, such as work, education, interpersonal relations. More and more research indicates that stigmatization of obesity begins in childhood and continues into adolescence and throughout life. Obese children and adolescents are exposed to stigma and discrimination from peers, teachers and family [5–10].

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During adolescence, stigmatization and discrimination based on weight can lead to body dissatisfaction, lower self-esteem, overeating and other unhealthy eating behaviors, eating disorders, depressive symptoms, social isolation, substance abuse, lower academic achievement, lower education, and unsatisfactory interpersonal relationships [11, 12].

Stigmatization is a significant source of stress and can further aggravate the health problems that obese adolescents already face, such as insulin resistance, hypertension, dyslipidemia, chronic inflammation, and the like [13, 14].

Although numerous studies on stigmatization of obese adolescents have been conducted in a number of countries, a similar research has not been conducted in Serbia so far.

The aim of this study is to determine whether obese adolescents in Serbia are exposed to stigma and which are the most common forms of stigmatization they face.

METHODS

The research was conducted at the Center for Prevention and Treatment of Obesity in Children and Adolescents ("Čigotica", Zlatibor) during 2014 and 2015. Adolescents who were on treatment were involved in the research. The study included 335 adolescents aged 10 to 19 years, 194 (57.9%) girls, and 141 (42.1%) boys. The average age of the participants was 14.27 years (SD = 1.89). One hundred and thirty-three (39.6%) adolescents were in early adolescence, 151 (44.9%) in middle adolescence, and 52 (15.5%) in late adolescence. Forty-seven (14%) participants were overweight, and 289 (86%) were obese.

The adolescents were weighed, their height was measured and the BMI was calculated. For the diagnosis of overweight and obesity the WHO Growth Reference Data were used.

Participation in the study was voluntary. The participants were informed of the aim of the study and gave their written consent to participate in the research. The participants independently completed the Questionnaire about Weight-based Stigmatization, which was prepared by researchers. The questions were formulated according to the forms of stigmatization most often cited in the literature. The following data were collected by the Questionnaire: gender and age of the respondents, obesity of their family members, and participants' experiences of weight-based stigmatization. The respondents answered by selecting one of the multiple-choice answers on a four-point Likert scale. They had 30 minutes to fill out the Questionnaire.

The data were analyzed using the IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). To show the presence of certain categories or a response, relevant variables were displayed as frequencies and percentages. For the analysis of numerical data, standard procedures of descriptive and comparative statistics were used. Within descriptive statistics, the data are presented in the form of means, standard deviations, and frequencies and percentages. Within the methods of comparative statistics, Student's t-test was used to test the differences between two independent samples, and for determining the significance of differences between more than two groups, unifactorial variance analysis (ANOVA) was used. The levels of significance were set at $p < 0.05$ (the difference is statistically significant) and $p < 0.01$(the difference is highly significant).

RESULTS

Table 1 shows stigmatization that participants experienced due to overweight/obesity and the incidence of these experiences.

The experience of stigmatization by gender is shown in Table 2. The differences between girls and boys in the average score for each question in the Questionnaire were tested using the Student's t-test for independent samples. When the entire sample (10 do 19 years of age) was taken into account, the boys were teased or hit because of weight more often than girls. Comparing other forms of stigmatization, there was no statistically significant difference between girls and boys.

The frequency of exposure to various forms of stigmatization of adolescents in the early, middle, and late adolescence was tested using the univariate analysis of variance (ANOVA). There is a statistically significant difference ($p = 0.029$) between the age groups regarding teasing only. The oldest age group (late adolescence) achieved the highest average score, while participants from the middle adolescence group had the lowest average score. Post hoc comparisons using the Tukey HSD test showed that in terms of exposure to teasing, there is a significant difference between respondents both from the oldest and the youngest age group (early adolescence) in comparison to respondents from the middle adolescence age group.

Student's t-test was used to test gender differences within age groups, and it was observed that girls in early adolescence (1.84 ± 1.06) reported more often than boys (1.43 ± 0.79) that someone had stared at them because of obesity ($t(131) = -2.53$; $p = 0.014$).

Six percent of participant stated that their family was ashamed of their obesity; 222 (66.7%) participants had other obese members in their family (mother, father, or both parents). Between adolescents whose parents are obese and those whose parents are not obese there was no statistically significant difference regarding the feeling of adolescents that their family is ashamed of their obesity. There were no statistically significant differences by age and gender in relation to stigmatization by obese or non-obese parents.

One fifth (19%) of participants experienced stigmatization from healthcare workers on one or more occasions. Girls in late adolescence reported statistically significantly more often than boys of the same age (girls: 1.40 ± 0.00; boys: 1.00 ± 0.81) that a doctor or nurse stigmatized them and commented on their weight ($t(50) = -2.30$; $p = 0.012$).

DISCUSSION

Stigmatization and discrimination against obese people represent serious social issues. It has been estimated that

Table 1. Experiences of weight-based stigmatization of participants

Question	Never	Once in life	Several times in life	Many times in life
	% of participants			
1. I was teased that I am fat	80.9	9.3	7.2	2.7
2. I was insulted because of weight	40.8	15.8	24.4	19.0
3. I was hit or beaten because of weight	91.7	3.0	1.8	3.6
4. I was ignored by my peers	76.3	7.8	9.6	6.3
5. I was excluded from the peer group	75.0	8.3	9.2	7.4
6. Peers were spreading rumors about me	52.5	14.9	17.3	15.2
7. Some people have had negative assumptions about me (I am lazy, stupid)	54.8	15.8	18.2	11.3
8. I encountered some obstacles due to my weight (e.g., the chair was too small for me, I could not jump over the vaulted horse)	59.2	13.4	20.2	7.1
9. The doctor or nurse behaved badly towards me and commented on my weight	80.9	9.3	7.2	2.7
10. My family is ashamed of my weight	94.0	2.1	1.5	2.4
11. My friend is ashamed of my weight	85.7	7.4	4.5	2.4
12. I was stared at	60.1	14.6	15.8	9.5

Table 2. Stigmatization experiences of participants by gender

Question	Gender	Mean	SD	t-test	p
1. I was teased that I am fat	male	2.80	1.04	23.11	0.021*
	female	2.53	1.12		
2. I was insulted because of weight	male	2.28	1.16	0.863	0.389
	female	2.17	1.18		
3. I was hit or beaten because of weight	male	1.29	0.79	2.710	0.007*
	female	1.09	0.45		
4. I was ignored by my peers	male	1.54	0.96	1.418	0.157
	female	1.40	0.86		
5. I was excluded from the peer group	male	1.58	1.03	1.404	0.161
	female	1.43	0.86		
6. Peers were spreading rumors about me	male	1.89	1.16	-0.890	0.374
	female	2.00	1.13		
7. Some people have had negative assumptions about me (I am lazy, stupid)	male	1.87	1.12	0.088	0.930
	female	1.86	1.05		
8. I encountered some obstacles due to my weight (e.g., the chair was too small for me, I could not jump over the vaulted horse)	male	1.80	1.02	0.773	0.440
	female	1.72	1.01		
9. The doctor or nurse behaved badly towards me and commented on my weight	male	1.30	0.68	-0.448	0.655
	female	1.33	0.75		
10. My family is ashamed of my weight	male	1.14	0.55	0.546	0.586
	female	1.11	0.51		
11. My friend is ashamed of my weight	male	1.27	0.64	0.964	0.336
	female	1.21	0.64		
12. I was stared at	male	1.63	1.01	-1.714	0.087
	female	1.83	1.05		

the prevalence of stigmatization and discrimination against adult obese people in the USA is very high and could be compared to the prevalence of racial discrimination. In the period between 2004 and 2006, 12% of obese people were exposed to discrimination due to obesity and 11% to racial discrimination [15, 16].

A high percentage of participants of our research were exposed to various types of stigmatization and discrimination. Forty-five percent of the participants reported that people had prejudice against them (as being stupid, lazy, etc.), 47.5% of participants were the subject of gossip, 25% were excluded from social life by the peer group, and 14% reported that their obesity ashamed their friends. Bacchini et al. [17] reported that obese children and adolescents were often the subject of gossip among their peers (11.5–14.5%), were ignored (10.1–14.5%) by their peer group or excluded from it or from its activities (14.3–18.5%).

Due to obesity, 59.2% of our participants experienced offence. In contrast, Puhl et al. [18] reported that 83% of adolescents aged 14–18 years in the weight loss treatment-seeking sample experienced insults. According to our results, 19.1% of participants were teased due to their weight. Similar results were reported by Madowitz et al. [19]. These findings are of great importance as teasing and social rejection were connected to psychological problems, lower academic achievements, unhealthy weight control behaviors such as strict dieting, fasting, self-induced vomiting, excessive physical activity, misuse of diet pills, diuretics, and laxatives [19].

Bucchianeri et al. [20] reported that weight-based teasing and harassment were more prevalent than teasing and harassment associated with race, gender, or socio-economic status. Weight-based teasing was associated with lower self-esteem and body satisfaction. According to our results, there were no significant differences between girls and boys in prevalence of weight-based teasing. However, results from the USA clearly show that female participants were teased due to their weight significantly more often [20].

When comparing the prevalence of any form of weight-based stigmatization in the early, middle, and late adolescence, the participants who belonged to the late adolescent group reported weight-based teasing most frequently. In contrast, bearing in mind the fact that late adolescence is a period when young people are becoming significantly more tolerant of differences and physical impairments, show more empathy and are better socialized, generally have better insight into their own values and qualities regardless of obesity, it would be expected that teasing often occurs as unpleasant experience during the early and middle, but not in late adolescence. Haines et al. [21] reported results similar to our own – teasing due to weight remains frequent throughout adolescence until young adulthood and it even becomes more frequent in male adolescents in this age group.

During the research, the participants have been asked if and how many times they had an unpleasant weight-based experience, but the age when they were exposed to these experiences was not the subject of our research. Therefore, we are not able to draw any conclusions as to whether teasing as the most commonly reported type of stigmatization has been reported by participants belonging to the oldest age group because they had the longest period to be teased (cumulative effect) or because they reported teasing as the type of stigmatization that affected them the most and as a result had been memorized the most and the longest.

Every seventh participant (14%) reported that his or her friends were ashamed of him or her due to obesity and it points to the stigmatization of obese adolescents by peers, as well as their view of obese adolescents as inferior compared to others. We did not found similar research in the available literature.

Eight percent of our participants reported to have been victims of physical violence. Bacchini et al. [17] also point out the fact that overweight and obese children and adolescents are far more likely to be victims of physical violence than their counterparts with healthy weight.

When all weight-based negative experiences are taken into account, male adolescents faced overt forms of stigmatization such as verbal insult and physical violence significantly more often than female adolescents. Female adolescents, especially in the early adolescence, reported non-verbal forms of stigmatization ("they stared at me") significantly more often. Pearce et al. [6] also came to the conclusion that male adolescents reported overt stigmatization such as weight-based teasing and harassment more often, while female adolescents reported relational peer victimization such as exclusion more often.

It is well known that adolescents are preoccupied with their appearance and it is disturbing if they are different from their peers. It is likely that female adolescents are more vulnerable to non-verbal signals than male adolescents, therefore reporting more often that somebody stared at them. Eisenberg et al. [22] and Rojo-Moreno et al. [23] reported that teasing due to body weight is reported more often by female than by male adolescents. It is necessary to carry on additional research in order to find out whether there are differences in exposure of girls and boys to stigmatization or it is a matter of difference in their perception and vulnerability to certain forms of stigmatization.

Six percent of participants stated that their family felt ashamed because of their body weight and there was no significant difference when it comes to either gender or age. Leme et al. reported [24] that 39.9% female adolescents experienced weight-based teasing by family members. These results cannot be directly compared to the results of our research, but it seems that families in Serbia are more tolerant in regard to adolescents' obesity or are not aware of the problem.

If a parent feels guilty for an overweight child, especially if this feeling is accompanied by unsuccessful attempts to reduce body weight, it is possible that the parent expresses his anger, feeling of helplessness and frustration through stigmatizing attitudes and behaviors such as criticizing and negative comments about their overweight child. Berge et al. [25] stated that unpleasant conversations in the family referring to body weight are more often initiated by mother and older siblings than by other family members. Conversations initiated by mothers focused on negative health consequences of being overweight, while conversation initiated by fathers and siblings mainly focused on appearance and had a form of teasing.

According to the findings of our research there was no significant difference in stigmatization between families of our participants whose parents were overweight and those whose parents were of healthy weight.

Nineteen percent of our participants had unpleasant experiences with healthcare workers. In the period of late adolescence, girls reported significantly more often than boys that health workers misbehaved towards them. It is possible that girls are more vulnerable than boys to stigmatizing behavior of healthcare workers in this period and that they easily recognize these forms of stigmatization. Findings of different researchers point out that doctors and other healthcare workers have strongly negative attitudes towards overweight people [26, 27, 28]. Many healthcare workers believe that overweight patients are lazy and lacking self-discipline and are personally responsible for their weight because they do not stick to the prescribed treatment and therefore deserve to be the subject of offensive jokes.

Despite the abundance of data about stigmatization of obese adult people by healthcare workers, we found only two papers about negative attitudes and anti-fat bias among healthcare workers who work with children and adolescents. According to the findings of Neumark-Sztainer et al. [29], more than 50% of school nurses have prejudice and negative attitudes towards overweight persons. Garcia et al. [30] also report weight biased attitudes towards obese pediatric patients among pediatric nurses and clinical support staff.

This research has been carried out as a cross-sectional study and has included only adolescents who were on a hospital treatment of obesity. It would be useful to research prevalence of weight-based stigmatization in the general population in Serbia. Carrying out a longitudinal research would make it possible to monitor stigmatization based on body weight during adolescence in different age groups.

CONCLUSION

A significant percent of obese adolescents in Serbia are stigmatized due to their weight. They are most often exposed to the stigmatization by peers, but there are a significant proportion of adolescents who are exposed to stigma from healthcare workers, as well as parents.

Male adolescents are more often exposed to insults and physical violence, while adolescent girls in early adolescence perceive covert forms of stigmatization more often than boys of the same age. Female adolescents are exposed to stigmatization by health professionals more than males.

A longitudinal study of weight-based stigmatization in the general population could provide answers to questions about the presence of stigma among normal-weight, overweight, and obese adolescents, as well as the incidence and forms of stigmatization in different age groups.

It is necessary to educate healthcare workers and the general population about the stigma of body weight and its harmful effects, in order to implement measures to mitigate the consequences of stigmatization of obese adolescents and to plan and implement measures to prevent the stigmatization.

REFERENCES

1. World Health Organization. The WHO child growth standards [Internet]. WHO 2017 [cited 2017 March 17]. Available from: http://www.who.int/childgrowth/en/
2. Carroll MD, Navaneelan T, Bryan S, Ogden CL. Prevalence of obesity among children and adolescents in Canada and the United States. NCHS data brief, no 211. Hyattsville, MD: National Center for Health Statistics; 2015.
3. Boričić K, Vasić M, Grozdanov J, Gudelj-Rakić J, Živković Šulović M, Jaćović-Knežević N, et al. Rezultati istraživanja zdravlja stanovnika Republike Srbije 2013. godina. Beograd: Institut za javno zdravlje Srbije „Dr Milan Jovanović Batut", Ministarstvo zdravlja Republike Srbije; 2014.
4. Puhl RM, Latner JD. Stigma, obesity, and the health of the nation's children. Psychol Bull. 2007; 133(4):557–80.
5. Di Pasquale R, Celsi L. Stigmatization of overweight and obese peers among children. Front Psychol. 2017; 8:524.
6. Pearce M, Boergers J, Prinstein M. Adolescent obesity, overt and relational peer victimization, and romantic relationships. Obesity. 2002; 10(5):386–93.
7. Kim SG, Yun I, Kim JH. Associations between body weight and bullying among South Korean adolescents. J Early Adolesc. 2015; 36(4):551–74.
8. Puhl RM, Wall MM, Chen C, Austin B, Eisenberg ME, Neumark-Sztainer D. Experiences of weight teasing in adolescence and weight-related outcomes in adulthood: A 15-year longitudinal study. Prev Med. 2017; 100:173–9.
9. Lynagh M, Cliff K, Morgan PJ. Attitudes and beliefs of nonspecialist and specialist trainee health and physical education teachers toward obese children: evidence for "anti-fat" bias. J Sch Helath. 2015; 85(9):595–603.
10. Eli K, Howel K, Fisher PA, Nowicka P. "Those comments last forever": parents and grandparents recount how they became aware of their own body weights as children. PLoS One. 2014; 9(11):e111974.
11. Vander Wal JS, Mitchell ER. Psychological complications of pediatric obesity. Pediatr Clin North Am. 2011; 58(6):1393–401.
12. Hill AJ. Obesity in children and the "Myth of psychological maladjustment": self-esteem in the spotlight. Curr Obes Rep. 2017; 6(1):63–70.
13. Sypniewska G. Laboratory assessment of cardiometabolic risk in overweight and obese children. Clin Biohem. 2015; 48(6):370–6.
14. Jackson SE, Kirschbaum C, Steptoe A. Perceived weight discrimination and chronic biochemical stress: A population-based study using cortisol in scalp hair. Obesity (Silver Spring). 2016; 24(12):2515–21.
15. Andreyeva T, Puhl RM, Brownell KD. Changes in perceived weight discrimination among Americans: 1995–1996 through 2004–2006. Obesity (Silver Spring). 2008; 16(5):1129–34.
16. Puhl RM, Andreyeva T, Brownell KD. Perceptions of weight discrimination: prevalence and comparison to race and gender discrimination in America. Int J Obes (Lond). 2008; 32(6):992–1000.
17. Bacchini D, Licenziati MR, Garrasi A, Corciulo N, Driul D, Tanas R, et al. Bullying and victimization in overweight and obese outpatient children and adolescents: an Italian multicentric study. PLoS One. 2015; 10(11):e0142715.
18. Puhl R, Peterson JL, Luedicke J. Weight-based victimization: bullying experiences of weight loss treatment. Pediatrics. 2013; 131(1):e1–9.
19. Madowitz J, Knatz S, Maginot T, Crow SJ, Boutelle KN. Teasing, depression and unhealthy weight control behaviour in obese children. Pediatr Obes. 2012; 7(6):446–52.
20. Bucchianeri MM, Eisenberg ME, Wall MM, Piran N, Neumark-Sztainer D. Multiple types of harassment: associations with emotional well-being and unhealthy behaviors in adolescents. J Adolesc Health. 2014; 54(6):724–9.
21. Haines J, Hannan PJ, van den Berg P, Eisenberg ME, Neumark-Sztainer D. Weight-related teasing from adolescence to young adulthood: longitudinal and secular trends between 1999 and 2010. Obesity (Silver Spring). 2013; 21(9):E428–34.
22. Eisenberg ME, Neumark-Sztainer D, Story M. Associations of weight-based teasing and emotional well-being among adolescents. Arch Pediatr Adolesc Med. 2003; 157(8):733–8.
23. Rojo-Moreno L, Rubio T, Plumed J, Barberá M, Serrano M, Gimeno N, et al. Teasing and disordered eating behaviors in Spanish adolescents. Eat Disord. 2013; 21(1):53–69.
24. Leme AC, Philippi ST. Teasing and weight-control behaviors in adolescent girls. Rev Paul Pediatr. 2013; 31(4):431–6.
25. Berge JM, Hanson-Bradley C, Tate A, Neumark-Sztainer D. Do parents or siblings engage in more negative weight-based talk with children and what does it sound like? A mixed-method study. Body Image. 2016; 18:27–33.
26. Tomiyama AJ, Finch LE, Belsky AC, Buss J, Finley C, Schwartz MB, et al. Weight bias in 2001 versus 2013: contradictory attitudes among obesity researchers and health professionals. Obesity (Silver Spring). 2015; 23(1):46–53.
27. Phelan SM, Dovidio JF, Puhl RM, Burgess DJ, Nelson DB, Yeazel MW, et al. Implicit and explicit weight bias in a national sample of 4,732 medical students: the medical student CHANGES study. Obesity (Silver Spring). 2014; 22(4):1201–8.
28. Sabin JA, Marini M, Nosek BA. Implicit and explicit anti-fat bias among a large sample of medical doctors by BMI, race/ethnicity and gender. PLoS One. 2012; 7:e48448.
29. Neumark- Sztainer, Story M, Harris T. Beliefs and attitudes about obesity among teachers and school health care providers working with adolescents. J Nutr Educ. 1999; 31(1):3–9.
30. Garcia JT, Amankwah EK, Hernandez RG. Assessment of weight bias among pediatric nurses and clinical support staff toward obese patients and their caregivers. J Pediatr Nurs. 2016; 31(4):e244–51.

Стигма гојазности у адолесценцији

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САЖЕТАК

Увод/Циљ Гојазна деца и адолесценти су изложени стигматизацији и дискриминацији од вршњака, просветних радника и породице, што може да доведе до бројних здравствених и психосоцијалних проблема.

Циљ овог истраживања је да утврди да ли су и колико гојазни адолесценти у Србији изложени стигматизацији и који су најчешћи облици стигматизације којима су изложени.

Методе Укључено је 335 адолесцената хоспитализованих због гојазности. Свима је измерена телесна маса и висина, израчунат је индекс телесне масе и самостално су попунили Упитник о стигматизацији због гојазности, који је сачињен за потребе овог истраживања. Упитник је садржао и податке о полу, узрасту испитаника и гојазности других чланова породице.

Резултати Доживело је увреде 59% испитаника, 19% је задиркивано, 47,5% је било предмет оговарања, а 25% искључено из вршњачке групе; 45% испитаника је навело да су други имали предрасуде о њима. Адолесценти су чешће од адолесценткиња били изложени отвореној стигматизацији/дискриминацији као што су увреде или физичко насиље. Од здравствених радника је стигматизовано 19% испитаника, а 6% је навело да се породица стиди њихове гојазности.

Закључци Значајан проценат гојазних адолесцената је изложен стигматизацији, најчешће у виду увреда, оговарања и искључивања из вршњачке групе. Најчешће су изложени стигматизацији од вршњака, али је значајан удео доживео стигматизацију од здравствених радника.

Кључне речи: адолесцент, гојазан; гојазност; стигма; телесна маса

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

A combination of acute and delayed contralateral epidural hematoma

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SUMMARY

Introduction An acute bilateral extradural hematoma is an uncommon presentation of a traumatic head injury; however, it leads to higher mortality rate than an acute unilateral hematoma. A delayed epidural hematoma (DEDH) is a hematoma not present on the initial computed tomography (CT) scan but is found on a subsequent CT scan. While reviewing the literature, we could not find recently published papers considering supratentorial DEDH after primary operated contralateral epidural hematoma.

Case outline A comatose 14-year-old male patient with Glasgow Coma Scale score of 4 and the right mydriatic pupil on the side of the blunt trauma to the head was admitted to the intensive care unit after he had survived a traffic accident. The initial brain CT scan showed an acute temporoparietal epidural hematoma on the right side of the cranium, with impressive midline shift and bilateral linear skull fracture. Surgery was performed and an intracranial pressure (ICP) monitor was implanted, which showed increased values of ICP. A control brain CT scan performed within 24 hours showed a new contralateral occipitoparietal epidural hematoma. Another operation was performed. A second, control CT brain scan showed favorable findings. The patient was transferred after 25 days to the rehabilitation center, with the disability rating score of 11, which was reduced to 1 after three months.

Conclusion A contralateral DEDH is a life-threatening neurosurgical emergency case which can occur during the first 24 hours after decompressive craniectomy. Control CT scans should be performed one day after the operation in order to verify and treat DEDH timely. A high degree of vigilance and ICP monitoring is recommended in these cases, especially after surgical decompression.

Keywords: brain trauma; delayed bleeding; extradural hematoma; intracranial pressure monitoring

INTRODUCTION

An epidural hematoma (EDH) occurs when blood accumulates between the skull and the dura mater due to a severe cranial trauma. A typical location of these hematomas is the temporal one, as the most common cause of bleeding is a lesion of the middle meningeal artery. The pterion region, which overlies it, is relatively weak and prone to injury. Nevertheless, other locations of EDH are not so uncommon and are reported in 20–30% of cases [1]. It is usually found on the same side of the cranium that was impacted by the blow, but very rarely it can be due to a counter coup brain injury. Epidural blood clot, while expanding, strips the dura from tabula interna of the skull, forming a mass that causes brain shifting, and consequently compression on the cerebral blood vessels and cranial nerves. Usually, EDH grows within the first four to six hours, after which profound deterioration starts in the form of contralateral limb weakness, coma, and ipsilateral pupil fixation and dilatation.

This condition is reported in 1–3% of head injuries [2]; 15–20% of EDHs are fatal, with only 5% in children population [3, 4].

Intracranial EDH is considered to be the most serious complication of head injury, requiring immediate diagnosis and surgical intervention. It usually occurs in young adults, and it is rare before the age of two and after the age of 60. Intracranial EDH may be acute (58%), subacute (31%) or chronic (11%) [5]. Bilateral EDH accounts for 2–10% of all acute EDHs in adults, being exceedingly rare in children [6].

A traumatic delayed epidural hematoma (DEDH) can be defined as a hematoma that is insignificant or not present on the initial computerized tomography (CT) scan made after the trauma; however, a subsequent CT scan shows sizeable epidural bleeding [7]. The reported incidence of DEDH varies from 5.6% to 13.3% [8, 9].

While reviewing the literature, we could not find recently published papers considering supratentorial DEDH after primary operated contralateral EDH. We only found cases after the operation of a contralateral subdural or intracerebral hematoma [10, 11, 12].

CASE REPORT

Herein we present a case of a 14-year-old boy who sustained severe injuries as a pedestrian in a traffic accident. His polytrauma injuries included the left lung contusion, extensive

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parietal bilateral skull fracture, and a typically located large EDH, temporoparietal on the right side, detected on a CT scan (Figure 1). On admission, the patient's Glasgow Come Scale score was 4, he had the left-sided hemiplegia, and the right pupil was fixed and dilated.

Urgent craniotomy was performed, as well as the evacuation and hemostasis of massive extradural hematoma combined with modest dura and brain laceration. An intracranial pressure (ICP) monitor was implanted in the subdural space, and it showed the values that indicated intracranial hypertension. The initial ICP was higher than 40 mmHg during the first postoperative hour and declined to around 24 (the average ICP value was 24.3 mmHg) in the next 20 hours. The right pupil shrank to the normal size. During the first 12 hours, the patient was sedated so that his state of consciousness was unavailable, except for the short period of time between two sedations. Due to ICHT and reduced possibilities of assessing Glasgow Come Scale score, a control CT brain scan was performed. A new, contralateral occipitoparietal DEDH was found, which was a bit smaller than the initial one (Figure 2). Another operation was performed, and under the contralateral fracture an EDH was evacuated. In the next three days, the values of ICP measured around 20 mmHg. The average daily ICP values were 19.4, 20.8, and 18.2, respectively, and in the last three days of ICP monitoring the values were around 15 mmHg. Meanwhile, blood samples routinely obtained in the emergency room were analyzed for coagulation parameters, including prothrombin time, platelet counts, activated partial thromboplastin time, fibrinogen level, and the international normalized ratio. All values were normal. One day after the second operation, the brain CT scan showed favorable findings (Figure 3). Eye exam was done at the seventh postoperative day, but no signs of papilledema were found. Long-term recovery, tracheotomy, and intensive physical rehabilitation followed the second operation. The patient was discharged from the hospital after three weeks and transferred to the rehabilitation facility and had disability rating score of 11. Three months after the accident, his DRS was 1.

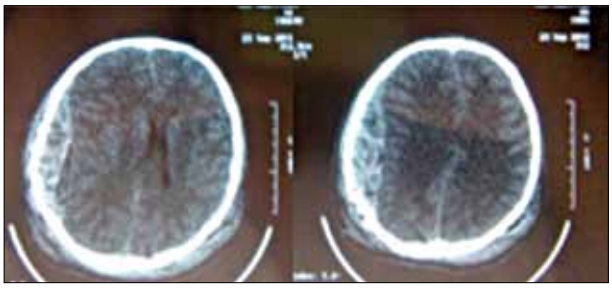

Figure 1. Initial epidural hematoma in the right temporoparietal region

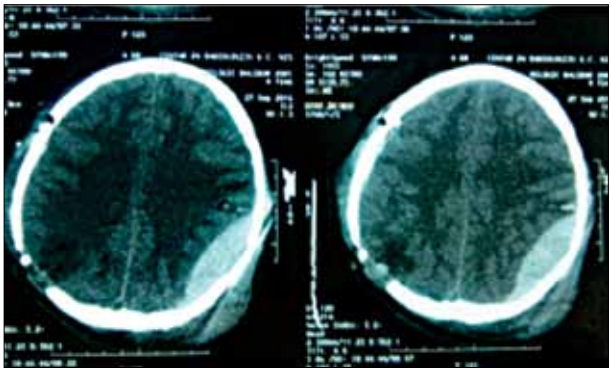

Figure 2. Contralateral delayed epidural hematoma in the left occipitoparietal region – a hematoma newly formed after the first operation

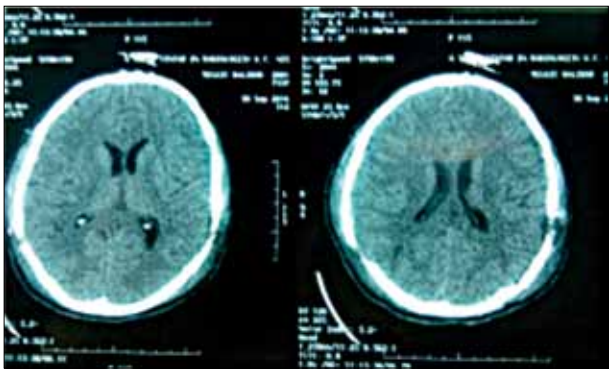

Figure 3. A control brain CT scan after the second operation – normal postoperative finding

DISSCUSION

The question is whether a hematoma that is not present on the initial CT scan but is found on a subsequent CT scan represents an enlargement of an EDH from invisible to visible on high-quality CT or is a newly-formed subacute extradural hemorrhage promoted by some risk factors.

The risk factors responsible for the delayed appearance of the EDH "tamponade" effect are usually increased endocranial pressure and post-traumatic arterial hypotension, as well as coagulopathy in a limited number of cases [13, 14, 15]. Post-traumatic nasal and ear leakage of the cerebrospinal fluid may result in the occurrence of DEDH. Some of the risk factors are iatrogenic, including the operation of cerebellar expansive lesions, rapid intravenous infusion or transfusion after the development of hemodynamic shock in a traumatized patient, intraventricular cerebrospinal fluid drainage, overdrainage during ventriculoperitoneal shunting. A case of a DEDH in the spinal region, after facet joint infiltration in a chronic back pain patient, has also been described [16].

Some authors suggest repeating a brain CT scan within the first 36 hours after sustaining an injury in patients with a small, asymptomatic EDH, as the mean time to EDH enlargement is about eight hours [17]. We performed the control CT brain scan within 24 hours as the neurological status of the patient remained unclear and potentially unfavorable. Nevertheless, ICP monitoring and continuous neurological monitoring could be crucial in the early discovering of DEDH. Post-traumatic restlessness may lead to hyperventilation and blood pressure elevation with lowering of the ICP, both of which may provoke bleeding into EDH. However, in the series of Sakai et al. [18], all of the ICP-monitored patients had either unchanged or increased ICP. Early diagnosis of DEDH can be facilitated by the liberal use of intracranial pressure monitoring as its

sensitivity could be up to 80% [19, 20]. In the case we presented, after the first evacuation of the epidural clot, ICP dropped from 40 mmHg to 24 mmHg and that event could have triggered the subsequent bleeding from a fractured skull contralateral. Still, the ICP values remained higher than normal (average ICP > 20 mmHg) until the time of the second evacuation of the epidural clot, although normalization of ICP values was to be expected. It turned out that DEDH maintained the intracranial hypertension. The ICP values were lower or equal to 20 mmHg for the next three days. Normalization of ICP occurred on the fourth postoperative day. Therefore, ICP monitoring can be of great help, especially in a continuously sedated patient.

Eye examination did not show any signs of the papilledema since it was performed a week after the accident. Normal results were to be expected according to the fundoscopic examination dynamic finding after severe brain trauma [21]. This dynamic is quite different from fundoscopic examination finding after severe spine injury, in which papilledema occurs much later [22].

Enlargement of EDH in its acute phase is often explained by continuous hemorrhage and re-hemorrhage from either the arterial or venous vessels. Some authors emphasize that venous hemorrhage does not generate enough pressure to strip dura mater from the bone or to overcome the clot-induced tamponade effect [23]. A decrease in clot density combined with the formation of membranes with permeable sinusoids usually after the fifth day after the trauma could lead to a new hemorrhage and further enlargement of the hematoma [24]. This slight increase in size between days 5 and 16 is manifested in 50% of cases, and some patients require emergency craniotomy when signs of herniation occur [24]. DEDH in our patient occurred much earlier, in the first 24 hours, probably due to the extensive bilateral fracture.

Rarely reported in mild head traumas [25], DEDH is commonly associated with skull fractures [20]. DEDH development in the infratentorial compartment is tenfold higher in patients with fracture line in the posterior fossa than in patients with supratentorial fractures [26]. Rapid deterioration of an injured patient, especially if DEDH is formed in the posterior fossa, could be lethal despite urgent CT brain scan and prompt operation [25]. This is explained by an irreversible damage to some of the vital centers located in the brain steam.

Atypical occipitoparietal location and modest volume of DEDH presented in this case report are relevant for the patient's prognosis, as it is unlikely to cause brain herniation or pressure on the brain steam. However, if it remains unrecognized timely, DEDH can be life-threatening.

REFERENCES

1. Graham DI, Gennareli TA. Chapter 5. Pathology of Brain Damage After Head Injury. In: Cooper P, Golfinos G. Head Injury. 4th ed. New York: Morgan Hill; 2000.
2. Mishra A, Mohanty S. Contre-coup extradural haematoma: a short report. Neurol India. 2001; 49(1):94–5.
3. Sanders MJ, McKenna K. Head and Facial Trauma. Chapter 22. In: Mosby's Paramedic Textbook, 2nd revised ed. New York: Mosby; 2001.
4. Binder H, Majdan M, Tiefenboeck TM, Fochtmann A, Michel M, Hajdu S, et al. Management and outcome of traumatic epidural hematoma in 41 infants and children from a single center. Orthop Traumatol Surg Res. 2016; 102(6):769–74.
5. Dähnert W. Radiology Review Manual 7th edition. Epidural Hematoma of Brain. Philadelphia: Lippincott Wiliams&Wilkins; 2012. p. 289.
6. Dharker SR, Bhargava N. Bilateral epidural haematoma. Acta Neurochir (Wien). 1991; 110(1-2):29–32.
7. Radulovic D, Janosevic V, Djurovic B, Slavik E. Traumatic delayed epidural hematoma. Zentralbl Neurochir. 2006; 67(2):76–80.
8. Oertel M, Kelly DF, McArthur D, Boscardin WJ, Glenn TC, Lee JH, et al. Progressive hemorrhage after head trauma: predictors and consequences of the evolving injury. J Neurosurg. 2002; 96(1):109–16.
9. Ashkenazi E, Constantini S, Pomeranz S, Rivkind AI, Rappaport ZH. Delayed epidural hematoma without neurologic deficit. J Trauma. 1990; 30(5):613–5.
10. Su TM, Lee TH, Chen WF, Lee TC, Cheng CH. Contralateral acute epidural hematoma after decompressive surgery of acute subdural hematoma: clinical features and outcome. J Trauma. 2008; 65(6):1298–302.
11. Shen J, Pan JW, Fan ZX, Zhou YQ, Chen Z, Zhan RY. Surgery for contralateral acute epidural hematoma following acute subdural hematoma evacuation: five new cases and a short literature review. Acta Neurochir (Wien). 2013; 155(2):335–41.
12. Solomiichuk VO, Drizhdov KI. Contralateral delayed epidural hematoma following intracerebral hematoma surgery. Surg Neurol Int. 2013; 4:134.
13. Domenicucci M, Signorini P, Strzelecki, Delfini R. Delayed post-traumatic epidural hematoma. A review Neurosurg Rev. 1995; 18(2):109–22.
14. Brown MW, Yilmaz TS, Kasper EM. Iatrogenic spinal hematoma as a complication of lumbar puncture: What is the risk and best management plan? Surg Neurol Int. 2016; 7(Suppl 22):S581–9.
15. Takahashi Y, Sato T, Hyodo H, Kawamata T, Takahashi E. Symptomatic epidural haematoma after cervical laminoplasty: a report of three cases. J Orthop Surg (Hong Kong). 2016; 24(1):121–4.
16. Velickovic M, Ballhause TM. Delayed onset of a spinal epidural hematoma after facet joint injection. SAGE Open Med Case Rep. 2016; 4:2050313X16675258.
17. Sullivana TP, Jarvika JG, Cohen WA. Follow-up of Conservatively Managed Epidural Hematomas: Implications for Timing of Repeat CT. AJNR. 1999; 20:107–13.
18. Sakai H, Takagi H, Ohtaka H, Tanabe T, Ohwada T, Yada K. Serial changes in acute extradural hematoma size and associated changes in level of consciousness and intracranial pressure. J Neurosurg. 1988; 68(4):566–70.
19. Borovich B, Braun J, Guilburd JN, Zaaroor M, Michich M, Levy L, et al. Delayed onset of traumatic extradural hematoma. J Neurosurg. 1985; 63(1):30–4.
20. Poon WS, Rehman SU, Poon CY, Li AK. Traumatic extradural hematoma of delayed onset is not a rarity. Neurosurgery. 1992; 30(5):681–6.
21. Joshua SP, Agrawal D, Sharma BS, Mahapatra AK. Papilloedema as a non-invasive marker for raised intra-cranial pressure following decompressive craniectomy for severe head injury. Clin Neurol Neurosurg. 2011; 113(8):635–8.
22. Catz A, Appel I, Reider-Grosswasser I, Grosswasser Z, Mendelson L, Gepstein R. Late-onset papilledema following spinal injury. Case report. Paraplegia. 1993; 31(2):131–5.
23. Bender MB, Christoff N. Nonsurgical treatment of subdural hematomas. Arch Neurol. 1974; 31(2):73–9.
24. Pang D, Horton JA, Herron JM, Wilberger JEJ, Vries JK. Nonsurgical management of extradural hematomas in children. J Neurosurg. 1983; 59(6):958–71.
25. Resigo P, Piquer J, Bottela C, Orozco M, Navarro J, Cabanes J. Delayed extradural hematoma after mild head injury: report of three cases. Surg neurol. 1997; 48(3):226–31.
26. Kırcelli A, Özel Ö, Can H, Sarı R, Cansever T, Elmacı İ. Is the presence of linear fracture a predictor of delayed posterior fossa epidural hematoma? Ulus Travma Acil Cerrahi Derg. 2016; 22(4):355–60.

Комбинација акутног и одложеног контралатералног епидуралног хематома

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САЖЕТАК

Увод Акутни билатерални епидурални хематоми (ЕДХ) нису чест налаз после повреде главе, али су узрок знатно веће смртности у поређењу са акутним унилатералним хематомом. Одложени епидурални хематом (ОЕДХ) епидурално је крварење које није присутно на иницијалној компјутеризованој томографији (КТ), али је нађено на накнадној КТ. У литератури нисмо нашли рад са описом супратенторијалног ОЕДХ после операције контралатералног ЕДХ.

Приказ случаја После саобраћајне несреће примљен је 14 година стар дечак у коми (Глазгов кома скор 4) и са проширеном зеницом на страни тупе трауме главе. Иницијална КТ мозга показала је темпоропаријетални ЕДХ на десној страни кранијума, са израженим померењем средњелинијских структура и билатералном линераном фрактуром лобање. Повређени је оперисан и започет је мониторинг интракранијалног притиска (ИКП), који је био повишен. Контролна КТ мозга унутар прва 24 часа показала је нови контралатерални окципито-паријетални ЕДХ. Предузета је нова операција. Други, контролни налаз КТ мозга је био уредан. После 25 дана болесник је преведен у Рехабилитациони центар, са степеном неспособности оцењеним са 11. После три месеца болесник је био готово без последица повређивања.

Закључак Контралатерални ОЕДХ је стање непосредне животне угрожености, који се може појавити унутар прва 24 часа од краниотомије. Потребно је брижљиво праћење стања болесника, укључујући контролну КТ и праћење ИКП.

Кључне речи: траума мозга; одложено крварење; епидурални хематом; мерење интракранијалног притиска

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Surgical treatment of a cranio-facial dermoid cyst

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SUMMARY
Introduction Intracranial extension is rarely seen with craniofacial dermoid cysts, with few cases reported in the literature.
Case outline We report a case of a 30-year-old woman who initially presented with a subcutaneous mass of the frontotemporal region. The patient underwent a right craniectomy by a frontal approach. Histopathologic analysis confirmed the diagnosis of a dermoid cyst.
Conclusion Craniofacial dermoid cysts may be associated with an intracranial extension.
Keywords: dermoid cyst; congenital tumor; frontotemporal region; intracranial extension

INTRODUCTION

Craniofacial dermoid cysts are presented as solitary, slow-growing, subcutaneous masses [1–4]. During congenital development they result from sequestration of epidermal and dermal cells and consist of epithelium-lined cysts with skin appendages. Dermoid cysts are associated with mature adnexal structures (hair follicles, sebaceous and eccrine glands) and this differentiates them from epidermoid cysts. They are visible at birth or in childhood as a slow-growing, subcutaneous mass, which can sometimes become inflamed or infected [5]. Rarely, dermoid cysts of the frontotemporal region may be associated with an intracranial extension [4, 5].

We report an unusual case of a 30-year-old female patient with a fronto-temporal dermoid cyst presenting as a massive subcutaneous mass associated with intracranial involvement.

CASE REPORT

A 30-year-old female patient was admitted to our department of neurosurgery with severe headaches and a loss of eyesight on the right side. She had a history of more than 12 years of a slowly progressing mass in the right frontal region. A neurologic clinical examination revealed right sided supraorbital subcutaneous mass with exophthalmos resulting in diplopia and reduced visual acuity. There was no organic problem in her medical history and there was no family history of oncologic diseases. Routine hematological and biochemical parameters were normal. The patient denied any kind of trauma to this region.

A routine X-ray of the scull was made and lesion of the frontal bone was detected (Figure 1). A magnetic resonance imaging (MRI) brain scan showed an enhancing extradural lytic bone lesion of 6.16 × 7.21 cm in size, well-defined hyperdense, on T2-weighted image, mass lesion in the right frontal lobe without perilesional edema (Figure 2). Preoperative cerebral

Figure 1. Scull X-ray showing extradural lytic bone lesion.

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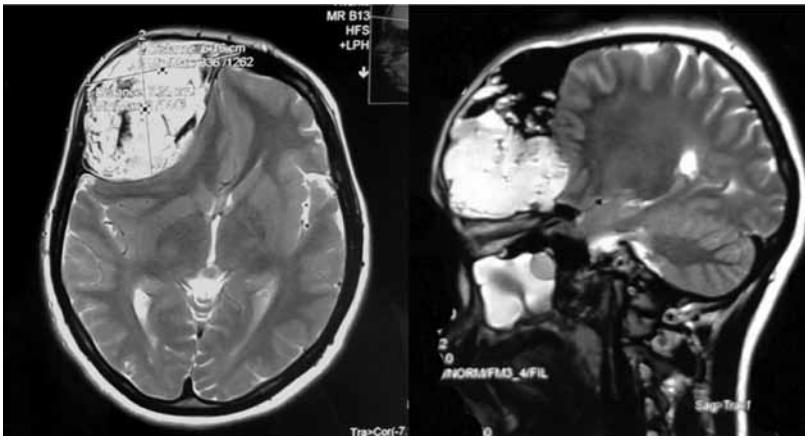

Figure 2. MR image showing a well-circumscribed, heterogeneous and fat-density mass involving the right frontal wall

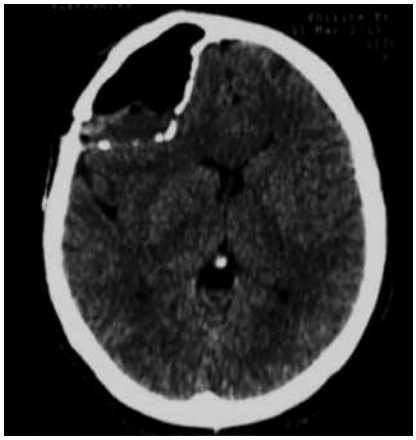

Figure 3. MR image six months after cranioplasty showing no recurrence of the dermoid cyst

angiography was undertaken to check the blood supply of the mass and eliminate vascular anomalies: abnormalities were not observed. No further neuroradiological examination was needed because the present finding clearly showed an extracerebral mass with frontal bone erosion.

Complete removal of the lesion was carried out through a right frontal craniectomy under general anesthesia. A curved incision was performed in the frontal region of the scalp and a large cyst was found to have created a cavity in the frontal bone and intracranially. The dura was intact. The cyst was yellow, containing dirty brown, grumous, oily material. Hair and other dermal elements were observed.

Microscopic examination revealed a cystic lesion of the dermoid type. Histologic examination showed a keratinized stratified squamous epithelial lining, associated with mature adnexal structures (hair follicles and shafts, sebaceous and eccrine glands).

The patient was then referred to our maxillofacial unit for treatment. We performed a second operation together with a maxillofacial specialist. We performed a reconstruction of the bone deficit with cranioplasty and a reconstruction of the frontal sinus (Figure 3).

Postoperative recovery was uneventful, and the patient was discharged 10 days after the second surgery. In the early postoperative period, improvement was evident. During the following six months after the surgery there was no evidence of tumour recurrence.

DISCUSSION

Dermoid cysts are benign soft tissue cysts of embryonic origin that arise along the lines of skin fusion. During congenital development they result from sequestration of epidermal and dermal cells and consist of epithelium-lined cysts with skin appendages (hair follicles, sebaceous and eccrine glands). They are described as "oil cysts" by Hirschberg [6], and they represent a common mass of the orbitofacial region in the pediatric population. Very rarely they can be found in adults, as slow-growing subcutaneous masses of the head and face region. Our case presents a 30-year-old woman who initially presented a subcutaneous mass of the frontotemporal region, which revealed an intracranial dermoid cyst, so we emphasize that a dermoid cyst should be included in the differential diagnosis of all nodular cyst-like lesions in the head and face region.

In 1993, Bartlett et al. [7] proposed a topographic dermoid segregation into three groups: frontotemporal, orbital, and nasoglabellar. The algorithm was based on the potential extension of the lesions to the contiguous structures (meninges, orbital soft tissues, skin). According to Barlett et al. [7], frontotemporal and orbital dermoids with definable margins are superficial, slow-growing masses that can be excised, without an extensive radiologic diagnostic workup. However, orbital dermoid cysts required a thin-section MRI because of their propensity to extend beyond the bone (into the orbit, intracranially). In contrast to this research and other data we were able to find, intracranial involvement very rarely occurs with frontotemporal dermoids and there are only several cases of it [7, 8, 9]. This is more common with midline nasal and scalp cysts [7, 8, 9].

Our case represents frontotemporal dermoid in a 30-year-old adult with intracranial extension and close contact with meninges and orbital soft tissues which caused exophthalmus resulting in diplopia and reduced visual acuity.

The diagnosis of dermoid cyst was suggested by imaging (skull radiographs, CT scan, MRI) and confirmed by histology. MRI scan allows for good assessment of both skull involvement and intracranial extension and reveals the exact site, limits, and characteristic bone defects of these lesions. Differential diagnosis should include epidermoid cyst, hydatid cyst, cholesterol granuloma, eosinophilic granuloma, and meningioma [10]. It is particularly common to misdiagnose a dermoid cyst as an epidermoid cyst, as the difference between them is mainly histological. The definite diagnosis can be achieved by surgical removal and histopathological confirmation.

The indications for surgery include cosmetic effect, prevention of progression of psychiatric symptoms and neurological deficit, treatment of osteomyelitis, and resection of cysts with malignant degeneration [11, 12]. Most cranial dermoids are small and do not extend intracranially, but progressive growth may result in large

cranial defects or compression of the brain and vascular structures [5, 6]. There are two considerations about surgical treatment of dermoid cysts. The first concern is the recurrence and potential for malignant transformation, which results from an incomplete excision, especially when a long-standing dermoid cyst extends deeply intracranially. The second concern are the possible complications, including inflammation, osteomyelitis, meningitis, and cerebral abscess.

Removal of these tumors and subsequent cranioplasty, despite their large size, are recommended, particularly for very large dermoid cysts associated with significant bony defects [11]. Total removal of these cysts is associated with a very good long-term prognosis [8, 9]. Recurrence is likely if the cyst wall is not completely removed, with a recurrence rate of 8–25% and potential malignant transformation [5, 11, 12]. In our patient, we were able to remove the cyst and capsule completely with combined intracranial–extracranial approach proposed by Sessions [13]. Repeated washing of the cavity with 0.9% saline prevented aseptic meningitis and recurrence. A postoperative antibiotic regimen was implemented to prevent infection.

The orbitofacial dermoid typically presents as a slow-growing, non-fixed, asymptomatic mass. These features may not be apparent in intracranial situated lesions. It is important to be aware that the subcutaneous mass of the face and head region may represent the "tip of the iceberg" of a deep dermoid cyst. For this reason, early recognition and accurate diagnosis by means of CT scan or MRI facilitate successful treatment.

Although rare, all nodular cysts-like lesions in the head and neck (orbitofacial) region, in adults, should be included in the differential diagnosis of dermoid cysts. Failure to recognize and treat these lesions may lead to a progressive neurological deficit, bone distortion, or recurrent infections with severe complications such as meningitis or cerebral abscess. For this reason, early clinical recognition and diagnostic procedures like CT scan or MRI facilitate successful treatment.

REFERENCES

1. Gordon PE, Faquin WC, Lahey E, Kaban LB. Floor-of-Mouth Dermoid Cysts: Report of 3 Variants and a Suggested Change in Terminology. J Oral Maxillofac Surg. 2013; 71(6):1034–41.
2. Hachach-Haram N, Benyon S, Shanmugarajah K, Kirkpatrick NW. Back to basics: A case series of angular dermoid cyst excision. J Plast Reconstr Aesthet Surg. 2013; 66(1):57–60.
3. Golden BA, Jaskolka MS, Ruiz RL. Craniofacial and Orbital Dermoids in Children. Oral Maxillofac Surg Clin North Am. 2012; 24(3):417–25.
4. Sillifant P, Duncan C. Dermoid cysts in the craniofacial region: the Liverpool experience. British Journal of Oral and Maxillofacial Surgery. 2011; 49:S101–2.
5. Reissis D, Pfaff MJ, Patel A, Steinbacher DM. Craniofacial dermoid cysts: histological analysis and inter-site comparison. Yale J Biol Med. 2014; 87(3):349–57.
6. Hirschberg J. Oil cyst of orbit. Arch Ophthalmic. 1879; 8:373–5.
7. Bartlett SP, Lin KY, Grossman R, Katowitz J. The surgical management of orbitofacial dermoids in the pediatric patient. Plast Reconstr Surg. 1993; 91(7):1208–15.
8. Steele MH, Suskind DL, Moses M, Kluka E, Liu DC. Orbitofacial masses in children: an endoscopic approach. Arch Otolaryngol Head Neck Surg. 2002; 128(4):409–13.
9. Hong SW. Deep frontotemporal dermoid cyst presenting as a discharging sinus: a case report and review of literature. Br J Plast Surg. 1998; 51(3):255–7.
10. Živković N, Marković M, Mihajlović G, Jovanović M. Surgical Treatment of Intradiploic Epidermoid Cyst Treated as Depression. Srp Arh Celok Lek. 2014; 142(1-2):67–71.
11. Ayhan A, Tuncer ZS, Bilgin F, Kucukali T. Squamous cell carcinoma arising in dermoid cyst. Eur J Gynaecol Oncol. 1996; 17(2):144–7.
12. Stephenson GC, Ironside JW. Squamous cell carcinoma arising in a subcutaneous dermoid cyst. Postgrad Med J. 1991; 67(783):84–6.
13. Sessions RB. Nasal dermal sinuses—new concepts and explanations. Laryngoscope. 1982; 92:1–28.

Хируршко лечење кранио-фацијалне дермоидне цисте

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САЖЕТАК

Увод Интракранијална екстензија је ретко виђена код краниофацијалних дермоидних циста, са неколико случајева пријављених у литератури.

Приказ болесника Код 30-годишње жене првобитно је уочена субкутана маса фронтотемпоралног региона. Урађена је краниотомија фронталним приступом. Хистопатолошка анализа потврдила је дијагнозу дермоидне цисте.

Закључак Краниофацијална дермоидна циста може бити повезана са интракранијалним ширењем.

Кључне речи: дермоидна циста; урођен тумор; фронтотемпорална област; интракранијално ширење

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Subacute liver failure of unknown origin

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SUMMARY

Introduction Acute liver failure is a rare and very complex clinical syndrome, a consequence of sudden and severe liver dysfunction. There are several causes of this condition (viruses, medications, toxins, metabolic, autoimmune and malignant diseases), but etiological agent often remains undiscovered.

Case outline A 40-year-old male patient had suddenly taken ill with signs and symptoms of acute hepatitis, which was confirmed through biochemical analyses. The cause of acute liver failure was not determined. Despite all therapeutic measures, the clinical course of the disease was unfavorable: severe icterus, decreased synthetic function of the liver and hepatic encephalopathy developed. In the later, subacute course of the disease, ascites and episodes of hepatic encephalopathy developed, and biochemical findings indicated chronic hepatocellular failure. After three months of treatment in hepatic coma there was lethal outcome. Histopathological findings confirmed the diagnosis of decompensated liver cirrhosis of unknown origin.

Conclusion The cause of acute liver failure often remains unclear; potential causes should be looked for in infections by unknown viruses or in exposures to toxins. The disease is most commonly presented as a subacute failure with the development of liver cirrhosis. Survival rate is low.

Keywords: subacute liver failure; acute hepatitis non A-E; liver cirrhosis; hepatic encephalopathy

INTRODUCTION

Acute liver failure (ALF) is a complex clinical syndrome which develops as a consequence of massive or submassive hepatic cell necrosis, with a development of hepatic encephalopathy (HE) and a severe disturbance in liver functions. It is usually fatal (in 60–90%), most often within the first week of the disease [1]. Since there are several etiological factors, with different clinical course and outcome of the disease and many complications, different authors give diverse classifications of ALF [2, 3]. The researches of King's College Hospital, based on experience with 558 patients with ALF and 47 patient with later-developed liver failure, gave a new classification of ALF. Their suggestion is that ALF should be used as a frame term, which should be predetermined with prefixes hyper- or sub-, which would be two extremes of this clinical syndrome. The term 'hyperacute liver failure' relates to patients who develop encephalopathy within seven days after the onset of jaundice. This group of patients has significant survival rate (around 40%) with the use of usual medications. For patients who develop encephalopathy eight to 28 days after the appearance of jaundice the term 'acute liver failure' is used. These patients have extremely low survival rate (7%). For patients in whom encephalopathy develops after four weeks (29–84 days after the appearance of jaundice) the term 'subacute liver failure' should be used. Survival rate for the last group is low, about 14%. The most common etiological factor was acute hepatitis non-A, non-B, making 83% of all cases [4]. Adopting this terminology allowed for standardized approach and interpretation of controlled clinical studies, and also for the application of new therapeutical methods, including bioartificial liver support and liver transplantation.

In addition to time elapsing between the appearance of jaundice and encephalopathy, other prognostic factors of outcome of ALF were discovered, such as the level of serum bilirubin, ammonemia, international normalized ratio (INR), thyroid status, etc. By combining these factors different prognostic models were made in order to predict mortality, and to timely indicate the need for liver transplantation, the only remaining therapeutic option [5]. This is especially important for ALF of unknown origin since there is no specific therapy.

CASE REPORT

A 40-year-old male patient from Belgrade, married, with two children, was admitted to the Clinic for Infectious and Tropical Disease in Belgrade, Clinical Centre of Serbia, due to nausea, loss of appetite, aversion to food, dark urine, and yellowing of the eyes. The disease started 10 days before his admission to the hospital. Epidemiological data excluded the possibility of liver infection by primary and potentially hepatotropic viruses, and acute toxic liver failure (caused by alcohol, medications, herbs, different supplements, etc.). At admission, the patient was afebrile, had jaundice, the liver was palpable 2 cm below the right rib cage, and there were no signs of HE. Biochemical

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analysis suggested acute hepatitis without hepatocellular insufficiency: aspartate aminotransferase (AST) 1,249 U/L, alanine aminotransferase (ALT) 2,907 U/L, total-value bilirubin (TBil) 393 μmol/L, direct bilirubin (DBil) 169 μmol/L, gamma-glutamyl transferase 194 U/L, alkaline phosphatase 115 U/L, prothrombin time (PT) 62.3%, INR 1.3. Hematological analyses were normal. Virological tests excluded hepatitis B virus (HBV) infection (HBsAg, anti-HBc IgM, and HBV DNA were negative), hepatitis C virus (HCV) infection (anti-HCV and HCV RNA were negative), hepatitis A virus (HAV) infection (anti-HAV IgM was negative), hepatitis E virus (HEV) infection (anti-HEV IgM negative), as well as the Epstein–Barr virus, cytomegalovirus, adenovirus, herpes simplex virus, and West Nile virus infection (IgM-class antibodies were negative measured by ELISA). Autoimmune liver disease, Wilson disease and hemochromatosis were excluded as well. A several-fold increase of the levels of alpha-fetoprotein (AFP) – 659 ng/L – was pointing to the regenerative potential of the liver. Ultrasound examination of the abdomen excluded the obstruction of the bile ducts, even though a gallstone of 1 cm in diameter was detected in the gallbladder. Thrombosis of the hepatic veins was excluded as well. A hematologist excluded hematology disease with possible liver infiltration.

In the further course of the disease, fatigue and loss of appetite continued, with an increase in serum transaminases (AST 3,113 U/L; ALT 4,957 U/L), jaundice (TBil 655 μmol/L; DBil 256 μmol/L) and a gradual fall of the liver synthetic function (albumin level 31 g/L; PT 46%; INR 1.61; AFP 129 ng/L). Since there was progressive liver failure with threatening hepatocellular insufficiency, prednisone and 20% human albumins were included in the therapy. In the further course there was no positive therapeutic response; hence, on the 30th day of the treatment the patient fulfilled the criteria for ALF – PT 40%, INR 1.81. Three days later, the flapping tremor (asterixis) appeared as a sign of the second phase of HE. Lactulosis, L-ornithine-L-aspartate (LOLA) and fresh frozen human plasma were added to the preceding therapy. In the further course of the disease the patient had episodes of HE with severe jaundice (TBil around 500 μmol/L), low AFP (17.5 ng/L), and hepatocellular insufficiency (PT 36%, INR 2.01). At the end of two months of treatment, for the first time, abdominal ultrasound verified inhomogeneous liver parenchyma, splenomegaly (12.5 cm) and some ascites in the abdomen. Our conclusion was that our patient had subacute liver failure with cirrhotic transformation. The patient was put on the transplant waiting list.

Further course of the disease corresponded to decompensated liver cirrhosis with HE. Biochemical analysis showed inversion of transaminases activity (AST 302 U/L; ALT 281 U/L), hyperbilirubinemia (TBil up to 639 μmol/L), hepatocellular insufficiency (albumin level 30 g/l, PT 27%, INR 2.28), and hyperammonemia (177 nmol/L). Magnetic resonance imaging scan of the abdomen and magnetic resonance cholangiopancreatography was performed – cirrhotic liver and multiple nodular lesions with atypical magnetic resonance imaging characteristics were found. Free fluid in the abdomen, portal hypertension, and a gallstone were also observed.

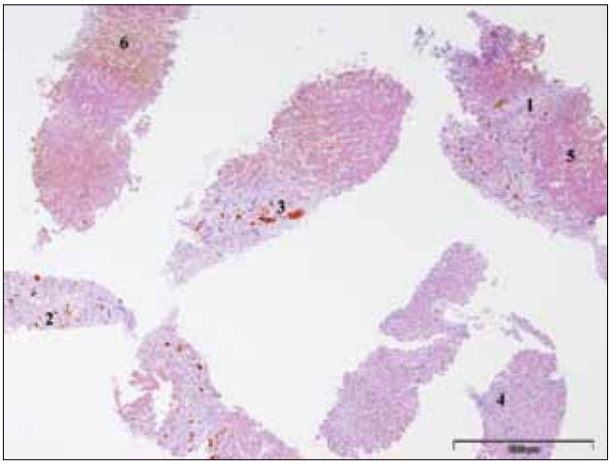

Figure 1. Postnecrotic cirrhosis with signs of liver insufficiency; fibrosis septa are seen around parenchymal nodules (1); there is proliferation of biliary ductules (2); bile stasis is seen in some of the dilated ducts (3); inflammatory infiltrates are scant (4); the parenchyma shows a nodular appearance (5); there are cellular and canalicular cholestasis (6); some hepatocytes show ischemic change

After three months of treatment the patient's disorder of consciousness deepened, up to the level of coma with hyperpyrexia. A lethal outcome occurred 102 days after the onset of the disease, in deep coma. Necropsy of the liver was performed and a cylindrical sample of 3.5 cm in diameter was obtained. The architecture of the liver was damaged in the cirrhotic manner. Cholestasis was severe and there were large zones of ischemic necrosis of hepatocytes. Iron staining results were negative, as well as copper-associated protein staining. There was no tumor tissue of hepatocellular carcinoma (Figure 1).

DISCUSSION

ALF with multiple organ dysfunctions, i.e. insufficiency, can be caused by many agents and pathological conditions: viruses, medications, toxins, alcohol, congenital metabolism disorders, autoimmune liver disease, cardiovascular disease, leukemia, reticulosis, etc. [6]. Globally, HAV and HEV infections are the most common cause of ALF in developing countries, with the mortality rate over 50% [7]. Of the known primary hepatotropic viruses, HBV is the most common (67.8%) cause of ALF in our country [1]. Over the last several years in Western Europe and the USA, there are an increased number of occurrences of herbal products causing hepatotoxicity; cases with ALF with lethal outcome have also been reported [8]. Around 50% of ALF in the United States are caused by medications, especially acetaminophen [9].

ALF of unknown origin (undetermined cause) is registered with diverse frequency worldwide and is not dependent on epidemiological characteristics of the area – from 11% in Sweden to 38% in Sudan [10, 11]. In our previous research, undetermined cause of ALF was the second most frequent cause (12.6%), just behind HBV infection. These patients had the worst prognosis, and the mortality rate was 100%.

Clinical course of the disease was either acute or subacute liver failure [12]. Our patient had subacute course of liver failure (signs of HE appeared 33 days after jaundice) with undetermined cause – infection with known primary and potentially hepatotropic viruses were excluded, as well as occult HBV and HCV infection, autoimmune liver disease, Wilson disease and hemochromatosis. Based on a detailed anamnesis, biochemical analysis and histopathological findings, as well as regarding previous researches, this could be the case of infection by an unknown hepatotropic virus [13].

The way the hepatocytes die or, to be more precise, the amount of simultaneously died hepatocytes and intraacinus localization of necrosis are at the center of today's histological classifications of acute viral hepatitis (AVH). Therefore, there are four basic histological forms of AVH: with focal necrosis, with confluent bridging necrosis, with panacinar necrosis, and with periportal necrosis [14]. The outcome of AVH with confluent bridging necrosis varies. Complete or almost complete healing can occur, by recovering of the parenchyma with rare remaining fibrosis. In some patients, lethal outcome is possible in the first 10 days of the disease with signs of ALF, or in two or three months of the disease with signs of subacute liver failure with fibrosis. In rare cases, real cirrhosis and nodular regeneration hyperplasia of the parenchyma can be found [15]. In our patient, subacute course of the disease and histopathologically proved liver cirrhosis could relate, by the course and the outcome, to acute viral hepatitis with confluent bridging necrosis. Liver transplantation is the last treatment option in patients with ALF, when conservative treatment options fail and lethal outcome is imminent [16]. Our patient was put on the transplant waiting list.

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REFERENCES

1. Delić D. Akutna insuficijencija jetre. Beograd: Zavod za udžbenike i nastavna sredstva; 1999.
2. Lucke B, Mallory T. Fulminant form of epidemic hepatitis. Am J Pathol. 1946; 22(5):867–945.
3. Bernuau J, Rueff B, Benhamou JP. Fulminant and subfulminant liver failure: definitions and causes. Sem Liv Dis. 1986; 6(2):97–106.
4. O'Grady J, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993; 342(8866):273–5.
5. Kumar R, Shalimar, Sharma H, Goyal R, Kumar A, Khanal S, et al. Prospective derivation and validation of early dynamic model for predicting outcome in patients with acute liver failure. Gut. 2012; 61(7):1068–75.
6. Mas A, Eodes J. Fulminant hepatic failure. Lancet. 1997; 349(9058):1081–5.
7. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013; 369(26):2525–34.
8. Stournaris E, Tziomalos K. Herbal medicine-related hepatotoxicity. World J Hepatol. 2015; 7(19):2189–93.
9. Reuben A, Koch DG, Lee WM, Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010; 52(6):2065–76.
10. Wei G, Bergquist A, Broome U, Lindgren S, Wallerstedt S, Almer S, et al. Acute liver failure in Sweden: etiology and outcome. J Intern Med. 2007; 262(3):393–401.
11. Mudawi HMY, Yousif BA. Fulminant hepatic failure in an Africa setting: etiology, clinical course, and predictors of mortality. Dig Dis Sci. 2007; 52(11):3266–9.
12. Urošević A. Etiologija, kliničke karekteristike, faktori prognoze i histopatološki nalaz kod bolesnika sa akutnom insuficijencijom jetre. Magistarska teza. Beograd: Medicinski fakultet; 2012.
13. Delić D, Mitrović N, Radovanović Spurnić A, Stojković Švirtlih N, Simonović Babić J. Epidemiological characteristics and clinical manifestations of acute non-A-E hepatitis. Vojnosanit Pregl. 2010; 67(11):903–9.
14. Scheuer PJ. Viral Hepatitis. In: MC Sween RNM, Anthony PP, Scheuer PJ, editors. Pathology of the Liver. Edinburg: Churchill Livingstone; 1987. p. 202–23.
15. Begić Janeva A. Patologija jetre i žučne bešike i žučnih puteva. Gornji Milanovac: Dečije novine; 1991.
16. Altinbas A, Bechmann LP, Akkiz H, Gerken G, Canbay A. Acute liver failure. In: Mauss S, Rockstroh J, Wedemeyer H, Berg T, Sarrazin C, editors. Hepatology. A clinical textbook. Hamburg: Medizin Fokus Verlag; 2017. p. 715–29.

Субакутна инсуфицијенција јетре непознате етиологије

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САЖЕТАК

Увод Акутна инсуфицијенција јетре је редак и веома сложен клинички синдром, настао као последица изненадне и тешке дисфункције јетре. Узроци су бројни (вируси, лекови, токсини, метаболичке, аутоимунске и малигне болести) и врло често се не открију.

Приказ болесника Мушкарац узраста 40 година разболео се нагло са тегобама и знацима акутног хепатитиса, што је биохемијским анализама и потврђено. Узрочник акутног оштећења јетре није доказан. И поред предузетих терапијских мера, клинички ток болести је неповољан: изражен иктерус, пад синтетске функције јетре, развој хепатичке енцефалопатије. У даљем, субакутном току болести долази до појаве асцитеса, епизода хепатичке енцефалопатије и биохемијских показатеља хроничне хепатоцелуларне инсуфицијенције. После три месеца лечења, у хепатичкој коми, долази до смртног исхода. Хистопатолошким прегледом ткива јетре потврђена је дијагноза декомпензоване цирозе јетре непознате етиологије.

Закључак Узрок акутне инсуфицијенције јетре често остаје нејасан; потенцијалне узрочнике треба тражити у инфекцијама са непознатим вирусима или у изложености токсинима. Болест се најчешће презентује као субакутна инсуфицијенција са развојем цирозе јетре. Степен преживљавања је низак.

Кључне речи: субакутна инсуфицијенција јетре; акутни хепатитис не-А-Е; цироза јетре; хепатичка енцефалопатија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Simultaneous bilateral spontaneous pneumothorax

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SUMMARY
Introduction Simultaneous bilateral spontaneous pneumothorax (SBSP) is a potentially life-threatening state that may imitate many lung diseases.
The aim of this report was to describe the presentation and highlight potential difficulties in diagnosis and management of patients with SBSP.
Case outline A 23-year-old female patient was urgently assessed because of a progressive two-day-long dyspnoea with associated bilateral chest pain. Lung auscultation revealed equally diminished breath sounds on both sides. During the initial examination, there was evidence of symptomatic deterioration with bilateral pleuritic chest pain, increased dyspnoea, and agitation. The patient was found to have type II respiratory failure with the following biochemical parameters: pH 7.34, $PaCO_2$ 6.3 kPa, and PaO_2 7.9 kPa. A chest radiograph confirmed bilateral partial pneumothoraces of approximately 30%. Both left- and right-sided thoracostomies with large-bore chest drain insertions were performed emergently, followed by partial resolutions of pneumothoraces. CT of the chest demonstrated residual pneumothoraces bilaterally with multiple apical bullae. In the further course, the patient subsequently underwent video-assisted thoracoscopic surgery with bilateral apicoectomies, bullectomies, and pleural abrasion. Her chest drains were removed three days after surgery and a post-treatment chest radiograph demonstrated resolution of the pneumothoraces. She was discharged without complications.
Conclusion Using clinical presentation, diagnostic algorithm and therapeutic management applied in the case of our patient, we emphasized a few mandatory steps in establishing the diagnosis of SBSP and further treatment.
Keywords: pneumothorax, classification, etiology, therapy; thoracic surgery; thoracoscopy, methods; chest tubes

INTRODUCTION

Pneumothorax is the presence of air in the pleural space [1]. According to its etiology, it can be classified as spontaneous, traumatic, or iatrogenic [2]. Spontaneous pneumothorax (SP) is categorized into primary and secondary [3]. Primary spontaneous pneumothorax (PSP) occurs in otherwise healthy individuals, whereas secondary spontaneous pneumothorax (SSP) is associated with underlying lung disease [2]. The incidence of SP is 9/100,000 people, and only 1.9% of SP are simultaneous bilateral SP (SBSP) [4, 5, 6]. SBSP is a potentially life-threatening state that may imitate many lung diseases. To make the accurate diagnosis, prompt chest radiography is essential [7]. The management of SBSP is acute and includes an urgent chest drain insertion, before definitive surgical intervention in order to reduce the risk of recurrence [6, 8]. This case report describes the presentation and highlights potential difficulties in diagnosis and management of an otherwise healthy patient with SBSP.

CASE REPORT

A 23-year-old female patient was urgently assessed because of a progressive two-day-long dyspnoea with associated bilateral chest pain. She had neither cough nor fever. The previous medical history recorded no significant diseases. There was no data conserning recent air travel or trauma. She was a smoker with an approximate four pack-year history.

On initial assessment, the findings were generally within normal ranges: oxygen saturations of 96% on room air, cardiorespiratory compensated with a respiratory rate of 15 breaths/min., blood pressure of 125/80 mmHg, heart rate of 89 beats/min. and a temperature of 36.6°C. Lung auscultation revealed equally diminished breath sounds on both sides. During initial examination, there was the evidence of symptomatic deterioration with bilateral pleuritic chest pain, increased dyspnoea and agitation. She was found to have type II respiratory failure with the following biochemical parameters: pH 7.34, $PaCO_2$ 6.3 kPa, and PaO_2 7.9 kPa. A chest radiograph confirmed bilateral partial pneumothoraces of approximately 30% (Figure 1).

Both left- and right-sided thoracostomies with large-bore chest drain insertions were performed emergently, followed by a partial resolution of the pneumothoraces (Figure 2). MSCT of the chest demonstrated residual pneumothoraces bilaterally with multiple apical bullae (Figure 3).

In the further course, the patient subsequently underwent video-assisted thoracoscopic surgery (VATS) with bilateral apicoectomies,

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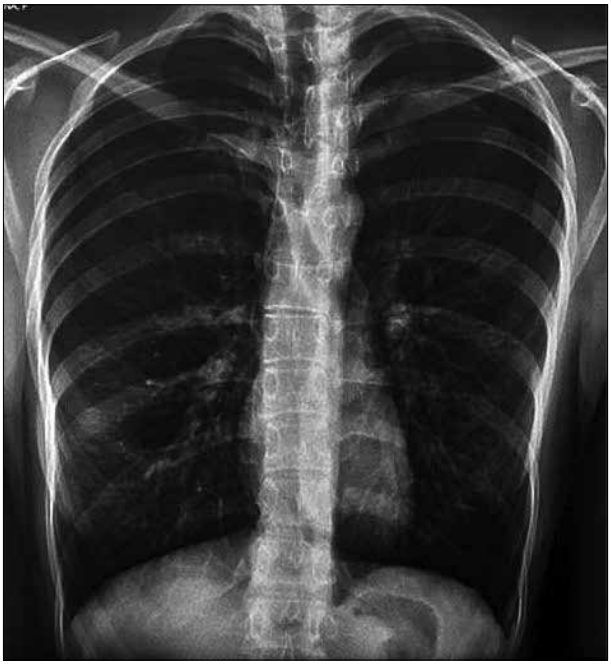

Figure 1. Chest radiograph on admission demonstrating bilateral pneumothoraces

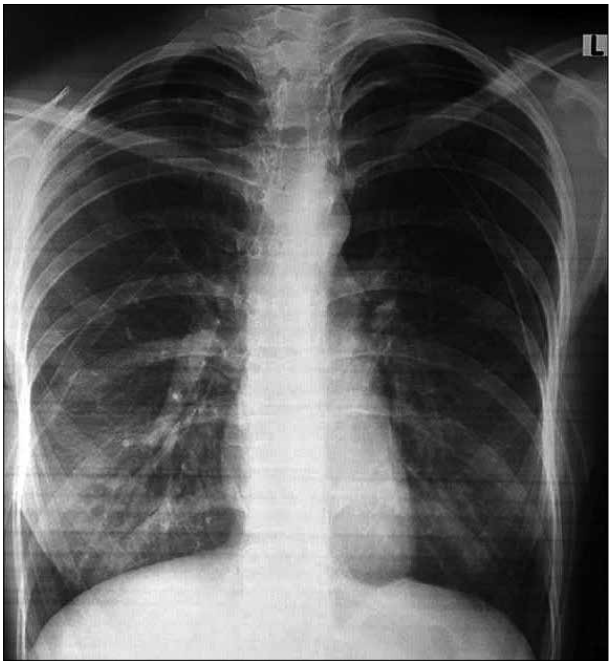

Figure 2. Post-treatment chest radiograph demonstrating partial resolution of the pneumothoraces

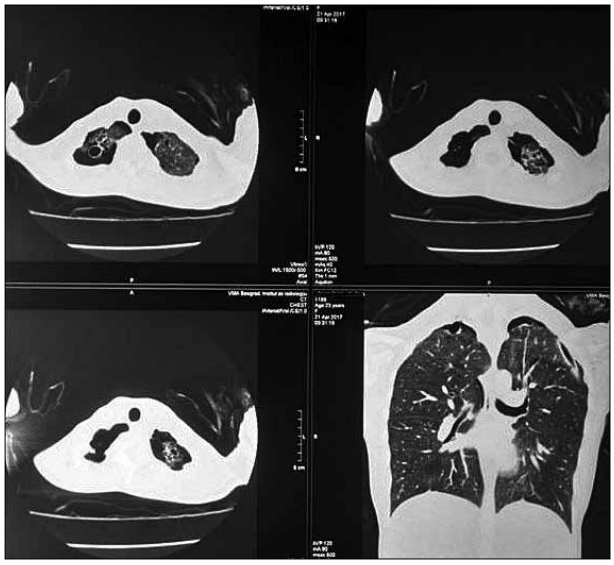

Figure 3. MSCT of the chest demonstrating residual pneumothoraces bilaterally with associated multiple apical bullae

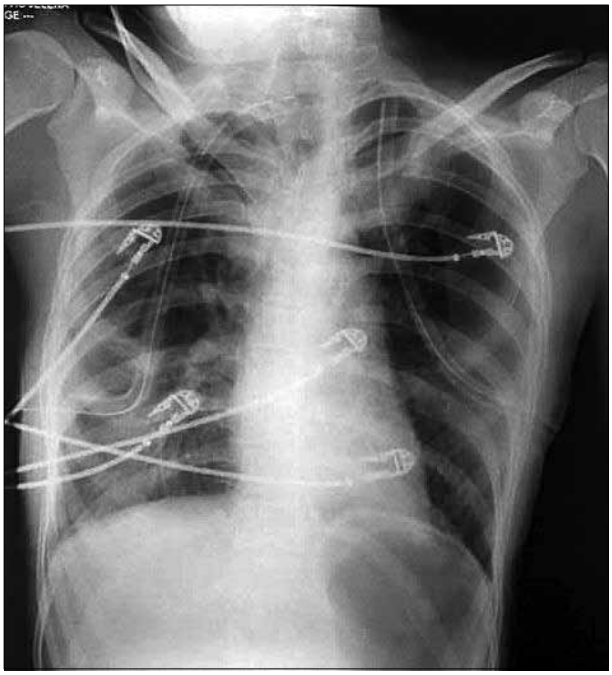

Figure 4. Post-treatment chest radiograph demonstrating complete resolution of the pneumothoraces

bullectomies, and pleural abrasion. Her chest drains were removed three days after the surgery and a post-treatment chest radiograph demonstrated resolution of the pneumothoraces (Figure 4). She was discharged without complications.

In this case, the patient had a histologically confirmed evidence of fibrous-walled bullae in the extirpated lung tissue. The clinical presentation, simultaneous bilateral occurrence, and radiological findings, as well as histology reports, confirmed the diagnosis and it may therefore be classified as primary SBSP.

DISCUSSION

PSP usually occurs in otherwise healthy males of a characteristic constitution – tall and thin [2]. Although patients with PSP do not have associated lung disease, subpleural blebs and bullae are found to be essential in the pathogenesis of PSP [2, 3, 9]. SSP is often seen in patients with underlying lung disease, usually associated with affected cardiopulmonary reserve. This is the reason why SSP is more life threatening and difficult to manage than PSP [7, 10].

SBSP occurs extremely rarely [4, 5, 6]. There are only several studies and case reports dealing with SBSP [6, 7. 8]. Some data suggest that only 56 patients with SBSP have been described in the literature [11]. A 20-year-long Swiss study recorded the incidence of SBSP of 4% among patients with SP [11].

In comparison to unilateral pneumothoraces, it is more likely linked with underlying lung pathology, including infectious and congenital diseases, proliferation of mesenchymal and epidermal cells, as well as chronic obstructive pulmonary disease and anorexia nervosa. It is essential to do postoperative histopathological analysis of the excised tissue in order to rule out malignancy [2].

The common symptoms of SP are dyspnoea and pleuritic chest pain [10].The clinical presentations in SBSP range from the absence of symptoms to tension pneumothorax and cardiorespiratory failure [6, 8, 11]. The characteristics such as acute onset, reduced breath sounds, and decreased chest expansion and rapid cardiovascular compromise are seen most often [8]. The clinical symptoms and signs of SBSP may mimic common respiratory pathologies such as exacerbations of asthma or chronic obstructive pulmonary disease [6, 8]. Our findings do not support the previous position that bullous lung disease is not associated with SBSP [11]. In order to avoid potential difficulties in diagnosing SBSP, prompt chest radiography is indicated [7].

Immediate chest drain insertion is essential in the initial management of SBSP, and bilateral chest drainage has been recommended [10, 12]. Furthermore, early definitive surgical intervention is mandatory, in order to reduce the risk of recurrence [12]. After chest drain insertion, there is currently no gold standard treatment for SBSP [10, 12, 13]. In this case, the patient underwent bilateral VATS apicoectomy, bullectomy and pleural abrasion. Open thoracotomy and VATS are two surgical options for definitive treatment and involve surgical pleurectomy, pleural abrasion, talc pleurodesis, and bullectomy [12]. Some data suggested that VATS pleurectomy is comparable to open pleurectomy, but there is a slight increase in recurrence rate [14].

Using the clinical presentation, diagnostic algorithm, and therapeutic management applied in the case of our patient, we emphasized several mandatory steps in establishing the diagnosis of SBSP and further treatment. The acute onset and respiratory symptoms progression required urgent chest radiography that established the diagnosis of bilateral pneumothoraces. The treatment was started with bilateral intercostal chest drains. Subsequently, the patient was subjected to VATS bullectomy. Generally speaking, the long-term prognosis of our patient is going to be influenced by her pulmonary status, but the short-term prognosis was certainly significantly improved by the early surgical treatment.

REFERENCES

1. Itard JE. Dissertation sur le pneumothorax ou les congestions gaseuses quise forment dans la poitrine. (Thesis). Paris; 1803.
2. Luh SP. Diagnosis and treatment of primary spontaneous pneumothorax. J Zhejiang Univ Sci B. 2010; 11(10):735–44.
3. Parrish S, Browning RF, Turner FJ, Zarogoulidis K, Kougioumtz I, Dryllis G, et al. The role for medical thoracoscopy in pneumothorax. J Thorac Dis. 2014; 6(S4):S383–91.
4. Melton LJ, Hepper NCG, Offord KP. Incidence of spontaneous pneumothorax in Olmsted County, Minnesota: 1950–1974. Am Rev Respir Dis. 1979; 120(6):1379–82.
5. Athanassiadi K, Kalavrouziotis G, Loutsidis A, Hatzimichalis A, Bellenis I, Exarchos N. Treatment of spontaneous pneumothorax: ten-year experience. World J Surg. 1998; 22(8):803–6.
6. Wing Sang Chau V, Patel P, Meghjee S. Simultaneous bilateral spontaneous pneumothoraces in a patient with occupational asthma. BMJ Case Rep. 2013; 2013.
7. Wilkie SC, Hislop LJ, Miller S. Bilateral spontaneous pneumothorax—the case for prompt chest radiography. Emerg Med J. 2001; 18:145–6.
8. Sayar A, Turna A, Metin M, Küçükyağci N, Solak O, Gürses A. Simultaneous bilateral spontaneous pneumothorax report of 12 cases and review of the literature. Acta Chir Belg. 2004; 104(5):572–6.
9. Abdala OA, Levy RR, Bibiloni RH, Viso HD, De Souza M, Satler VH. Advantages of video assisted thoracic surgery in the treatment of spontaneous pneumothorax. Medicina (B Aires). 2001; 61(2):157–60.
10. Sahn S, Heffner J. Spontaneous pneumothorax. N Engl J Med. 2000; 342(12):868–74.
11. Graf-Deuel E, Knoblauch A. Simultaneous bilateral spontaneous pneumothorax. Chest. 1994; 105(4):1142–6.
12. Henry M, Arnold T, Harvey J. BTS guidelines for the management of spontaneous pneumothorax. Thorax. 2003; 58(Suppl II):ii39–52.
13. Eguchi T, Hamanaka K, Kobayashi N, Saito G, Shiina T, Kurai M, et al. Occurrence of a simultaneous bilateral spontaneous pneumothorax due to a pleuro-pleural communication. Ann Thorac Surg. 2011; 92(3):1124–6.
14. Barker A, Maratos EC, Edmonds L, Lim E. Recurrence rates of video-assisted thoracoscopic versus open surgery in the prevention of recurrent pneumothorax: a systematic review of randomised and non-randomised trials. Lancet. 2007; 370(9584): 329–35.

Симултани билатерални спонтани пнеумоторакс

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САЖЕТАК

Увод Симултани билатерални спонтани пнеумоторакс (СБСП) јесте потенцијално животно угрожавајуће стање, које може имитирати бројна плућна обољења.

Циљ овог приказа је био да изнесе клиничку слику, тешкоће у дијагностиковању и лечењу болесника са СБСП.

Приказ болесника Жена стара 23 године јавила се у хитну помоћ због прогресивне диспнеје и обостраног бола у грудном кошу, који трају два дана. Аускултацијом плућа утврђено је ослабљено дисање у пројекцији оба плућна врха. За време прегледа долази до интензивирања тегоба уз појаву агитираности. Анализом гасова артеријске крви утврђена је респираторна инсуфицијенција (тип 2) са параметрима: *pH* = 7,34, $PaCO_2$ = 6,3 *кPa* и PaO_2 = 7,9 *кPa*. Хитном радиографијом плућа је визуализован обострани парцијални пнеумоторакс (око 30%). Учињена је хитна билатерална торакална дренажа са парцијалном резолуцијом пнеумоторакса обострано. КТ грудног коша указује на резидуални пнеумоторакс обострано са мултиплим апикалним булама. Потом је болесница подвргнута видео-асистираној торакоскопији са обостраном апикоектомијом, булектомијом и плеуралном абразијом. Дренови су одстрањени трећег постоперативног дана, а контролна радиографија је показала потпуну обострану резолуцију пнеумоторакса. Отпуштена је на кућно лечење без компликација.

Закључак За правовремену дијагнозу и успешно лечење болесника са СБСП битно је правовремено препознавање клиничке слике и поштовање дијагностичког и терапијског алгоритма.

Кључне речи: пнеумоторакс, класификација, етиологија, лечење; грудна хирургија; торакоскопија; грудни дрен

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Extraskeletal Ewing sarcoma in the anterior abdominal wall

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SUMMARY

Introduction Extraskeletal Ewing sarcoma (ES) is a highly malignant neoplasm occurring most commonly in the thoracic wall and the paravertebral region. ES belongs to the group of small round cell tumors and displays pathognomonic structural abnormalities of the *EWS* gene.

The aim of this article was to present extraskeletal ES in an extremely rare anatomic location, an unusual clinical presentation, and modified treatment strategy.

Case outline A 15-year-old boy was admitted to the hospital with acute abdominal pain in the right iliac region. During urgent operation, because of suspected appendicitis with periappendicular infiltrate, partly hemorrhagic tumor tissue was discovered in the preperitoneal space. Histopathological and immunohistochemical analyses revealed a tumor resembling extraskeletal ES. A postoperative CT scan showed the tumor rest, which was completely removed in the second operation. Molecular genetic analysis confirmed extraskeletal ES by finding the *EWSR1-FLI1* fusion gene. Chemotherapy and radiotherapy according to the VAC protocol were started, and the patient is free of the disease eight months after the first operation.

Conclusion Our case is the fourth case of extraskeletal ES located in the abdominal wall, the second case confirmed by the molecular genetic finding, and the first case described in children at this anatomic site. Due to an extremely rare location, unusual clinical presentation, and needed genetic analysis, the tumor treatment strategy was modified with good short-term results.

Keywords: extraskeletal Ewing sarcoma; primitive neuroectodermal tumor; soft tissue; abdominal wall; surgery

INTRODUCTION

Ewing sarcoma (ES) is an uncommon neoplasm, with an incidence reported at one to three per million people per year, mainly appearing in patients younger than 20 years, with peak incidence during the second decade of life. After osteosarcoma, ES is the second most common bone sarcoma in children and young adults, with slight male predominance. About 10–20% of cases rise in extraskeletal sites, most commonly in the soft tissue of the thoracic wall, paravertebral region, lower extremities, head, neck, and pelvis [1, 2].

ES belongs to a group of small, round cell tumors. It shows a varying degree of neuroectodermal differentiation, and typically demonstrates diffuse membranous immunohistochemical CD99 positivity. The cells of origin of ES are either neural crest-derived stem cells or mesenchymal stem cells. Most of the ES harbor a somatic reciprocal chromosomal translocation, t(11;22)(q24;q21), which results in pathognomonic fusion of *EWSR1* to *FLI1* genes, generating the EWSR1-FLI1 oncoprotein. In about 15% of ES, the *EWSR1* gene can be involved in alternative translocations with *ERG*, *ETV1*, *ETV4,* or *FEV* genes [1, 2].

The term ES comprises tumor entity formerly differentiated into classical bone ES, Askin's tumor of the chest wall, and peripheral neuroectodermal tumor (PNET). Formerly, PNET had been defined as ES with more prominent neural differentiation, predominant extraskeletal location, and closely related with central nervous system PNETs [2, 3]. This is why some authors still use the term ES/PNET for this group of neoplasms.

The aim of this work was to present a case of a 15-year-old boy with extraskeletal ES/PNET in an extremely rare anterior abdominal wall location, unusual clinical presentation, and modified strategy of treatment.

CASE REPORT

A 15-year-old boy was admitted to our department as an emergency case with acute abdominal pain that started on the previous day after he took part in a football match. There was no clear evidence of trauma. Clinical examination revealed a painful mass in the right iliac region. Ultrasound examination confirmed the existence of well-localized hyperechogenic mass, with smaller hypoechogenic zones inside, mea-

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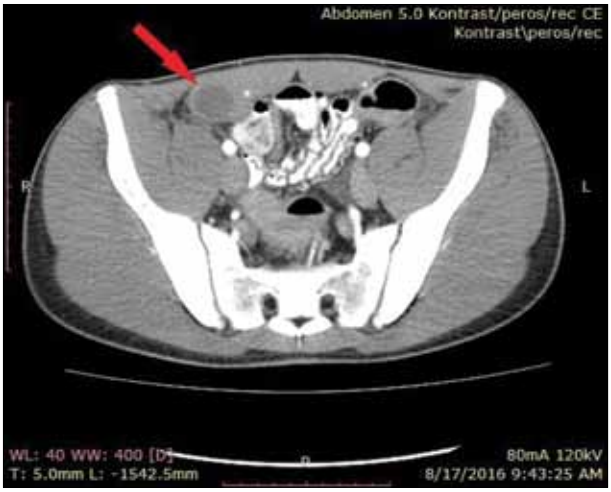

Figure 1. CT finding of the tumor in the abdominal wall

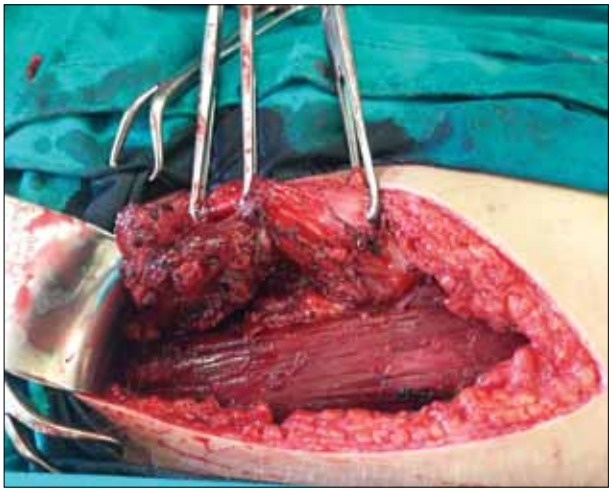

Figure 2. Intraoperative finding of ES/PNET beyond rectus abdominis muscle

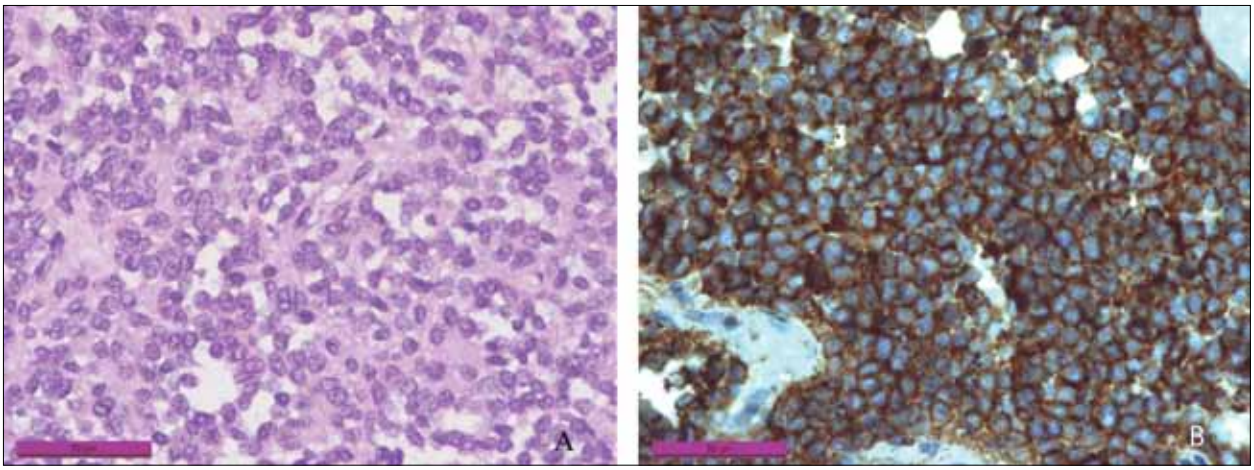

Figure 3. Microscopic features of the tumor tissue; A) typical characteristics of the small round cell tumor in childhood; B) intense CD99 immunopositivity of all tumor cells indicating the extraskeletal Ewing sarcoma

suring 50 × 40 mm, without internal color Doppler signal, which could resemble periappendicular infiltrate. There were neither any changes in the abdominal organs nor enlarged lymphatic nodes. Abdominal plain radiography was normal. Moderate leukocytosis (12.6 × 10^9/L) was present, and all other standard hematological and biochemical analyses were within normal ranges. The patient had no previous diseases, and there were no significant data in the family history, including the absence of malignancies.

Because of the persistence of the right iliac tenderness, with the suspicion of periappendicular inflammatory infiltrate, the patient was operated on on the same day, using the McBurney incision. After the division of muscular layers, in the preperitoneal fat tissue, a large amount of mushy semiliquid hemorrhagic masses with tissue parts appeared. The visible mass was removed and sent to histopathological (HP) examination. There was a clinical suspicion of an old abdominal wall hematoma, considering the patient's intense sports activities (football training and matches). Microbiological culture of the tissue revealed no growth of microorganisms. The patient's recovery was uneventful.

HP examination revealed necrotic tissue, with inflammatory component and hemorrhage, but parts of viable tumor tissue were also found. Small round tumor cells were hyperchromatic with a lack of cytoplasm, forming pseudorosettes, and showing numerous mitoses and apoptoses. Immunohistochemistry revealed strong positive membranous staining for CD99, partly on vimentin and sporadically on synaptophysin, and negative staining for the leukocyte common antigen, desmin, myogenin, epithelial membrane antigen, CD68, chromogranin, and Wilms tumor-1 antigen (WT-1). Results of immunostaining with anti-FLI1 antibody were assessed as unreliable. The pathologists' conclusion was that mostly necrotic small round cell malignant tumor had immunohistochemical characteristics that typically indicate ES/PNET. It was emphasized that genetic analyses are necessary for an accurate definitive diagnosis. The tissue sample was sent to a foreign medical institution for these analyses. It took a relatively long time to obtain the genetic results. In the meantime, computed tomography (CT) showed a partly solid, partly cystic heterodense mass measuring 3.8 × 2.6 × 3.7 cm beside and beyond the right rectus muscle. There were changes neither in the intraperitoneal lymphatic nodes and abdominal organs nor in the thoracic cavity (Figure 1). A new operation was undertaken. A partly colliquated

tumor, measuring 4 cm, was found close to the rectus abdominis muscle, not infiltrating the muscle but infiltrating the underlying peritoneum (Figure 2). The whole tumor was removed with underlying peritoneum. It was obvious that the tumor generated from preperitoneal fat tissue. The recovery was uneventful. The new HP analysis confirmed the high probability of ES/PNET, and the reverse transcriptase polymerase chain reaction analysis of the tumor specimen confirmed the *EWSR1-FLI-1* transcript, so the diagnosis of extraskeletal ES in the anterior abdominal wall was proved (Figure 3). The tumor process was classified as the second stage. The boy received six courses of chemotherapy according to CWS protocol from 2012, consisting of ifosfamide, vincristine, and doxorubicin and is now on radiotherapy regimen. The patient has neither clinical nor CT scan evidence of tumor recurrence or metastatic spreading eight months after the initial surgical treatment, but further follow-up will show the overall result of the treatment.

DISCUSSION

Histopathological aspect, immunohistochemical profile, and, especially, genetic finding of *EWSR1-FLI-1* fusion gene indicate extraskeletal ES in our patient. Some cases of ES have been reported in patients between 14 months and 77 years of age, but peak incidence is during the second decade of life, as was in our patient [1, 2].

Anatomic site of extraskeletal ES in the preperitoneal fat tissue of the abdominal wall in our patient is exceptionally rare, considering that the most common locations of this highly aggressive neoplasm are the thoracic wall, paravertebral region, lower extremities, head, neck and pelvic region [1, 2]. However, there are several case reports or small series of extraskeletal ES/PNET with primary location in the kidney, lung, pancreas, uterus, urinary bladder, ovary, testis, parotid gland, mesenterium, skin, and subcutaneous tissue [4, 5]. After an extensive literature search on the PubMed, using keywords "Ewing sarcoma," "primitive neuroectodermal tumor," and "abdominal wall," we found only three cases of neoplasms in this primary location [6, 7, 8]. Another three cases of extraskeletal ES in the abdominal wall location were reported, but all of them were described as tumors confined to the subcutaneous adipose tissue, so we consider that they should not be included in the group of abdominal wall neoplasms [4, 9, 10].

To the best of our knowledge, the first case of extraskeletal ES in the abdominal wall was reported by Aydinli et al. [6] in 2006. They described a 65-year-old male patient with a painless mass, measuring 5 cm in diameter, in the left upper quadrant of the abdominal wall, infiltrating the left rectus muscle. After probably complete tumor resection, the chemotherapy was carried out including vincristine, doxorubicin, cyclophosphamide, and etoposide for six cycles, and the patient had no evidence of tumor recurrence during a one-year follow-up. The second case was extraskeletal ES with the largest diameter of 6.5 cm, involving the left anterolateral muscle group of the abdominal wall in a 35-year-old woman. After the diagnostic incisional biopsy, neoadjuvant chemotherapy was started including vincristine, cyclophosphamide, and Adriamycin for three cycles. Because of poor response to chemotherapy, surgery was required, but authors did not report any data of the follow-up [7]. Roncati et al. [8] reported a third case of small extraskeletal ES/PNET measuring 1.5 cm, located in the subcutaneous tissue with deep muscle infiltration, appearing in a 45-year-old man. After elemental microanalysis, the authors described findings of a heavy metal bioaccumulation into the tumor cells, correlating with the chronic exposure to a transdermal delivery of heavy metal salts during local therapy of the irritated skin. Common *EWSR1-FLI-1* translocation was also found, and after a complete tumor excision and chemotherapy, the patient was without tumor recurrence one year after surgery [8].

Our case is the fourth case of extraskeletal ES located in the abdominal wall, the second case confirmed by the molecular genetic finding of characteristic structural abnormality of the *EWS* gene on 22q12, and the first case described in children in this anatomic location.

Extraskeletal ES/PNET has a high malignant potential. Kushner et al. [11], on a series of 43 patients without distant metastases at the time of diagnosis, reported the tumor recurrence rate of 25% during the first 24 months. Another 11 patients had metastases at the time of the diagnosis. Kimber et al. [12], on a series of 26 patients, reported an overall survival rate of 42%, while Zimmermann et al. [13] reported survival rate of 53% on a series of 13 patients. Sarkar and Bähr [14] made a meta-analysis and reported an overall number of 102 patients with Askin tumor, with a mortality rate of 41%, and the recurrence rate of 14% in the follow-up period in survivors. The treatment of ES/PNET consists of surgery, chemotherapy and radiotherapy [15–18]. There are controversies in the literature about the timing of the operative treatment, but nowadays the majority of authors prefer pre-operative chemotherapy, with tumor regression in up to 95% of the cases, enabling surgeons a radical tumor excision, without spilling and disseminating tumor cells. The initial surgery, if undertaken, must not be mutilated or too risky if the tumor infiltrates adjacent organs or vascular structures [15, 16, 17]. We believe that initial surgery should be performed and the tumor removed, if imaging methods indicate that adjacent organs are not infiltrated, as was in our patient. Even after successful radical surgery, postoperative chemotherapy and radiotherapy must be performed, because extraskeletal ES/PNET carries a great risk of local recurrence and distant metastases. The operation must be performed even if preoperative chemotherapy has achieved complete tumor regression, in order to remove scattered viable malignant cells [12].

In our patient, extraskeletal ES was located in the preperitoneal fat tissue, manifested by spontaneous pain and tenderness on examination in the right iliac region, the symptom and sign quite unusual for malignant tumors. The initial operation had been performed under suspicion of acute abdominal disease, i.e. for acute appendicitis with periappendicular infiltrate formation. The second operation was undertaken before the chemotherapy regimen started,

because of the delay in obtaining molecular genetic analysis results needed for the accurate diagnosis. The standard therapy protocol could have been changed because imaging analyses indicated the possibility of radical surgery.

In this paper, an extremely rare case of extraskeletal ES with primary location in the abdominal wall is presented. The therapy regimen was modified due to the atypical clinical presentation of the disease and the delay in obtaining the genetic analysis results.

REFERENCES

1. De Alava E, Lessnick SL, Sorensen PH. Ewing sarcoma. In: Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, editors. World Health Organization Classification of Tumours of Soft Tissue and Bone. IARC Press, Lyon: 2013; 306–9.
2. Potratz J, Dirksen U, Jurgens H, Craft A. Ewing sarcoma: clinical state-of-the-art. Pediatr Hematol Oncol. 2012; 29(1):1–11.
3. Batsakis JG, El-Naggar AK. Ewing's sarcoma and primitive neuroectodermal tumours: cytogenetic cynosures seeking a common histiogenesis. Adv Anat Pathol. 1997; 4:207–20.
4. Betal D, Shaygi B, Babu R, Jamil K, Sainsbury RJ. Primitive neuroectodermal tumour (PNET) in subcutaneous abdominal wall: a case report. Intern Sem Surg Oncol. 2009; 6:10.
5. Marić H, Cvijanović R, Ivanov I, Gvozdenović L, Ivanov D, Lalović N. Peripheral primitive neuroectodermal tumor of the small bowel mesentery – report of a case. Srp Arh Celok Lek. 2015; 143(9-10):619–22.
6. Aydinli B, Ozturk G, Yildirgan MI, Polat Yalcin K, Basoglu M, Gundogdu C, et al. Extraskeletal Ewing's sarcoma in the abdominal wall: a case report. Letter to the editor. Acta Oncol. 2006; 45(4):484–6.
7. Askri A, Ben Farhat L, Ghariani B, Rabeh A, Dali N, Said W, et al. Extraskeletal Ewing sarcoma of the abdominal wall. Cancer Imaging. 2008; 8:156–8.
8. Roncati L, Gatti AM, Capitani F, Barbolini G, Maiorana A, Palmieri B. Heavy metal bioaccumulation in an atypical primitive neuroectodermal tumor of the abdominal wall. Ultrastruct Pathol. 2015; 39(4):286–92.
9. Somers GR, Shago M, Zielenska M, Chan HS, Hgan BY. Primary subcutaneous primitive neuroectodermal tumor with aggressive behavior and an unusual karyotype: case report. Pediatr Dev Pathol. 2004; 7(5):538–45.
10. Taylor GB, Chan YF. Subcutaneous primitive neuroectodermal tumour in the abdominal wall of a child: long-term survival after local excision. Pathology. 2000; 32(4):294–8.
11. Kushner BH, Hajdu SI, Gulati SC, Erlandson RA, Exelby PR, Lieberman PH. Extracranial primitive neuroectodermal tumors: the Memorial Sloan-Kettering Cancer Center experience. Cancer. 1991; 67(7):1825–9.
12. Kimber C, Michalski A, Spitz L, Pierro A. Primitive neuroectodermal tumors: anatomic location, extent of surgery, and outcome. J Pediatr Surg. 1998; 33(1):39–41.
13. Zimmermann T, Blütters-Sawatzki R, Flechsenhar K, Padberg WM. Peripheral primitive neuroectodermal tumor: challenge for multimodal treatment. World J Surg. 2001; 25(11):1367–72.
14. Sarkar MR, Bähr R. Der Askin-Tumor. Chirurg. 1992; 63:973–6.
15. Bernstein M, Kovar H, Paulluscen M, Randall RL, Schucke A, Teot LA, et al. Ewing's sarcoma family of tumors: current management. The Oncologist. 2006; 11(5):503–19.
16. Vukašinović Z, Stevanović V, Spasovski D, Živković Z. Savremeno shvatanje Juingovog (Ewing) sarkoma. Srp Arh Celok Lek. 2006; 134(7-8):348–55.
17. Marinova L. Retroperitoneal primitive neuroectodermal tumour (PNET). A case report and review of the literature. Rep Pract Oncol Radiother. 2009; 14(6):221–4.
18. Soma S, Shetty SK, Bhat S. PNET of the Abdominal Wall: A Rare Presentation. J Clin Diagn Res. 2015; 9(8):XD01–XD02.

Екстраскелетни Јуингов сарком у предњем трбушном зиду

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САЖЕТАК

Увод Екстраскелетни Јуингов сарком (ЈС) веома је малигна неоплазма која се најчешће развија у зиду грудног коша и паравертебралној регији. Спада у групу тумора малих округлих ћелија са патогномоничном структурном абнормалношћу гена *EWS*.

Циљ овог рада је да прикаже случај екстраскелетног ЈС са изузетно ретком локализацијом, необичном клиничком презентацијом и модификованом стратегијом лечења.

Приказ болесника Дечак стар 15 година примљен је у болницу због акутног абдоминалног бола у десној илијачној регији. У току хитне операције због сумње на апендицитис са периапендикуларним инфилтратом, у преперитонеалном простору је нађено делимично хеморагично туморско ткиво. Патохистолошка и имунохистохемијска анализа указале су на вероватни екстраскелетни ЈС. Постоперативна КТ указала је на локални остатак тумора, који је комплетно одстрањен другом операцијом. Молекуларно-генетичким налазом фузионог гена *EWSR1-FLI1* потврђена је дијагноза екстраскелетног ЈС. Лечење је настављено хемиотерапијом и радиотерапијом по *VAC* протоколу и осам месеци после прве операције код болесника нема знакова рецидива болести.

Закључак Екстраскелетни ЈС у предњем трбушном зиду код нашег болесника представља четврти случај ЈС на тој локализацији приказан у литератури, од тога други случај са дијагнозом потврђеном молекуларно-генетичком анализом и први описан у дечјем узрасту. Због екстремно ретке локализације, необичне презентације и неопходне генетичке анализе, стратегија лечења тумора је модификована са добрим краткорочним резултатом.

Кључне речи: екстраскелетни Јуингов сарком; примитивни неуроектодермални тумор; мека ткива; трбушни зид; хирургија

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Long-term results of laparoscopic gastric sleeve resection due to morbid obesity and metabolic syndrome

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SUMMARY

Introduction The aim of this paper was to presents long-term results of a laparoscopic gastric sleeve resection in a "super super" obese patient and a follow-up period of eight years.

Case outline A patient with body mass index of 70 kg/m^2 and Stage 3 obesity according to the King's Obesity Staging Criteria, with metabolic syndrome and cardiovascular risk of over 20%, and a pronounced severe obstructive sleep apnea, underwent a laparoscopic gastric sleeve resection. After two years, the patient reached body mass index of 28.4 kg/m^2 and eight years after the surgery has a body mass index of 34.3 kg/m^2, and the percentage of excess body mass index loss of 79.3%. According to the King's Obesity Staging Criteria, he falls under Stage 0.

Conclusion Laparoscopic gastric sleeve resection may be performed as a stand-alone procedure in "super super" obese patients, with excellent long-term results.

Keywords: morbid obesity; bariatric surgery; laparoscopy; sleeve gastrectomy; weight loss

INTRODUCTION

Laparoscopic gastric sleeve resection (LGS) is a bariatric and metabolic procedure that has been performed extensively in the past decade throughout the world, either as a stand-alone procedure or as the first phase of the biliopancreatic diversion [1–4]. It gained popularity among not only surgeons but patients as well, due to its simplicity, small number of complications, good short-term results, positive effects on metabolic syndrome, and the fact that food does not change its path through the digestive tract [5, 6, 7]. However, certain papers speak of the disadvantages of LGS, the most significant being regaining weight a few years after the operation and newly developed gastroesophageal reflux disease [8, 9, 10]. In recent years, there have been papers on long-term results of LGS in the treatment of obesity and metabolic syndrome [11]. Our report presents, according our knowledge, the first case of LGS in Serbia, which was performed in 2008 and had a follow-up period of eight years, and we observed long-term results in the treatment of a patient with "super super" obesity.

CASE REPORT

The patient is a 36-year-old male who, prior to the procedure, weighed 214 kg, was 175 cm tall and had a body mass index (BMI) of 70 kg/m^2 (Figure 1). Personal anamnesis revealed that the patient had myocarditis in childhood, while family history revealed that both his father and uncle suffer from type II diabetes mellitus. The patient was showing signs of mild anxiety and social isolation, although he had a sedentary

Figure 1. Before the procedure

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Table 1. Clinical and laboratorial characteristics of metabolic syndrome of the patient

Parameter	Preoperative		Eight years after the operation	
Weight (kg)	214		105	
Systolic blood pressure (mmHg)	180		100	
Diastolic blood pressure (mmHg)	100		70	
Fasting glucose (mmol/l)	6.7	HOMA-IR: 11.8	4.7	HOMA-IR: 1.67
Fasting insulin (μIU/ml)	39.8		8.07	
HbA1c (%)	/		5.1	
Total cholesterol (mmol/l)	5.4		4.93	
HDL (mmol/l)	1.51		2.13	
LDL (mmol/l)	3.72		2.6	
Triglyceride (mmol/l)	1.06		0.53	
LDL/HDL	2.5		/	
Atheroscleroses index	/		1.2	
CRP (mg/L)	/		1.8	
Fibrinogen (g/l)	4.7			

HbA1c – glycated hemoglobin; HDL – high-density lipoprotein; LDL – low-density lipoprotein; CRP – C-reactive protein; HOMA-IR = [fasting insulin (μIU/ml) × fasting glucose (mmol/l)] / 22.5

Figure 2. Eight years after the procedure

job. He had been smoking more than 20 cigarettes a day for 20 years. During his youth (at the age of 15), the patient was treated in hospital conditions with a dietary treatment supervised by an internist. On that and several other occasions after that one, he would lose 30–40 kg, but would always gain ever more weight after that. During the preoperative treatment, the patient was found to have untreated hypertension (maximum blood pressure values were 180/100 mmHg), obstructive sleep apnea diagnosed during a sleep study as being "severe, predominantly obstructive sleep apnea (Apnea–Hypopnea Index: 86.7), with strong desaturations during breathing crises and high oxygen desaturation index (82.6)." Laboratory findings that reflect the existence of metabolic syndrome prior to the procedure in 2008 are presented in Table 1.

The procedure was performed on October 31, 2008, at the Clinic for Thoracic Surgery, Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica. LGS resection was performed using five trocars, with Echelon Flex™ (Ethicon Inc., Bridgewater, NJ, USA) 60 mm stapler device through a 38 Fr bougie. Immediately after the surgery, the patient was given fluids and was recommended a month-long dietary regime of liquid and pureed foods. The postoperative period was uneventful; the patient was on proton pump inhibitors for two weeks and subcutaneous injections of low-molecular-weight heparin for 30 days after the procedure.

Maximum weight loss was achieved two years after the procedure, when the patient weighted 87 kg and had BMI of 28.4 kg/m^2.

Eight years after the procedure, the patient weights 105 kg and has BMI of 34.3 kg/m^2 (Figure 2).

Laboratory results eight years after the procedure are presented in Table 1.

The main weight-loss parameters two and eight years after the procedure are presented in Table 2.

DISCUSSION

LGS resection has been performed extensively in the past decade throughout the world as a stand-alone procedure due to its technical simplicity and good short-term and medium-term results [1, 6]. However, there are not many studies, especially large-scale ones, which assess the success of LGS in a period longer than six years [2, 11].

We present the patient who was, according to our knowledge, the first one to undergo LGS in Serbia, with an eight-year follow-up period, which falls under long-term results. The indication for the procedure was established based on morbid obesity (BMI = 70 kg/m^2), and significant co-morbidities that also define the existence of metabolic syndrome: arterial hypertension, prediabetes, dyslipidemia, sleep apnea, and abdominal obesity. His initial BMI classified him among "super super" obese patients. According to the new criteria for the severity of obesity, King's Obesity Staging Criteria (KOSC), the patient was suffering from the most severe stage (Stage 3) with cardiovascular risk of over 20% [12].

Table 2. Results two and eight years after the operation

Parameters	Two years after the operation	Eight years after the operation
BMI (kg/m^2)	28.4	34.3
%EWL	87.5	75
%TWL	59.3	51
%EBMIL	92.4	79.3

%EWL – percentage of excess weight loss, calculated as: (initial weight – current weight) / (initial weight – ideal weight) × 100; %TWL – percentage of total weight loss, calculated as: (initial weight – current weight) / initial weight × 100;

%EBMIL – percentage of excess body mass index loss, calculated as: (initial BMI – current BMI) / (initial BMI – 25) × 100

The procedure was performed by calibrating the stomach with a 38 Fr bougie. Some authors received better results with thinner bougies, but larger (wider) bougies are also used in LGS [2, 13]. We drew from our experience in surgical procedures of the esophagus and the procedures with Swedish adjustable gastric band, which is why we used a 38 Fr bougie. The size of the bougie through which LGS is to be performed has not been standardized, although the fourth consensus conference (2012) on LGS revealed that approximately one third of surgeons use a 36 Fr bougie [13]. Recent studies have found that bougie size is not crucial for the long-term success of the procedure [14, 15]. The surgical technique for complete removal of the gastric fundus after complete immobilization is more important than bougie size. The percentage of stomach stenosis after LGS is approximately 1% and is higher in patients with whom thinner bougie was used [13, 16]. Double-contrast barium enema study of our patient's esophagus and stomach eight years after LGS indicated no neo-fundus or stenosis, which are the most frequent late-stage complications of LGS; therefore, a 38 Fr bougie may be considered adequate.

Initial BMI is an important success factor of LGS, since it was determined that patients with lower initial BMI (under 40 kg/m^2) have a higher success rate in short-term and medium-term results, whereas "super super" obese patients (BMI > 60 kg/m^2) experience less success due to subsequent weight gain [2, 16]. For such patients, LGS is the operation of choice, since other procedures are coupled with increased intraoperative and postoperative risk of complications [17]. According a to 20-year analysis of biliopancreatic diversion made by Biron et al. [18], the criteria for a successful bariatric procedure based on the initial BMI have been adopted. Since our patient belonged to the "super super" obese group, the success of the procedure is considered long-term if the BMI is under 40 kg/m^2. The result after eight years indicates that BMI is now 34.3 kg/m^2 and, according to this criterion, LGS has proven successful. In regard to the percentage of excess weight loss (%EWL), an ideal procedure should achieve a 100% loss of excess weight [2, 19]. In practice, however, this occurs only in a negligible number of patients, and is certainly not the case with "super super" obese patients. However, the two-year and eight-year %EWL that amounted to 89.7% and 77%, respectively, indicates that LGS was successful in our patient, both medium-term and long-term. Along with %EWL, BMI is the second parameter and is considered borderline if it equals 35 kg/m^2, which our patient maintains as long as eight years after LGS [20]. Some authors recommend the so-called percentage of excess BMI loss (%EBMIL) as a success parameter for the performed bariatric procedure, and the starting point for its calculation is the achieved BMI of 25 kg/m^2 [11, 21, 22]. This occurs much easier in patients whose initial BMI was under 50 kg/m^2, and much harder in patients whose BMI was over 50 kg/m^2, as was the case with our patient. Also recognized is the significance that a three-month %EBMIL (over 20%) has on the long-term result, which should be over 50%. Eight years after the procedure, our patient's %EBMIL is 79.3%, which classifies LGS as a very successful procedure for this "super super" obese patient. Other studies have also confirmed LGS as a successful bariatric procedure.

In relation to the KOSC, eight years after LGS, our patient no longer takes any medication for any of the co-morbidities he had been suffering from before the procedure. He has normal blood pressure, his cardiovascular risk is under 10%, and glycosylated hemoglobin is 5.1% (Stage 0 of the KOSC).

LGS resection may be successfully performed as a stand-alone procedure in selected "super super" obese patients, with excellent long-term results in terms of both anthropological measures and KOSC.

REFERENCES

1. Angrisani L, Santonicola A, Iovino P, Formisano G, Buchwald H, Scopinaro N. Bariatric surgery worldwide 2013. Obes Surg. 2015; 25(10):1822–32.
2. Seki Y, Kasama K, Hashimoto K. Long-term outcome of laparoscopic sleeve gastrectomy in morbidly obese Japanese patients. Obes Surg. 2016; 26(1):138–45.
3. Cottam D, Qureshi FG, Mattar SG, Sharma S, Holover S, Bonanomi G, et al. Laparoscopic sleeve gastrectomy as an initial weight-loss procedure for high-risk patients with morbid obesity. Surg Endosc. 2006; 20(6):859–63.
4. Regan JP, Inabnet WB, Gagner M, Pomp A. Early experience with two-stage laparoscopic Roux-en-Y gastric bypass as an alternative in the super-super obese patient. Obes Surg. 2003; 13(6):861–4.
5. Iannelli A, Dainese R, Piche T, Facchiano E, Gugenheim J. Laparoscopic sleeve gastrectomy for morbid obesity. World J Gastroenterol. 2008; 14(6):821–7.
6. Alexandrou A, Athanasiou A, Michalinos A, Felekouras E, Tsigris C, Diamantis T. Laparoscopic sleeve gastrectomy for morbid obesity: 5-year results. Am J Surg. 2015; 209(2):230–4.
7. Lee WJ, Almulaifi A. Recent advances in bariatric/metabolic surgery: appraisal of clinical evidence. J Biomed Res. 2015; 29(2):98–104.
8. Biertho L, Lebel S, Marceau S, Hould FS, Lescelleur O, Marceau P, et al. Laparoscopic sleeve gastrectomy: with or without duodenal switch? A consecutive series of 800 cases. Dig Surg. 2014; 31(1):48–54.
9. Stenard F, Iannelli A. Laparoscopic sleeve gastrectomy and gastroesophageal reflux. World J Gastroenterol. 2015; 21(36):10348–57.
10. Crawford C, Gibbens K, Lomelin D, Krause C, Simorov A, Oleynikov D. Sleeve gastrectomy and anti-reflux procedures. Surg Endosc. 2017; 31(3):1012–21.

11. Arman GA, Himpens J, Dhaenens J, Ballet T, Vilallonga R, Leman G. Long-term (11+years) outcomes in weight, patient satisfaction, comorbidities, and gastroesophageal reflux treatment after laparoscopic sleeve gastrectomy. Surg Obes Relat Dis. 2016; 12(10):1778–86.
12. Valderhaug TG, Aasheim ET, Sandbu R, Jakobsen GS, Småstuen MC, Hertel JK, et al. The association between severity of King's Obesity Staging Criteria scores and treatment choice in patients with morbid obesity: a retrospective cohort study. BMC obesity. 2016; 3:51.
13. Gagner M, Deitel M, Erickson AL, Crosby RD. Survey on laparoscopic sleeve gastrectomy (LSG) at the Fourth International Consensus Summit on Sleeve Gastrectomy. Obes Surg. 2013 23(12):2013–17.
14. Spivak H, Rubin M, Sadot E, Pollak E, Feygin A, Goitein D. Laparoscopic sleeve gastrectomy using 42-French versus 32-French bougie: the first-year outcome. Obes Surg. 2014; 24(7):1090–3.
15. Parikh M, Issa R, McCrillis A, Saunders JK, Ude-Welcome A, Gagner M. Surgical strategies that may decrease leak after laparoscopic sleeve gastrectomy: a systematic review and meta-analysis of 9991 cases. Ann Surg. 2013; 257(2):231–7.
16. Gluck B, Movitz B, Jansma S, Gluck J, Laskowski K. Laparoscopic sleeve gastrectomy is a safe and effective bariatric procedure for the lower BMI (35.0–43.0 kg/m2) population. Obes Surg. 2011; 21(8):1168–71.
17. Gagner M, Gumbs AA, Milone L, Yung E, Goldenberg L, Pomp A. Laparoscopic sleeve gastrectomy for the super-super-obese (body mass index >60 kg/m(2)). Surg Today. 2008; 38(5):399–403.
18. Biron S, Hould FS, Lebel S, Marceau S, Lescelleur O, Simard S, et al. Twenty years of biliopancreatic diversion: what is the goal of the surgery? Obes Surg. 2004; 14(2):160–4.
19. Brolin RE, Kenler HA, Gorman RC, Cody RP. The dilemma of outcome assessment after operations for morbid obesity. Surgery. 1989; 105(3):337–46.
20. Christou NV, Look D, Maclean LD. Weight gain after short- and long-limb gastric bypass in patients followed for longer than 10 years. Ann Surg. 2006; 244(5):734–40.
21. Biter LU, Gadiot RPM, Grotenhuis BA, Dunkelgrün M, van Mil SR, Zengerink HJ, et al. The Sleeve Bypass Trial: a multicentre randomized controlled trial comparing the long term outcome of laparoscopic sleeve gastrectomy and gastric bypass for morbid obesity in terms of excess BMI loss percentage and quality of life. BMC Obes. 2015; 2:30.
22. Baltasar A, Perez N, Serra C, Bou R, Bengochea M, Borrás F. Weight loss reporting: predicted body mass index after bariatric surgery. Obes Surg. 2011; 21(3):367–72.

Дугорочни резултат лапароскопске ресекције желуца због екстремне гојазности и метаболичког синдрома

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САЖЕТАК

Увод Циљ овог рада је био да прикаже дугорочан резултат лапароскопске „рукавне" ресекције желуца код „супер супер" гојазног болесника са периодом праћења од осам година.

Приказ болесника Код болесника са индексом телесне масе (ИТМ) 70 *kg/m*^{2}, са трећим стадијумом гојазности према *Kings Obesity Staging Criteria* (*KOSC*), метаболичким синдромом и кардиоваскуларним ризиком преко 20% и израженим синдромом апнеја у сну, изведена је лапароскопска „рукавна" ресекција желуца 2008. године, прва оваква процедура у Србији. Две године после операције болесник је достигао ИТМ 28,4 *kg/m*^{2}, а осам година после операције ИТМ 34,3 *kg/m*^{2} и утврђени губитак индекса телесне масе од 79,3%. Према *KOSC*, стадијум овог болесника је најнижи.

Закључак Лапароскопска „рукавна" ресекција желуца може се успешно извести код „супер супер" гојазног болесника као самостална процедура са одличним дугорочним резултатом.

Кључне речи: екстремна гојазност; хирургија гојазности; лапароскопска „рукавна" ресекција желуца; губитак тежине

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Penile leiomyosarcoma

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SUMMARY
Introduction Leiomyosarcoma of the penis (LSP) is an extremely rare form of penile tumor. LSP can be divided into two subtypes: deep and superficial.
The goal of this paper is to present a very rare case of LSP.
Case outline On examination, the patient presented with a slowly "growing penile bump," for which an initial diagnosis of non-inflamed penile atheroma was given. Further diagnostic workup was omitted. Outpatient excisional biopsy was performed, and the tumor was sent for pathohistological examination, which revealed penile leiomyosarcoma. The patient has not received any further treatment. The most recent follow up was two and a half years after surgery, and the patient continues to do well without any complaints.
Conclusion LSP is an extremely rare disease, which can be cured if it is diagnosed in its early stage. Pathohistological examination is necessary for diagnosing LSP.
Keywords: penile tumor; penile atheroma; penile fibroma; penile leiomyosarcoma

INTRODUCTION

The incidence of penile malignancy in Europe is less than one case per 100,000 men. The most common type of penile malignancy is squamous cell carcinoma (more than 95%). The remaining 5% is mostly comprised of melanoma, lymphoma, mesenchymal tumors, and metastases. Leiomyosarcoma of the penis is an extremely rare penile tumor of mesenchymal origin.

The goal of this paper is to present a very rare case of penile leiomyosarcoma and to remind us of the existence, clinical course, treatment, and prognosis of this very rare subtype of penile tumor.

CASE REPORT

A 25-year-old male patient presented to clinic concerned about a firm nodule in the middle of his penile shaft. The nodule had been present for over a year, was not painful, and had been slowly growing. The patient's history was significant for juvenile diabetes mellitus of 10 years' duration, complicated by retinopathy leading to blindness. Exam revealed a painless, oval shaped penile shaft tumor, approximately 1.5 × 1 cm. The tumor had an irregular surface and was of a rubbery consistency. Examination of the abdomen and remaining external genitalia was unremarkable and there was no groin lymphadenopathy. Clinical diagnosis of a non-inflamed penile atheroma was made. No further workup except for routine preoperative laboratory testing was pursued, with normal results.

Surgery was performed at an outpatient surgery center under local anesthesia. The tumor was completely excised and sent for histological examination. Intraoperatively, the clinical diagnosis was changed to penile fibroma due to its appearance and consistency. Histopathologic work-up included both routine hematoxylin and eosin staining and immunohistochemistry for smooth muscle actin, h-caldesmon, and S-100 protein (family of protein). Figure 1 contains four pictures: A and B – hematoxylin and eosin stain; C and D – immunoperoxidase with hematoxylin counterstain. Low magnification (40×) shows fascicular configuration (A). Higher magnification (400×) reveals conspicuous cytologic atypia and a mitotic figure below the center of the field (B). Tumor cells are strongly and diffusely immunopositive for h-caldesmon (C) and negative for S-100 protein with neural and perivascular structures as an internal positive control (D). Based on these findings, which are consistent with a malignant tumor of smooth muscle origin, a pathological diagnosis of penile leiomyosarcoma was made.

After obtaining the histopathology report, further metastatic work-up was pursued. Abdominal and pelvic computed tomography scan revealed one enlarged inter aorto-caval lymph node, 13 mm in size, though otherwise without evidence of the disease. The patient

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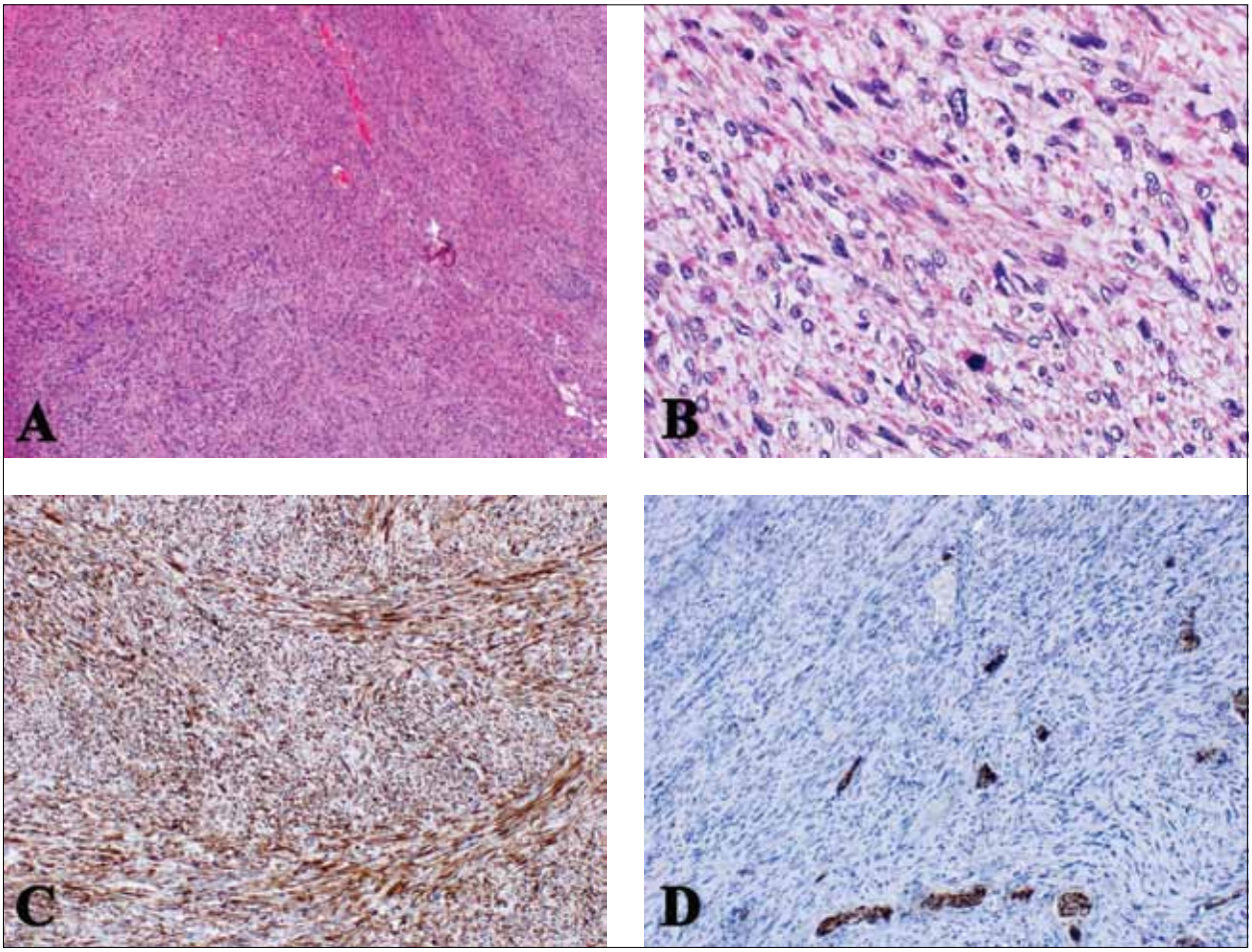

Figure 1. Intermingled fascicles of spindle tumor cells (H&E, ×40); B: pronounced cellular pleomorphism and mitotic activity (H&E, ×400); C: strong and diffuse immunoreactivity for h-caldesmon (immunoperoxidase with hematoxylin counterstain – immunopositive for h-caldesmon, ×100); D: no tumor cells positivity for S-100 protein (immunoperoxidase with hematoxylin counterstain – immunonegative for S-100 protein, ×100)

was followed with abdominal ultrasounds every three months for one year. No worrisome findings appeared on ultrasounds. One year after the surgery, the patient underwent repeat abdominal/pelvic computed tomography scan showing no signs of local or distant tumor recurrence, with the previously noted lymph node of unchanged size.

Further follow up was scheduled on an as-needed basis. The most recent follow up was two and a half years after surgery, and the patient continues to do well without any complaints or concerning symptoms.

DISCUSSION

Leiomyosarcoma of the penis is an extremely rare diagnosis. There are about 60 cases reported in the literature. The first case was described by Levi [1] in 1930. Clinically and histopathologically, there are two types of penile leiomyosarcoma: deep and superficial [2]. The more common superficial subtype originates from smooth muscle of superficial penile vessels (above tunica albuginea), dartos muscle of the penis, or erector pili muscle of the penile shaft. The deep subtype originates from the smooth muscle of the corpora cavernosa or spongiosa [2].

Recommended treatment of superficial penile leiomyosarcoma is wide local excision. This subtype has a much better prognosis compared to its deep counterpart. Superficial leiomyosarcoma shows a low recurrence rate and similarly low rates of metastasis (approximately 8%) [2, 3]. Incompletely resected superficial tumors tend to have a high recurrence rate and a wide re-excision should be pursued to guarantee negative margins. For deep leiomyosarcoma, partial or complete penectomy represent standard treatment. Lymph node involvement is rare and routine lymphadenectomy is not recommended [4]. Metastasis in the deep subtype can be up to 50%, with higher rates seen in patients with larger primary tumors [2].

The role of adjuvant chemotherapy and/or radiotherapy in the treatment of penile leiomyosarcoma is still not clear. However, due to the high rate of local recurrence and distant metastases even after complete excision of deep penile leiomyosarcoma, adjuvant chemotherapy and local radiation might be a reasonable option [5].

Because of the small number of cases reported so far, conclusions about standard treatment and prognosis of advanced leiomyosarcoma are difficult to draw [6].

In regard to this case specifically, the diagnosis of leiomyosarcoma came as a surprise to the performing urologist,

as the initial diagnosis of 'fibroma' or 'atheroma' gave way to the one of a penile cancer of extreme rarity. The authors would like once again to emphasize the importance of sending all excised tissue for routine histopathological examination, even in cases of clinically benign disease. In conclusion, because of the rarity of this disease, other than extirpative surgery for diagnosis, we lack firm recommendations for the optimal treatment of patients with these tumors (especially deep leiomyosarcoma). Each patient's treatment should be individualized, and should rely heavily on the involvement of a multidisciplinary team, including a urologist, pathologist, oncologist and radiologist.

REFERENCES

1. Levi I. On a case of primary fibrosarcoma of the skin of the penis: clinical and histological study. G Ital Dermatol. 1930; 71:1559–74.
2. Fetsch JF, Davis Jr CJ, Miettinen M, Sesterhenn IA. Leiomyosarcoma of the penis: clinicopathologic study of 14 cases with review of the literature and discussion of the differential diagnosis. Am J Surg Pathol. 2004; 28(1):115–25.
3. Greenwood N, Fox H, Edwards EC. Leiomyosarcoma of the penis. Cancer. 1972; 29(2):481–3.
4. Pow-Sang MR, Orihuela E. Leiomyosarcoma of the penis. J Urol. 1994; 151(6):1643–5.
5. Nanri M, Kondo T, Okuda H, Tanabe K, Toma H. A case of leiomyosarcoma of the penis. Int J Urol. 2006; 13(5):655–8.
6. Valadez RA, Waters WB. Leiomyosarcoma of penis. Urology. 1986; 27(3):265–7.

Лејомиосарком пениса

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САЖЕТАК

Увод Лејомиосарком пениса (ЛСП) врло је редак тип тумора пениса, а разликују се површни и дубоки тип.
Циљ овог рада је да прикаже врло редак случај ЛСП.
Приказ болесника Болесник се јавио због „растућег чвора на пенису" изгледа неинфламираног атерома на телу пениса. Додатне дијагностичке процедуре нису рађене. Амбулантно је урађена ексцизија тумора и промена послата на патохистолошки преглед (ПХП), којим је постављена дијагноза ЛСП. Нису коришћене друге методе лечења, а после редовних контрола у току 2,5 година нема рецидива болести.
Закључак Површни ЛСП је изузетно ретко уролошко обољење које може бити излечено уколико се дијагностикује у почетном стадијуму. За дијагнозу је неопходан ПХП.

Кључне речи: тумор пениса; атером пениса; фибром пениса; лејомиосарком пениса

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REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Pediatric renal stone disease

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SUMMARY
Pediatric renal stone disease is manifested as nephro/urolithiasis (UL) and/or nephrocalcinosis (NC). Compared to adults, UL in childhood is less common, and it is believed to be around 5% in industrialized countries, while the incidence of NC is even lower except for critically ill premature infants, in whom it may reach 64%. The formation of UL and NC is caused by increased concentrations of relevant solutes, and their aggregations and adherence to renal tubule cells is facilitated by factors such as urine pH, inability of natural crystallization inhibitors, stasis of urine, as well as renal tubule damage. UL is associated with significant morbidity because of pain, susceptibility to urinary tract obstruction and infections, and the necessity of surgical procedures. NC is usually asymptomatic but is frequently progressive, and leads to chronic renal failure more often than UL. Although other imaging modalities can be used in the diagnosis of renal stone disease, ultrasound has the least risk and is most cost-effective. The majority of cases of UL and NC in children is of metabolic origin; thus, they are prone to recurrence and may cause chronic renal damage. Therefore, they deserve, even after their initial presentation, a detailed metabolic evaluation. Genetic source of renal stone disease is suspected in the following conditions: early onset, familial prevalence, familial consanguinity, multiple or recurrent stones, and NC. For all UL/NC etiologies, early identification and personalized treatment of the basic disorder is of the utmost importance.
Keywords: nephrolithiasis; nephrocalcinosis; metabolic disorders; children; chronic renal failure

INTRODUCTION

Pediatric renal stone disease is manifested as nephro/urolithiasis (UL) and/or nephrocalcinosis (NC). UL is characterized by stones that may be found anywhere in the urinary tract, including kidney and/or ureter or bladder, while NC is defined as calcium salt deposition in the renal parenchyma including the tubular epithelium and interstitial renal tissue [1]. Both UL and NC may be discovered in children of all ages. Although other imaging modalities can be used in the diagnosis of UL/NC, ultrasound has the least risk and is the most cost-effective.

UL/NC is associated with significant morbidity because of pain, susceptibility to urinary tract infections, the necessity of surgical procedures, and/or progression to chronic kidney failure. The most cases of UL and NC in children are of metabolic origin and are thus prone to recurrence and may cause chronic renal damage. Therefore, they deserve, even after their initial presentation, a detailed metabolic evaluation.

There are important differences of UL and NC in children compared to those in adults. In this review article, the epidemiology, pathophysiology, clinical manifestations, diagnosis, and treatment of the pediatric renal stone disease are discussed. The most attention is paid to the hypercalciuric renal stone diseases, as these are more likely to present in childhood.

EPIDEMIOLOGY

Compared to adults, UL in childhood is less common, and it is believed to be approximately 10% of that in adults, which is around 5% in industrialized countries [2–6]. The infants constitute up to one third of all pediatric UL patients [3, 4]. Overall, reported incidence of pediatric UL varies from 5.6 to 36 per 100,000 children and adolescents younger than 18 years [5, 6]. The differences in incidence rates reported in children with UL reflect differences in genetic, geographic, and socioeconomic background, but also depend on the design and the time of the study [7]. Endemic UL is found in Southeast Asia, the Middle East, India, and Pakistan, while it is uncommon in children of African descent. It is very likely that the high consanguinity rate contributes to the higher incidence of UL/NC among ethnic groups that live in the Middle East and Asia. Additionally, the endemic calculi observed in these parts of the world are composed predominantly of ammonium and uric acid, and seem to correlate with dietary habits, malnutrition, urinary tract infections, and hot climate. Epidemiology of UL in the European population of the 19th century is similar to that of the 20th century population in Asia [8]. Changes that have occurred in the socio-economic sphere, as well as their consequences, primarily in dietary habits (food rich in proteins and calories), have influenced the incidence, the site (decreased rate of bladder stones) and chemical composition of calculi (raising rate of calcium oxalate and

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calcium phosphate stones) [7]. As in adults, an increased trend of UL incidence, the so-called "stone wave," has also been observed in children [9–15]. VanDervoort et al. [10] demonstrated that pediatric UL increased almost five-fold over the last decade in the United States. An increasing incidence of UL may be explained at least partially by the increasing rate of routine ultrasound examination in children with nonspecific symptoms, as well as with specific ones. As in adults, UL is more common in males than in females, although there are some opposite findings [12, 16]. Pediatric UL morbidity is responsible for 1/685 pediatric hospitalizations in the United States and for 2.5/1,000 pediatric hospitalizations in Croatia [11, 17].

The incidence of NC in children is even less known than that of UL due to its typically asymptomatic course. Thus, NC diagnosis is usually made accidentally by ultrasound examination for other reasons. Due to the increasing application of ultrasound in recent times, NC is more frequent than previously revealed. NC epidemiology in neonates is much better known than in older children, especially in premature babies. It is all the greater if the gestational age and birth body weight of the newborn is less and its condition is more critical [18]. Jacinto et al. [19] reported NC incidence of 64% in premature infants at a mean age of 39.3 ± 26.7 days of life. Infants with NC had shorter gestations (28.2 ± 1.8 vs. 31 ± 1.4 weeks) and lighter birth weights (924 ± 195 vs. 1,338 ± 100 g) than those infants without renal calcifications [19]. In another study, 26.6% of 79 infants born at less than 32 weeks' gestation developed NC [20]. Affected infants were significantly smaller (mean birth weight 940 g) and significantly less mature (mean gestation 26.9 weeks). Multivariate analysis showed that the strongest clinical indicator of NC was the duration of oxygen treatment. Infants who still required oxygen treatment at 28 days of life had a 62% chance of developing renal calcification [20]. Other predisposing factors for NC in newborns are the use of diuretics (furosemide), corticosteroids, parenteral nutrition, and hypocitraturia.

PATHOPHYSIOLOGY

A primary event in the formation of UL and NC is the increased concentration of relevant solutes (calcium phosphate, calcium oxalate, sodium urate, cystine, or other substances) in urine above their saturation threshold due to their increased rate of urinary excretion and/or a low urine volume. The formation of crystals of the relevant salts, their aggregations and adherence to the renal tubule cells are also influenced by other factors such as urine pH, inability of natural crystallization inhibitors (citrate, pyrophosphate, sulfate, and magnesium), stasis of urine, as well as renal tubule damage (due to urinary tract infections or some drugs). Crystal binding to the surface of tubular cells is facilitated by a number of luminal membrane molecules, including acidic fragment of nucleolin-related protein, annexin-II, osteopontin, and hyaluronan, which are exclusively expressed at the luminal surface of regenerating/(re)differentiating renal tubular cells [21].

Calcium oxalate is the predominant constituent of at least 75% renal calcifications in pediatrics as well as in adults from industrialized countries [21]. However, the initial role in their formation belongs to calcium phosphate crystals, which start forming apatite plaque (Randall plaques) at the basement membrane of the thin loops of Henle, location predisposed to urothelial erosion due to the urine flux [22]. Aggregations of calcium oxalate crystals at apatite plaques provide further stone formation attached to the papillary tip of the kidney. It is considered that calcium phosphate stones are developed from crystal aggregates deposited at the tip of the Bellini ducts [21].

The kidney itself has a great role in renal stone diseases in association with calcitropic hormones such as vitamin D_3 and parathyroid hormone. The intrinsic renal calcium-sensing receptor (*CaSR*) feedback system, the regulation of paracellular calcium transport involving claudins, and new paracrine regulators such as klotho, give kidney a crucial position not only in modulation of calciuria but also of calcium homeostasis [23]. Genetic disorders in any of these systems may cause calcium nephropathy.

ETIOLOGY

As compared with the adult population, a higher proportion of pediatric patients have a well-defined etiology of renal stones. The etiology may be classified as metabolic, infection-related, structural urinary anomalies causing obstruction, or idiopathic. Metabolic abnormalities account for 25–96% of UL/NC, while urinary tract infection and anatomical obstructive abnormalities account for 25% and 30%, respectively [24, 25]. Metabolic alterations include hypercalciuria, hypocitraturia, hyperuricosuria, phosphaturia with hypophosphatemia, distal renal tubular acidosis, idiopathic infantile hypercalcemia, Bartter and Dent diseases, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, cystinuria, hyperoxaluria, and renal hypouricemia [26–31]. Heritability has been one of the strongest risks for UL/NC; 35–65% of affected patients will have relatives with UL/NC, compared with 5–20% of those without renal stone who have relatives with UL/NC [6, 27]. At least 30 genes have been shown to cause monogenic UL/NC by autosomal-dominant, autosomal-recessive, or X-linked transmission [28]. Polygenic disorders have also a significant role in UL, such as idiopathic hypercalciuria, but they are less cleared.

The study by Halbritter et al. [32], which included an international cohort of 272 patients with UL/NC, has shown that the percentage of monogenic cases was 11.4% in adult and 20.8% in pediatric patient cohorts. Recessive monogenic diseases typically manifest earlier in life than dominant monogenic diseases [33]. In more than 40% of the cases in the aforementioned study, the genetic diagnoses contributed a new aspect to the previously established clinical diagnosis, suggesting practical implications, such as avoiding vitamin D (*CYP24A1*), initiating audiometry (*ATP6V1B1*), excluding the risk of recurrence in renal transplants (*CLCN5* or *CLDN16*), or pyridoxine sensitivity

in the presence of *AGXT* allele (Gly170Arg [32]. Based on the study results, Braun et al. [33] give recommendation for clinicians to be aware of the genetic source of UL/NC in the following conditions: early onset, familial prevalence, familial consanguinity, multiple or recurrent stones, and NC.

Hypercalciuria is the commonest metabolic abnormality causing UL in children. It may be associated with increased, decreased, or normal serum calcium levels (Tables 1–3). Idiopathic hypercalciuria (IH) is defined by hypercalciuria, normocalcemia, and the absence of diseases known to cause increased urine calcium excretion. In children, hypercalciuria is diagnosed if the urine calcium excretion is ≥ 0.1 mmol (≥ 4 mg)/kg/day in at least two separate collections of urine during 24 hours (24h). Adequate collection is estimated via measuring 24h-urine creatinine of 0.1–0.2 mmol/kg/24h. In situations where 24h-urine collection is not possible, random urine measurements are implemented, using spot urine ratio of the calcium and creatinine and comparing it with its age-related reference values (Table 4) [34]. Pathogenesis of IH is very complex and many potential factors can be involved, such as polymorphisms of the gene coding for proteins regulating tubular phosphate and calcium reabsorption [vitamin D receptor (*VDR*), *SLC34A1*, *SLC34A4, CLDN14,* and *CaSR*] and those responsible for proteins preventing calcium salt precipitation (*CaSR*, *MGP*, *OPN, PLAU,* and *UMOD)* or gene coding for a water channel in the proximal tubule *(AQP1)* [35]. Furthermore, in families with an autosomal dominant mode of IH, inheritance connection between IH and loci on chromosome 1q23.3-q24, which contains the human soluble adenylyl cyclase gene, chromosome 12q12-q14, which contains the *VDR* gene and chromosome 9q33.2-q34.2, were established [27]. Environmental factors may also significantly affect renal stone formation. Nutrient intake may change urine composition, but may also influence gene expression by epigenetic mechanisms [35].

Table 1. Hereditary diseases associated with hypercalcemia and hypercalciuria (modified [27])

Disorder	Clinical feature	Mode of inheritance	Gene product	Chromosomal location of the gene	Comment
FIHP	Familial isolated parathyroid tumors	A-r/A-d	menin parafibromin CaSR	11q13 1q31.2 3q21.1	PTH increased
MEN1	Parathyroid hyperplasia and/or tumors associated with pituitary and pancreaticoduodenal neuro-endocrine tumors	A-d	menin	11q13	PTH increased
MEN2a	Parathyroid tumors with medullary thyroid cancer and pheochromocytoma	A-d	ret	10q11.2	PTH increased
HPT-JT	Parathyroid tumors with ossifying fibromas of the jaw	A-d	parafibromin	1q31.2	PTH increased
IHH	Idiopathic hypercalcemia with hypercalciuria	A-r	CYP24A1		PTH decreased
Hypophosphatemic nephrolithiasis/ osteoporosis	Renal phosphate leak, hypophosphatemia, hypercalciuria urolithiasis, osteoporosis	A-d/A-r	NPT2a/SLC34A1 solute carrier family 34 (sodium phosphate), member 1	5q35	$1,25(OH)_2D_3$ increased

A-d – autosomal dominant; A-r – autosomal recessive; FIHP – familial isolated hyperparathyroidism; MEN – multiple endocrine neoplasia; HPT-JT – hyperparathyroidism – jaw tumor syndrome; IHH – idiopathic hypercalcemia with hypercalciuria; CaSR – calcium-sensing receptor; NPT2c/a – sodium–phosphate co-transporter type 2c/a; PTH – parathyroid hormone

Table 2. Hereditary diseases associated with hypocalcemia and hypercalciuria

Disorder	Clinical feature	Mode of inheritance	Gene product	Chromosomal location of the gene	Comment
ADHH	Hypocalcemia, hyperphosphatemia, hypomagnesemia	A-d	CaSR	3q21.1	PTH low – normal range
FHHNC	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	A-r	PCLN1/CLDN16	3q28	PTH raised
FHHNC	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis with ocular abnormalities	A-r	CLDN19	1p34.2	PTH raised
FIH	Hypoparathyroidism, familial isolated	A-d	GCM2	6p24.2	PTH low
APECED	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy	A-r	AIRE		PTH low
FIH, recessive	Hypoparathyroidism, autosomal recessive	A-r	11p153	PTH	PTH low
FIH, x-linked	Hypoparathyroidism, familial isolated –x linked	X-r	GCM2	Xq26-q27	PTH low
FIH, dominant	Hypoparathyroidism, autosomal dominant	A-d	PTH	11p153	PTH low

A-d – autosomal dominant; A-r – autosomal recessive; X-r – X-linked recessive; ADHH – autosomal dominant hypocalcemia with hypercalciuria; FHHNC – familial hypomagnesemia with hypercalciuria and nephrocalcinosis; FIH – familial isolated hypoparathyroidism; APECED – autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; AIRE – autoimmune regulator; CaSR – calcium-sensing receptor; PCLN1 – paracellin; CLDN16/19 – claudin 16/19; PTH – parathyroid hormone

Table 3. Hereditary diseases associated with normocalcemia and hypercalciuria (modified [27])

Disorder	Clinical feature	Mode of inheritance	Gene product	Chromosomal location of the gene	Comment
IH	Idiopathic hypercalciuria	AD	SACR VDR ?	1q23.3-q24 12q12-q14 9q33.2-q34.2	Hypercalciuria, normocalcemia
Bartter syndrome characterized by hypokalemic alkalosis, renal salt wasting that may lead to hypotension, hyperreninemic hyperaldosteronism, increased urinary prostaglandin excretion					
Type I	+ Hypercalciuria with nephrocalcinosis	A-r	SLC12A1/NKCC2	15q15-q21.1	Neonatal
Type II	+ Hypercalciuria with nephrocalcinosis	A-r	KCNJ1/ROMK	11q24	Neonatal
Type IV	+ Hypercalciuria with nephrocalcinosis + sensoneural deafness + CRF	A-r	BSND/CLCNKB	1p31, 1p36	
Type V	+ Hypercalciuria with nephrocalcinosis +hypocalcemia	A-d	CASR	3q21.1	
Type VI	+ Dent	X-r	CLCN5	Xp11.22	
Dent's disease	Hypercalciuria, Phosphaturia, Hypophosphatemia, low molecular weight proteinuria, CRF	X-r	ClCN5	Xp11.22	
Lowe's syndrome	Psychomotor retardation, Fancony syndrome, Hypercalciuria, Phosphaturia, Megalin deficiency, Congenital cataract	X-r	OCRL1	Xq25	
HHRH	Hypophosphatemic rickets with hypercalciuria	A-r	NPT2c/SLC34A3 solute carrier family 34 (sodium phosphate)	9q34	
dRTA A-d	Hypercalciuria, Hypocitraturia, Hypokalemia, rickets	A-d	SLC4A1/kAE1	17q21.31	
dRTA with sensorineural deafness	Hypercalciuria, Hypocitraturia, Hypokalemia, rickets Hearing loss	A-r	ATP6B1/ATP6V1B1	2p13	
dRTA with preserved hearing	Hypercalciuria, Hypocitraturia, Hypokalemia, rickets	A-r	ATP6N1B/ATP6V0A4	7q34	

A-d – autosomal dominant; A-r – autosomal recessive; X-r – X-linked recessive; HHRH – hereditary hypophosphatemic rickets with hypercalciuria; dRTA – distal renal tubular acidosis; SAC – human soluble adenylyl cyclase; VDR – vitamin D receptor; CaSR – calcium-sensing receptor; SLC12A1 – solute carrier family 12, member 1; NKCC2 – sodium–potassium–chloride co-transporter 2; KCNJ1 – potassium channel, inwardly rectifying, subfamily J, member 1; ROMK – renal outer medullary potassium channel; CLCNKB – chloride channel Kb; BSND – barttin; CLCN5 – chloride channel 5; OCRL1 – oculo-cerebro-renal syndrome of Lowe 1; NPT2c/a – sodium–phosphate co-transporter type 2c/a; SLC34A1/3 – solute carrier family 34, member 1/3; SLC4A1 – solute carrier family 4, member 1; kAE1 – kidney anion exchanger 1; ATP6B1 – ATPase, H+ transporting (vacuolar proton pump), V1 subunit B1; ATP6N1B – ATPase, H+ transporting, lysosomal V0 subunit a4

CLINICAL MANIFESTATION

Unlike adults and adolescents, only 10–14% of children with UL have classic renal colic [17, 34, 36]. Exceptionally, UL in children may be manifested by signs and symptoms of post renal acute kidney injury due to urethral or ureteral obstruction of both or single functioning kidney [37]. Instead, microscopic or macroscopic hematuria, flank or abdominal pain, as well as recurrent urinary tract infection, are predominant clinical presentations of UL in children [16]. Hematuria may precede noticeable UL for some time. Recurrent urinary tract infection or unexplained sterile pyuria in young children should arouse suspicion of UL. The recurrence rate of UL may be as high as 50% at five years [27]. In addition, signs and symptoms of lower urinary tract dysfunction, such as nocturnal enuresis and/or diurnal incontinence, suprapubic or urethral pain may be found in about 10% of children with UL [7]. Finally, 10–25% of young children have no symptoms of UL, which then may be discovered as an incidental finding during abdominal ultrasound imaging for any other reason [7, 34, 38].

Nephrocalcinosis is usually asymptomatic or occult symptomatic and is diagnosed incidentally during the search for causes of hematuria, abdominal pains, or sterile leukocyturia. NC is often progressive, and more often than UL leads to chronic renal failure [28, 31, 34, 38].

DIAGNOSTIC EXAMINATION

Given the complexity of children's UL/NC and especially its predominant metabolic hereditary etiology, it is advised, as the best solution, to perform the systemic diagnostic evaluation and personalized treatment in the Center for Pediatric Renal Stone Disease, as it is practiced in some Western countries [36]. System diagnostic evaluation includes a detailed medical history, careful and complete physical examination, followed by imaging studies and specific blood and urine analyses. In medical history, special attention should be given to information on family renal stones, hematuria, renal failure, but also on diet habits, fluid intake, medications, vitamin and mineral supplements,

Table 4. Normal values of solute for 24 hour urine collection, or for spot urine samples: creatinine ratios (solute/creatinine) (modified [34])

The age-specific parameter values	Ratio of solute to creatinine		Comments
	mmol/mmol	mg/mg	
Calcium			< 0.1 mmol (< 4 mg)/kg/24h After meals with milk, excretion increases up to 40%.
< 12 months	< 2	0.81	
1–3 years	< 1.5	0.53	
3–5 years	< 1.1	0.39	
5–7 years	< 0.8	0.28	
> 7 years	< 0.6	0.21	
Oxalates			< 0.5 mmol (< 45 mg)/1.73 m^2 For primary hyperoxaluria types I and II also examine urinary glycolate, L-glycerol and oxalate in plasma
0–6 months	< 325–360	288–260	
7–24 months	< 132–174	110–139	
2–5 years	< 98–101	80	
5–14 years	< 70–82	60–65	
> 16 years	< 40	32	
Citrate		g/g	> 1.9 mmol (365 mg)/1.73 m^2 (M); > 1.6 mmol (310 mg)/1.73 m^2 (F) > 180 mg (94 µmol/g (8.84 mmol) creatinine Decreased: RTA, premature infants, hypokalemia, renal transplantation
0–5 years	> 0.25	0.42	
> 5 years	> 0.15	0.25	
Magnesium	0.63	> 0.13	> 0.04 mmol (0.8 mg)/kg; > 88 mg (44 mmol)/1.73 m^2/24h There is no data for children < 2 years old
Phosphates	TmP/GFR		
< 3 months	< 3.3 mmol/l		
< 6 months	< 2.6 mmol/l		
2–15 years	< 2.44 mmol/l		
Sodium	< 3 mmol/kg/24h		
Potassium	> 3 mmol/kg/24h		
Acidum uricum	Age > 2 years < 0.56 mg/dl (33 µmol/l) / GFR (ratio × serum creatinine)		< 815 mg (4.9 mmol)/1.73 m^2/24h or < 35 mg (0.21 mmol)/kg/24h Higher in children than in adults; there is no data for children < 2 years old
Xanthine	30–90 µg (20–60 µmol)/24h		
Cystine	< 60 mg (0.5 mmol)/1.73 m^2/24h		< 10 years < 55 µmol (13 mg)/1.73 m^2; > 10 years < 200 (48 mg)/1.73 m^2

GFR – glomerular filtration rate; TmP/GFR – tubular maximum reabsorption rate of phosphate to glomerular filtration rate

immobilization, chronic bowel diseases, and, of course, on urological anomalies and urinary tract infections [34].

Diagnostic imaging should start with an ultrasound examination, which is widely available, non-invasive, without ionizing radiation, and very useful for detecting kidney stones, obstructive anomalies, and other aspects of the urinary tract anatomy [34]. Usually, renal ultrasound is the only method required, but for detection of small stones or stones in the ureter, computed tomography (CT) is more sensitive than ultrasound. Conventional radiography, with or without contrast (plain X-ray) may replace CT in infants and young children as it does not require sedation and gives off less ionizing radiation. However, radiolucent uric acid stones cannot be visualized by conventional radiography while struvite (magnesium ammonium phosphate), cystine stones, and stones composed of some drugs (ceftriaxone) can be difficult to detect from the surrounding tissue. For diagnosing NC in children, high-resolution renal ultrasound is the optimal method due to its high sensitivity (96%), and very good specificity (85%) [39].

A complete analysis of the first morning urine is essential in diagnosing UL/NC. By microscopic urine examination it is possible to differentiate glomerular from non-glomerular hematuria, to diagnose crystals (e.g. hexagonal cystine crystals, orange-brown 2,8-dihydroxyadenine), to notice leucocytes and bacteria. Urine pH (done by a glass electrode or by pH paper), urine-specific gravity or osmolality, urine protein and glucose are part of the routine examination of urine. It is important to note that the results of urinalysis are credible only in the absence of urinary tract infection. Therefore, urine culture is checked prior to the chemical urine analysis, which includes measurements of creatinine, calcium, uric acid, oxalic acid, phosphate, magnesium, and citrate. Cystine is examined by nitroprusside test or by amino acid chromatography. Preferably, it should be done for 24 hours, but when this is unavailable, it can be replaced by the spot urine ratio of the test substance and creatinine (Table 4). All patients should also be examined for serum calcium, phosphorus, magnesium, uric acid, alkaline phosphatase, pH, bicarbonate, and creatinine. In patients with hypercalciuria, it is advised to do blood analyses for the parathyroid hormone, vitamin D metabolites, and vitamin A. For the diagnosis of primary hyperoxaluria, it is required to measure plasma

and urine oxalate, and glycolate and L-glycerate in urine. Determining intestinal oxalate absorption and stool *Oxalobacter formigenes* colonization is preferable for secondary hyperoxaluria. Finally, genetic tests are required to confirm the clinical diagnosis and are very useful for personalized treatment and preventive strategy [27–33].

THERAPY

In cases of acute renal colic, pain is usually very intense due to the irritation of receptors during dilatation of the urinary system and release of pain mediators through to local irritation and swelling of the wall of the renal pelvis or ureter. The use of nonsteroidal antiinflammatory drugs may be indicated as the first choice. Renal stone expulsive treatment may be managed with open surgery, extracorporeal shock wave lithotripsy, laparoscopic or robot-assisted uretero-pyelolithotomy, percutaneous nephrolithotomy, rigid and/or flexible ureteroscopy and medical expulsive treatment (MET) [40]. Choice of treatment for a specific patient is determined based on the renal stone location, its size and composition, urinary system anatomy, as well as available technology, cost of the treatment, experience of the physician, and preferences of both the physician and the patient's parents [40]. Alpha-blockers and calcium channel blockers have been found to be more effective and successful for MET than other drugs (antimuscarinic drugs, phosphodiesterase type-5 inhibitors and steroids) [40]. Both of these eliminate or alleviate uncoordinated contractions induced by the stone and do not affect the normal peristalsis of the ureter. MET may be useful for small stones (5–10 mm) within the distal part of ureter, and are usually applied after the extracorporeal shock wave lithotripsy treatment.

Non-pharmacological measures are still the initial and basic treatment and preventive measures [38]. These include an increase in urine output and crystallization inhibitors, and the setting of optimal urine pH. Increasing the intake of fluids (≈ 3 l/m^2 of body surface area) provides urine output > 1 ml/kg/h [38]. Reduced intake of table salt (NaCl) and increased potassium intake should maintain the Na/K ratio in urine to < 2.5 [38]. It should not reduce calcium intake below the age-recommended dose (800 mg/day for pre-school and 1,300 mg/day for school age) because of the increased risk for osteopenia and hyperoxaluria. It is also advised to reduce the intake of animal protein. The intake of phytate and magnesium should increase, while the intake of sucrose, fructose, and high doses of vitamin C should be reduced [38].

Pharmacological measures are specific regarding the etiology of UL/NC. For hypercalciuria and/or hypocitraturia, it is advised to give K citrate (0.5–1.5 mEq or 0.1–0.15 g / kg of body weight per day divided into two or three doses each), which is metabolized to bicarbonate in the liver, thus reducing intratubular citrate reabsorption and therefore increasing urinary citrate excretion. Citrate forms a complex with calcium, reducing precipitation of calcium with other substances such as oxalate. Thiazides (hydrochlorothiazide 1–2 mg/kg/day divided into one to two doses) with or without amiloride also decrease calcium urine excretion [38]. In patients with dominant hypocalcemia, hyperphosphatemia, and hypercalciuria due to a gain-of-function *CaSR* mutation, vitamin D is not indicated as it worsens hypercalcemia and hypercalciuria. For hypercalciuria + phosphaturia, phosphates are given. Treatment options for the *CYP24A1* mutation disorders include avoidance of vitamin D supplementation, sunlight exposure, and tanning beds, along with high water intake, but treatment with the cytochrome inhibitor ketoconazole may be beneficial in severely affected patients [41, 42].

For primary hyperoxaluria type I, in addition to large water intake (> 3 l/m^2/day), citrate or orthophosphate, vitamin B_6 (5–20 mg/kg/day) is given, which in about 30% of patients (those with a distinct allele – Gly170Arg) may enhance the reduced activity of alanine/glyoxylate aminotransferase (AGT), thus reducing hyperoxaluria. In others, hepatic AGT activity should be restored by liver transplantation. Sequential liver–kidney or liver combined with kidney transplantation is performed in patients with advanced stages of chronic kidney failure. In secondary (absorptive) hyperoxaluria, it is necessary to treat the primary gastrointestinal disease, to reduce the intake of oxalate in the food, increase the intake of calcium (to bind fatty acids, thereby preventing the intestinal absorption of oxalate), with potassium citrate and probiotics.

Hyperuricosuria is treated with alkalinization of urine (by potassium citrate), dietary purine restriction, and, if needed, allopurinol can be added.

In patients with cystinuria, urine pH should be kept between 7.0 and 7.5 by potassium citrate and bicarbonate, in addition to abundant rehydration. Specific drugs for cystinuria are tiopronin, D-penicillamine and captopril, which cleave cystine into two cysteine-disulfide moieties that are 50-times more soluble than cystine. However, care must be taken of their side effects.

In distal renal acidosis, treatment of acidosis by potassium citrate and bicarbonate is the cornerstone of therapy.

CONCLUSION

UL/NC in children is a very important problem due to its complications and possibility to cause chronic renal failure. Every child with renal stone should undergo the diagnostic evaluation. For all UL/NC etiologies, early identification and personalized treatment of the basic disorder is of the utmost importance.

REFERENCES

1. Popović-Rolović M, Peco-Antić A, Marsenić O. Nefrolitijaza i nefrokalcinoza. U: Dončev M (ured). Lekarski priručnik iz dečje nefrologije. Bor: Grafomed; 2001. p. 213–20.
2. Croppi E, Ferraro PM, Taddei L, Gambaro G. Prevalence of renal stones in an Italian urban population: a general practice-based study. Urol Res. 2012; 40:517–22.
3. Güven A, Koyun M, Baysal YE, Akman S, Alimoflu E, Akbas H, et al. Urolithiasis in the first year of life. Pediatr Nephrol 2010; 25:129–34.
4. Serdaroğlu E, Aydoğan M, Özdemir K, Bak M. Incidence and causes of urolithiasis in children between 0–2 years. Minerva Urol Nefrol. 2017; 69:181–8.
5. Edvardsson V, Elidottir H, Indridason OS, Palsson R. High incidence of kidney stones in Icelandic children. Pediatr Nephrol. 2005; 20:940–4
6. Dwyer ME, Krambeck AE, Bergstralh EJ, Milliner DS, Lieske JC, Rule AD. Temporal trends in incidence of kidney stones among children: a 25-year population based study. J Urol. 2012; 188:247–52.
7. López M, Hoppe B. History, epidemiology and regional diversities of urolithiasis. Pediatr Nephrol. 2010; 25(1):49–59.
8. Asper R. Epidemiology and socioeconomic aspects of urolithiasis. Urol Res. 1984; 12:1–5.
9. Turney BW, Reynard JM, Noble JG, Keoghane SR. Trends in urological stone disease. BJU Int. 2012; 109:1082–7.
10. VanDervoort K, Wiesen J, Frank R, Vento S, Crosby V, Chandra M, et al. Urolithiasis in pediatric patients: a single center study of incidence, clinical presentation and outcome. J Urol. 2007; 177:2300–5.
11. Bush NC, Xu L, Brown BJ, Holzer MS, Gingrich A, Schuler B, et al. Hospitalizations for pediatric stone disease in United States, 2002-2007. J Urol. 2010; 183:1151–6.
12. Sas DJ, Hulsey TC, Shatat IF, Orak JK. Increasing incidence of kidney stones in children evaluated in the emergency department. J Pediatr. 2010; 157:132–7.
13. Routh JC, Graham DA, Nelson CP. Epidemiological trends in pediatric urolithiasis at United States freestanding pediatric hospitals. J Urol. 2010; 184:1100–4.
14. Dwyer ME, Krambeck AE, Bergstralh EJ, Milliner DS, Lieske JC, Rule AD. Temporal trends in incidence of kidney stones among children: a 25-year population based study. J Urol. 2012; 188:247–52.
15. Penido MG, Srivastava T, Alon US. Pediatric primary urolithiasis: 12-year experience at a Midwestern Children's Hospital. J Urol. 2013; 189:1493–7.
16. Yasui T, Iguchi M, Suzuki S, Kohri K. Prevalence and epidemiological characteristics of urolithiasis in Japan: national trends between 1965 and 2005. Urology. 2008; 71:209–13.
17. Milošević D, Batinić D, Turudić D, Batinić D, Topalović-Grković M, Gradiški IP. Demographic characteristics and metabolic risk factors in Croatian children with urolithiasis. Eur J Pediatr. 2014; 173:353–9.
18. Schell-Feith EA, Kist-van Holthe JE, van der Heijden AJ. Nephrocalcinosis in preterm neonates. Pediatr Nephrol. 2010; 25:221–30.
19. Jacinto JS, Modanlou HD, Crade M, Strauss AA, Bosu SK. Renal calcification incidence in very low birth weight infants. Pediatrics. 1988; 81:31–5.
20. Short A, Cooke RW. The incidence of renal calcification in preterm infants. Arch Dis Child. 1991; 66(4 Spec No):412–7.
21. Verkoelen CF, Verhulst A. Proposed mechanisms in renal tubular crystal retention Kidney Int. 2007; 72:13–8.
22. Moe OW. Kidney stones: pathophysiology and medical management. Lancet. 2006; 367:333–44.
23. Moor MB, Bonny O. Ways of calcium reabsorption in the kidney. Am J Physiol Renal Physiol. 2016; 310:F1337–50.
24. van't Hoff WG. Aetiological factors in paediatric urolithiasis. Nephron Clin Pract. 2004; 98(2):c45–8.
25. Cameron MA, Sakkhae K, Moe OW. Nephrolithiasis in children. Pediatr Nephrol. 2005; 20:1587–92.
26. Hunter DJ, Lange M, Snieder H, MacGregor AJ, Swaminathan R, Thakker RV, et al. Genetic contribution to renal function and electrolyte balance: a twin study. Clin Sci (Lond). 2002; 103:259–65.
27. Stechman MJ, Loh NY, Thakker RV. Genetic causes of hypercalciuric nephrolithiasis. Pediatr Nephrol. 2009; 24:2321–32.
28. Peco-Antić A, Smoljanić Z, Dimitrijević N, Kostić M, Marsenić O, Djordjević M. Lesch–Nyhan–ov sindrom. Srp Arh Celok Lek. 2001; 129(9–10):260–3.
29. Peco-Antić A, Dunjić R, Marsenić O, Živić G. Bartter-ov sindrom, nova podela, stara terapija. Srp Arh Celok Lek. 2001; 129(5–6):139–42.
30. Peco-Antić A, Konrad M, Milošević-Lomić G, Dimitrijević N. Familial hypomagnesaemia with hypercalciuria and nephrocalcinosis: the first four patients in Serbia. Srp Arh Celok Lek. 2010: 138:351–5.
31. Konard M, Weber S, Dötsch J, Kari JA, Seeman T, Misselwitz J, et al. CLDN16 Genotype Predicts the Progression of Renal Failure in Familial Hypomagnesiemia with Hypercalciuria and Nephrocalcinosis. JASN. 2008; 19(1):171–81.
32. Halbritter J, Baum M, Hynes AM, Rice SJ, Thwaites DT, Gucev ZS, et al. Fourteen monogenic genes account for 15% of nephrolithiasis/nephrocalcinosis. JASN. 2015; 26:543–51.
33. Braun DA, Lawson JA, Gee HY, Halbritter J, Shril S, Tan W, Stein D, et al. Prevalence of Monogenic Causes in Pediatric Patients with Nephrolithiasis or nephrocalcinosis. Clin J Am Soc Nephrol. 2016; 11(4):664–72.
34. Hoppe B, Kemper MJ. Diagnostic examination of the child with urolithiasis or nephrocalcinosis. Pediatr Nephrol. 2010; 25:403–13.
35. Arcidiacono A, Mingione A, Macrina L, Pivari F, Soldati L, Vezzoli G. Idiopathic Calcium Nephrolithiasis: A Review of Pathogenic Mechanisms in the Light of Genetic Studies. Am J Nephrol. 2014; 40:499–506.
36. Coward RJ, Peters CJ, Duffy PG, Corry D, Kellett MJ, Choong S, van't Hoff WG. Epidemiology of paediatric renal stone disease in the UK. Arch Dis Child. 2003; 88:962–5.
37. Patodia M, Sharma K, Sankhwar S, Goel A. Bladder calculus leading to acute renal failure in a girl child: a rare cause. BMJ Case Rep. 2017; 9:2017.
38. Alon US. Medical treatment of pediatric urolithiasis. Pediatr Nephrol. 2009; 24:2129–35.
39. Cramer B, Husa L, Pushpanathan C. Nephrocalcinosis in rabbits—correlation of ultrasound, computed tomography, pathology and renal function. Pediatr Radiol. 1998; 28(1):9–13.
40. Atan A, Balcı M. Medical expulsive treatment in pediatric urolithiasis. Turk J Urol. 2015; 41:39–42.
41. Peco-Antić A, Ivelja B, Miloševski-Lomić G, Paripović D, Konrad M. Hypercalciuria caused by CYP24A1 mutation – fourteen years of the patient's follow-up. Srp Arh Celok Lek. 2017; OnLine-First: March 31, 2017; (00):95–95. [DOI: https://doi.org/10.2298/SARH170116095P]
42. Sayers J, Hynes AM, Srivastava S, Dowen F, Quinton R, Datta HK, et al. Successful treatment of hypercalcaemia associated with a CYP24A1 mutation with fluconazole. Clin Kidney J. 2015; 8:453–5.

Обољења са бубрежним камењем код деце

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САЖЕТАК

Бубрежно камење код деце се испољава као постојање каменчићи у бубрезима и уринарним путевима – уролитијаза (УЛ), или као калцификација бубрежног паренхима – нефрокалциноза (НК). УЛ код деце је ређа у односу на одрасле и износи око 5% у индустријским земљама, а НК је још ређа, осим код критично болесних прематуруса, код којих може достићи чак 64%. Формирање УЛ и НК су условљени повећаном концентрацијом соли у урину, а њихова агрегација и адхеренција за бубрежне тубулске ћелије је олакшана факторима као што су *pH* урина, слабост природних инхибитора кристализације, стаза урина и оштећења тубула. УЛ прати значајан морбидитет због болова, подложности опструкцији и инфекцији уринарног тракта и честих потреба за хируршким интервенцијама. НК је обично асимптоматска, али је често прогресивна и много чешће од УЛ изазива хроничну бубрежну слабост. УЛ и НК се дијагностикују применом различитих испитивања која дају слику уринарног тракта, а ултразвучно испитивање је најмање ризично и најисплатљивије. У већини случајева УЛ и НК су метаболичког порекла те су склони поновном јављању и хроничном оштећењу бубрега. Због тога они заслужују, чак и при првој појави, да се детаљно испита узрок њиховог настанка. На генетички узрок калкулозе и НК треба помислити у следећим околностима: рана појава, фамилијарно оптерећење бубрежним болестима, консангвинитет, више калкулуса или њихово понављање и присуство НК. За све типове бубрежног камења веома је важна рана дијагноза и персонална терапија основне болести.

Кључне речи: нефролитијаза; нефрокалциноза; метаболичке болести; деца; хронична бубрежна инсуфицијенција

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ИСТОРИЈА МЕДИЦИНЕ / HISTORY OF MEDICINE

Елси Инглис (1864–1917) и Болнице шкотских жена у Србији у Великом рату – 1. део

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САЖЕТАК

Вест о великим победама херојске а мале Србије у Првом светском рату проширила се надалеко. Праћена апелом српских посланства и српског Црвеног крста, помоћ је пристизала са свих страна. Прве медицинске мисије и санитетска и друга помоћ дошла је из Русије. Следиле су медицинске мисије из Велике Британије, Француске, Грчке, Холандије, Данске, Швајцарске, Америке... Материјална помоћ и појединци стигли су из Пољске, Канаде, Аустралије, Новог Зеланда, Ирске, Норвешке, Индије, Јапана, Египта, Јужне Америке и других земаља. Искрени пријатељи српског народа су формирали разне фондове под окриљем Црвеног крста и других удружења. Септембра 1914. формиран је Српски потпорни фонд у Лондону, а новембра исте године у Шкотској је основана прва јединица Болнице шкотских жена за службу у иностранству.

Циљ овог рада је био да вратимо сећање на Болнице шкотских жена у Србији и са Србима у току Првог светског рата. Оне у историји српског народа заузимају посебно место. Настале су иницијативом др Елси Мод Инглис (1864–1917), лекарке, хирурга, борца за женска права, а подршком Шкотске федерације сифражетских друштава. Искључиво у саставу жена, Болнице шкотских жена су својим учешћем у рату великим делом допринеле родној и професионалној равноправности, посебно у области медицине. Многи ставови садашњице произишли су захваљујући генерацији првих лекарки, које су се изборише за равноправност при избору и обављању професије лекара, како у миру тако и у рату.

Кључне речи: Први светски рат; Болнице шкотских жена; Шкотска; Србија; Инглис Е.

УВОД

Непосредно после почетка Првог светског рата прве медицинске мисије и санитеска и друга помоћ дошла је из Русије, а убрзо из Велике Британије, Француске, Грчке, Холандије, Данске, Швајцарске, Америке... Материјална помоћ и појединци стигли су из Пољске, Канаде, Аустралије, Новог Зеланда, Ирске, Норвешке, Индије, Јапана, Египта, Јужне Америке и других земаља. Искрени пријатељи српског народа су формирали разне фондове под окриљем Црвеног крста и других удружења. Септембра 1914. формиран је Српски потпорни фонд у Лондону, а новембра исте године у Шкотској је основана прва јединица Болнице шкотских жена за службу у иностранству.

Крај 19. и почетак 20. века био је у знаку женске борбе за равноправност и еманципацију, која је допринела оснивању бројних женских друштава која су окупљала жене из свих слојева британског друштва, различитог образовања али и верског опредељења. Међу сифражеткињама издвајала се др Елси Инглис (*Dr. Elsie Maud Inglis*, 1864–1917), шкотска лекарка, која ће играти важну улогу у раним годинама деловања сифражетског друштва. Уочи великог рата др Елси Инглис је постављена за заповедника Шестог единбуршког добровољачког одреда, а убрзо и команданта Женског резервног санитетског одреда.

Циљ овог рада је био да изнесе нове чињенице, да истакне значај и врати сећање на Болнице шкотских жена у Србији и са Србима у току Првог светског рата и посебно на њиховог оснивача др Елси Инглис.

ДР ЕЛСИ МОД ИНГЛИС

Др Елси Инглис, једна од пионира шкотске медицине, учествовала је у раду Шкотске федерације жена сифражеткиња, где је изабрана за почасног секретара. На почетку Великог рата др Инглис оснива Болницу шкотских жена за службу у иностранству (*The Scottish Women's Hospitals for foreign service*). Оснивањем 14 болница које су пратиле ратишта целе Европе, од Француске, Малте, Белгије, Србије, Русије и Румуније, ушла је не само у историју медицине већ и у анале опште историје. Од укупног броја, десет Болница шкотских жена је било намењено за помоћ српском народу, четири болнице радиле су у Србији, три болнице су деловале на Солунском фронту, по једна болница на Руском фронту и Добруџи, на Корзици и Саланшеу, у Француској (Слика 1).

Др Елси Мод Инглис, лекарка и хирург, пре рата је обављала дужност почасног секретара Шкотске федерације жена сифражеткиња, која ће је подржати у оснивању Болнице шкотских жена. Била је то болница искључиво у женском саставу: са лекаркама,

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Слика 1. Др Елси Мод Инглис (1864–1917)
Figure 1. Dr. Elsie Maud Inglis (1864–1917)

Слика 2. Болница шкотских жена на путу за Србију
Figure 2. The Scottish Women's Hospital on its Way to Serbia

хирурзима, интернистима, епидемиолозима, микробиолозима, радиолозима, санитарним инспекторима, медицинским сестрама, болничаркама, администраторима, преводиоцима, женама возачима амбулантних кола, куварицама итд. У саставу Болница шкотских жена биле су Британке, Шкотланђанке, Иркиње, Аустралијанке, Канађанке, Американке, Новозеланђанке, а било је и британских поданица из Индије.

Др Инглис је организовала промоцију Болница шкотских жена, па тако је Кетлин Бурк (*Miss Kathleen Burke*) пронела мисију до Америке и Канаде, док је Елизабет Абот (*Mrs. Elizabeth Abbott*) отпутовала за Индију, Аустралију и Нови Зеланд. Подршка и помоћ пристизале су са свих страна. Организацију Болнице шкотских жена преузели су комитети, први са седиштем у Единбургу, коме ће се убрзо придружити новоосновани комитети у Лондону, Глазгову, Манчестеру, Ливерпулу, Бирмингему и Велсу.

Др Елси Инглис, Шкотланђанка, рођена је 16. августа 1864, у Најни-Толу, једној од најлепших станица у подножју Хималаја, у Индији. Одрасла је на Тасманији (Аустралија), школовала се и постала лекар и хирург у Шкотској. Лиценцу за лекара Елси Инглис је добила 4. августа 1892, у Единбургу на Краљевском колецу за лекаре и хирурге (*The Royal College of Physicians and Surgeons*) и на Факултету за лекаре и хирурге у Глазгову (*The Faculty of Physicians and Surgeons*). Лекарску каријеру започела је у новој болници за жене „Елизабет Герет Андерсон", али убрзо је изабрана за предавача за гинекологију на Медицинском факултету за жене у Единбургу.

Др Елси Инглис, оснивач и „покретачки дух" Болница шкотских жена широм Европе, дошла је у Србију априла 1915 (Слика 2), у помоћ др Елеонор Солто и Првој јединици у Крагујевцу. Основала је болнице у Ваљеву, Младеновцу и Лазаревцу, а окупацијом одбила да се повуче и остала да негује преко хиљаду рањеника и болесника у крушевачкој болници „Цар Лазар".

По повратку у домовину промовисала је српску борбу за ослобођење прославом Видовдана, организовала је нову болницу, која ће пратити Прву српску добровољачку дивизију на Руском фронту и Добруџи. Др Инглис је посетила Болницу шкотских жена на Корзици и била задовољна организацијом и успешним деловањем болнице у Ајачију.

Доласком у Србију, др Инглис је радила у Крагујевцу, где је руководила свим епидемиолошким болницама, које је она објединила у једну. Др Хачинсон ју је поставила за управницу болнице у Ваљеву, др Макгрегор за руководиоца болнице у Младеновцу, а др Холвеј за управницу болнице у Лазаревцу. На тај начин оформљене су четири ефикасне Болнице шкотских жена у Србији.

Српска влада је дала др Инглис пропусницу за бесплатну вожњу српским железницама. Она је сматрала да је била „изузетно срећна" што је почаствована таквим чином, јер је уживала у путовањима широм Србије, која су јој омогућила да боље упозна и земљу и њене интересантне људе. А суштина радости др Инглис у то време била је њена све већа љубав према Србима.

„Др Иглис је стигла у Србију кад су зараза и врућица већ скоро биле под контролом, а пред њом се налазило дуго топло и мирно лето. Требало је видети др Инглис тог лета. Њена писма из Србије су била препуна великог оптимизма. О свему је писала срцем. У Енглеској је оставила за собом одличну организацију у сваком одељку са женама пуним ентузијазма. Новац и донације су пристизале, док је цео програм добијао све већу подршку у целој Британији. Др Инглис је у Србији нашла могућност да њене организационе способности дођу до пуног изражаја. Имала је одличне сараднике у особљу Болница шкотских жена, којима је руководила" [2].

БОЛНИЦЕ ШКОТСКИХ ЖЕНА

Прва јединица Болнице шкотских жена у Крагујевцу

Прва јединица Болнице шкотских жена у Крагујевцу деловала је под управом др Грејс Еленор Солто (*Dr. Grace Eleanor Soltau*, 1877–1962), лекарке са Тасманије, Аустралија (Слика 3). Мада је одрасла и школовала се на Тасманији, Елеонор Солто је завршила медицину у Енглеској. Пре рата радила је у Краљевској бесплатној болници у Лондону.

Прва јединица, на челу са др Елеонор Солто, радила је у Крагујевцу од 5. јануара 1915. до великог повлачења. Особље се састојало од 30 чланица. Лекарску екипу су чинили: др Аделин Кембел (*Dr. Adeline H. Campbell*), хирург; др Едит Блејк Холвеј (*Dr. Edith Blake Hollway*); др Кетрин Макфејл (*Dr. Katherine S. Macphail*); др Френсис Маргарет Вејкфилд (*Dr. Frances Margaret Wakefield*); од марта др Лилијан Чесни (*Dr. Lilian Mary Chesney*), хирург; др Кетрин Корбет (*Dr. Catherine Louisa Corbett*); др Џенет Лерд (*Dr. Janet Stewart Laird*); од априла др Елси Инглис (*Dr. Elsie Maud Inglis*), хирург; од јула др Џорџина Дејвидсон (*Dr. Georgina E. Davidson*) и др Хелен Макдугал (*Dr. Helen McDougall*); од септембра др Лаура Хоуп (*Dr. Laura Margaret Hope*), епидемиолог, са супругом др Чарлсом Хоупом (*Dr. Charles Hope*). Главна медицинска сестра је била госпођица Беси Дора Баухил (*Miss Bessie Dora Bowhill*). За преводиоца др Инглис је ангажовала Ани Христић (*Miss Annie Christitch*) [3], новинара „Дејли Експреса" а унуку Николе Христића, познатог српског политичара. Др Душан Копша је био задужен за координацију са Болницом шкотских жена. Када се др Солто разболела од дифтерије, дошла је др Елси Инглис са својом екипом да је замени.

Болница у Крагујевцу била је намењена за хирургију, са 100 постеља, али избијањем велике епидемије примала је оболеле од пегавог тифуса и других инфективних болести. Болница је одиграла важну улогу у време велике епидемије пегавог тифуса. У великом повлачењу јединица, под командом др Елси Инглис, из Крагујевца се повукла у Крушевац, где ће радити у болници „Цар Лазар" до репатријације, фебруара 1916.

За заслуге и пожртвованост у време велике епидемије пегавог тифуса у Србији др Елеонор Солто је одликована Орденом Светог Саве, трећег реда.

Друга јединица Болнице шкотских жена у Ваљеву

Друга јединица Болнице шкотских жена у Ваљеву (Слика 4) деловала је под руководством др Алис Хачинсон (*Dr. Alice Hutchinson*, 1874–1953), која је рођена у Индији. Била је то пољска болница смештена испод 40 шатора, са особљем од 50 чланица, капацитета 250 постеља. Постављена је на обронцима изнад Ваљева, на Крушику, недалеко од касарне Петог пука. Лекарску екипу су чинили: др Мери Филипс (*Dr. Mary Elizabeth Phillips*), др Мери Бигнолт (*Dr. Mary Florence Bignolt*), др Алис Шарп (*Dr. Alice C. Sharp*), од јула др Сибил Луис (*Dr. Sybil Lonie Lewis*) и од августа др Елен Портер (*Dr. Ellen Porter*).

Јединица је била опремљена за хирургију, али је примала рековалесценте, пацијенте са старим неизлеченим ранама и стомачним проблемима. Др Милован Бањовић, који је завршио медицину у Русији, био је задужен за координацију са Болницом шкотских жена.

Др Инглис је посетила болницу и записала: „То је тако лепа болница. Болница је испод шатора, на обронцима с погледом на југ. Велики шатори за пацијенте, а мали за особље" [4].

Као руководилац Болнице шкотских жена у Ваљеву, др Хачинсон је радила од јуна 1915. до новембра 1915. Елис Хачинсон је била кћи др Џона Хачинсона, члана Британског војног санитета у Индији. Дипломирала је

Слика 3. Др Грејс Еленор Солто (1877–1962)
Figure 3. Dr. Grace Eleanor Soltau (1877–1962)

Слика 4. Болница шкотских жена у Кардифу, пре поласка за Ваљево
Figure 4. The Scottish Women's Hospital in Cardiff, before leaving for Valjevo

Слика 5. Др Беатрис Ен Макгрегор (1873–?)
Figure 5. Dr. Beatrice Anne MacGregor (1873–?)

Слика 6. Баронеса Евелин Хаверфилд (1867–1920)
Figure 6. Honorable Eveline Haverfield (1867–1920)

медицину 1903. на Универзитету у Единбургу. Имала је претходно искуство лекара у тропским и епидемичним просторима, пошто је била лекар у време епидемије колере у Индији. У Првом балканском рату била је у саставу женске јединице у Бугарској.

По окупацији Србије, др Хачинсон се са чланицама Болнице шкотских жена придружила медицинској мисији др Џејмса Берија у Врњачкој Бањи. Мисија на челу са др Хачинсон репатрирана је фебруара 1916. преко Мађарске и Швајцарске.

Трећа јединица Болнице шкотских жена у Младеновцу

По договору др Вилијема Хантера и др Елси Инглис одлучено је да Младеновац буде седиште рада Шкотске болнице за заразне болести, са комплетном болничком опремом под шаторима са 400 постеља. Поред тога, усвојено је да се у Младеновцу оснује станица за карантин, јер је варош на важној железничкој раскрсници иза друге, треће и прве армије [5, 6].

„Пројекат који је на крају био оформљен био је идеја пуковника Хантера. Он је предложио формирање три 'блокирајуће' болнице на северу Србије чији би задатак био да зауставе ширење зараза по целој земљи до јесени, кад Срби планирају да започну своју офанзиву. Др Инглис је много пута путовала горе-доле по Србији како би оформила три Болнице шкотских жена у Ваљеву, Лазаревцу и Младеновцу, које ће држати ту линију блокаде од зараза. Убрзо након др Инглис, др Елис Хачинсон и њена јединица су пристигле у Србију са 'најбољом пољском болницом која је икад послата на Балкан'. Лазаревац и Младеновац су били под командом др Холвеј и др Макгрегор. Др Инглис је преузела руководство болнице за повратну грозницу у Крагујевцу, које су радиле уједно, тако да је ускоро било четири ефикасне Болнице шкотских жена у Србији" [2].

Трећа јединица Болнице шкотских жена радила је под руководством др Беатрис Ен Макгрегор (*Dr. Beatrice Anne MacGregor*). Лекарску екипу су чинили: др Џенет Меквеа (*Dr. Janet Annie Macvea*) и др Елизабет Брук (*Dr. Elizabeth H. Brook*). Главне медицинске сестре биле су Ени Браун (*Miss Annie M. Brown*) и Нора Холвеј (*Miss Nora Hollway*), а администратор Гертруд Парес (*Miss Gertrude Pares*). Овој екипи се од јуна 1915. придружила и Вера Холм (*Vera Holme*), возач амбулантних кола, глумица, позната по активностима у сифражетском покрету. Болница шкотских жена у Младеновцу радила је од јуна до новембра 1915.

Др Беатрис Макгрегор, Шкотланђанка из Единбурга, дипломирала је медицину на Медицинском факултету Универзитета у Глазгову, а од 1899. радила је у Краљевској болници за мајку и дете у Единбургу (Слика 5).

Током стишавања епидемије и почетком лета др Макгрегор је у Младеновцу отворила диспанзер за мајку и дете. Овај диспанзер је био посвећен локалном становништву и за две недеље примљено је око 700 пацијената. По окупацији Србије, др Макгрегор је евакуисала болницу у Крагујевац, где је организовала амбуланту за хитну помоћ, која је примала и по 400 пацијената на дан. Из Крагујевца она се са својом јединицом повукла у Краљево, где је такође отворила амбуланту. Др Макгрегор је 5. новембра 1915. преузела команду једног дела британске медицинске мисије и придружила се колони српске војске у великом повлачењу. Србија је др Макгрегор одликовала Орденом Светог Саве, четвртог реда.

Војници Моравске дивизије, I позива, 1915. су сазидали меморијалну чесму, у знак сећања на хуманост и медицинску помоћ Болнице шкотских жена и њеном оснивачу и руководиоцу др Елси Инглис. На споменчесми у Младеновцу, на Црквенцу, стоји натпис: ЗА УСПОМЕНУ НА САНИТАРНЕ МИСИЈЕ ШКОТСКИХ ЖЕНА У СРБИЈИ И ЊИНОГ ОСНИВАЧА ДР ЕЛСИ ИНГЛИС.

Четврта јединица Болнице шкотских жена у Лазаревцу

Четврта јединица Болнице шкотских жена у Лазаревцу деловала је под руководством др Едит Блејк Холвеј (*Dr. Edith Blake Hollway*, 1874–1948). За администратора постављена је баронеса Евелин Хаверфилд (*Honorable Eveline Haverfield*, 1867–1920) (Слика 6) [7]. У екипи др Холвеј било је неколико медицинских сестара и болничарки. Домаћица болнице била је госпођа Мери Хјуз Грин (*Mrs. Mary Hughes Green*), која ће остати најдуже са Србима. Она је радила у Лазаревцу, окупираном Крушевцу, у Ајачију на Корзици и Острову, на Солунском фронту. По ослобођењу, Мери Грин се враћа у Србију као администратор Болнице шкотских жена у Врању, под руководством др Изабел Емсли.

У време санирања велике епидемије пегавог тифуса одлучено је да се постави једна блокирајућа болница у Лазаревцу, пошто је варошица била важна спона на путу Ваљево–Младеновац. Болница је имала капацитет 200 постеља и била је смештена у осам приватних кућа. У повлачењу особље се придружило осталим Шкотским женама, на челу са др Инглис. У време окупације, др Холвеј је са својим чланицама наставила да ради у болници „Цар Лазар“ у Крушевцу, одакле су све Шкотске жене репатриране у домовину фебруара 1916. преко Мађарске и Швајцарске.

REFERENCES

1. Popović-Filipović S, Filipović B. Doktor Elsi Inglis na čelu Bolnice škotskih žena u pomoć srpskom narodu u Prvom svetskom ratu. Zbornik radova sa III naučno-stručnog skupa Istorija medicine, farmacije, veterine i narodna zdravstvena kultura, 29–30. septembar 2011. Zaječar.
2. McLaren ES. Elsie Inglis: the Woman with the Torch. Chepter X Serbia. England: 1920.
3. Popović-Filipović S. Hrabrost između redova. Ani Hristić u Srbiji i vreme odvažnih. Beograd: Društvo istoričara Srbije "Stojan Novaković"; 2015.
4. Balfour F. Dr. Elsie Inglis. London: Hodder&Stoughton; 1918. p. 178–9.
5. Hanter W. Epidemije pegavog tifusa u Srbiji 1915. Novi Sad-Beograd: Prometej-Radiotelevizija Srbije; 2016.
6. Leneman L. In the Service of Life. The story of Elsie Inglis and the Scottish Women's Hospitals. Edinburgh: The Mercat Press; 1994.
7. Popović-Filipović S. Škotska baronesa Evelina Haverfield, nosilac srpskog Ordena Belog orla. Pančevo: Mali Nemo; 2012.

Elsie Inglis (1864–1917) and the Scottish Women's Hospitals in Serbia in the Great War – Part 1

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SUMMARY

The news about the great victories of the Gallant Little Serbia in the Great War spread far and wide. Following on the appeals from the Serbian legations and the Serbian Red Cross, assistance was arriving from all over the world. First medical missions and medical and other help arrived from Russia. It was followed by the medical missions from Great Britain, France, Greece, the Netherlands, Denmark, Switzerland, America, etc. Material help and individual volunteers arrived from Poland, Canada, Australia, New Zealand, Ireland, Norway, India, Japan, Egypt, South America, and elsewhere. The true friends of Serbia formed various funds under the auspices of the Red Cross Society, and other associations. In September 1914, the Serbian Relief Fund was established in London, while in Scotland the first units of the Scottish Women's Hospitals for Foreign Service were formed in November of the same year.

The aim of this work was to keep the memory of the Scottish Women's Hospitals in Serbia and with the Serbs in the Great War. In the history of the Serbian nation during the Great War, a special place was held by the Scottish Women's Hospitals – a unique humanitarian medical mission. It was the initiative of Dr. Elsie Maud Inglis (1864–1917), a physician, surgeon, promoter of equal rights for women, and with the support of the Scottish Federation of Woman's Suffrage Societies. The Scottish Women's Hospitals, which were completely staffed by women, by their participation in the Great War, also contributed to gender and professional equality, especially in medicine. Many of today's achievements came about thanks to the first generations of women doctors, who fought for equality in choosing to study medicine, and working in the medical field, in time of war and peacetime.

Keywords: World War I; Scottish Women's Hospitals, physicians, women; Scotland; Serbia; Inglis E.

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ИСТОРИЈА МЕДИЦИНЕ / HISTORY OF MEDICINE

Др Карло Кико (Karol Kiko, 1813–1869) – један од Словака у српском санитету у 19. веку

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САЖЕТАК
Др Карло Кико је био један од бројних лекара из некадашњег Аустријског царства који су у 19. веку живели и радили у Кнежевини Србији. Рођен је у Ухровецу, у Словачкој, која је тада била у саставу Мађарског краљевства – дела Аустријског царства. За доктора медицине промовисан је у Пешти 1845. године. У млађим годинама бавио се алтернативним начинима лечења, истраживао је лековито биље и минералне воде и објавио неколико стручних радова. Био је редован члан Краљевског мађарског природословног друштва. Као лекар у саставу трупа генерала Мора Перцела, учествовао је у Мађарској револуцији 1848/49. Кико је у Србији провео последњих једанаест година живота радећи као физикус Округа књажевачког, лекар београдске општине и војни лекар – хирург Војне болнице у Београду. Иако се и данас у Тренчинском крају, из ког је потекао, сматра угледном личношћу, у Словачкој није познато да је живео и преминуо у Србији. Циљеви овог рада су заокружење Кикове биографије „српским периодом" и представљање личности једног делатника у српском санитету у прошлости.
Кључне речи: Карло Кико; физикус; лекар; Словачка; српски санитет

УВОД

Уређење здравствене службе у Кнежевини Србији, започето на основу краткотрајног Сретењског устава (1835) и тада донетих законских аката, систематски је спроведено након доношења Четвртог хатишерифа – Турског устава (1838), установљењем Санитетског одељења Министарства унутрашњих дела. У делокруг Одељења, све до оснивања Главне војне управе (1859), спадали су и цивилни санитет (карантински санитет и физикат) и војни санитет. Број лекара у Србији се током година континуирано повећавао, али је све до Првог светског рата био недовољан према растућим потребама државе. До 1855. године, када је Београђанин Стеван Милосављевић промовисан за доктора медицине у Паризу, сви лекари у Србији били су страни држављани, већином из Аустријског царства. Поред војвођанских Срба, највише је било Словена. Чак и када су од шездесетих година 19. века почеле да стасавају генерације Србијанаца лекара, они су и даље били у мањини, те су странци и „пречани" још годинама преовлађивали у лекарским редовима. Многи од њих су се у Србији трајно настанили и својим радом значајно допринели њеном културном напретку. Међу њима је можда највише било Чеха и Пољака. Од Словака, којих је било нешто мање, посебно су заслужне и знамените личности др Јанко Шафарик (1814–1876), др Карло Пацек (1807–1876) и др Карло Белони (1811. или 1812–1881). Њихов земљак др Карло Кико, иако није оставио тако дубок траг, био је вредан и предузимљив делатник у српском санитету. У српској историографији његово име се само спорадично спомиње и могло би се рећи да је садашњим генерацијама историчара медицине остао непознат. У Словачкој, међутим, у крају из ког је потекао, Кико се сматра истакнутом личношћу, али се не зна да је живео и радио у Србији. Наиме, на сајту Јавне библиотеке Михала Решетку у Тренчину (*Verejná knižnica Michala Rešetku v Trenčíne*) доступни су публиковани календари годишњица важних догађаја у Крају Тренчин. Подаци о Кику налазе се у календарима за 2013. и 2017. годину. У календару за 2013. годину наведено је да је пре 200 година, 14. 12. 1813. године[1], у селу Ухровецу, у Тренчинском крају, рођен др Карло Кико, „лекар, ботаничар, народни културни делатник, чија је дисертација посвећена флори Тренчинског краја" [1]. У календару за 2017. годину наведено је да је Кико преминуо у Будимпешти 1847. године [2]. Осим у поменутим календарима, на Киково име наилази се и у другим словачким публикацијама новијег датума. Као једна од истакнутих личности родом из Ухровеца, споменут је 2008. године у часопису Тренчинског универзитета. Као чувени Ухровчани, у чланку су такође наведени Људовит Штур (*Ľudovít*

[1] У овереној копији Кикове докторске дипломе, која се налази у Архиву Србије (АС, МУД – С, 1858, V, 1), стоји да је Кико стар 26 година („Carolus Kiko, annorum viginti sex"), што би значило да се родио 1819. године. Међутим, тај податак подвучен је двоструком цртом, што би могло да указује и на грешку.

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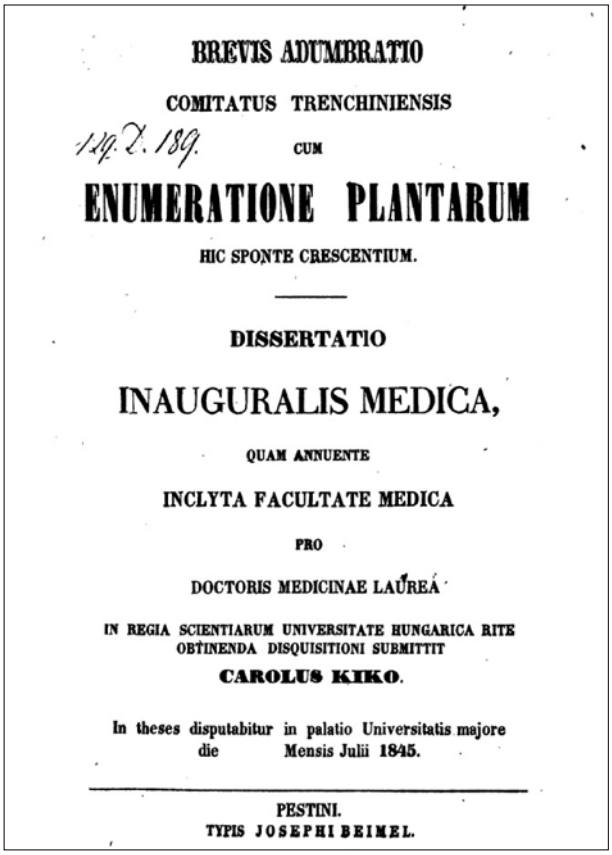
Štúr, 1815–1856)[2], филозоф, политичар, књижевник и кодификатор словачког језика и Александар Дубчек (*Alexander Dubček*, 1921–1992), политичар, комуниста, један од идејних вођа Прашког пролећа (1968) [3].

Кико је у Србији провео последњих 11 година живота. У Србији је, у Београду, и преминуо 6/18. новембра 1869. године. Био је први физикус Књажевачког округа, београдски општински лекар задужен за Варошку и окружну болницу и војни лекар. У Београду се бавио и приватном лекарском праксом.

ЖИВОТ И РАД ДР КАРЛА КИКА У АУСТРИЈСКОМ ЦАРСТВУ

У недостатку података о Киковом одрастању, могуће је само претпоставити да је похађао основну школу у родном Ухровецу, у којој је учитељ био Штуров отац.[3] У млађим годинама био је под утицајем идеја Словачког националног покрета, који се залагао за јачање националног идентитета Словака и за њихова национална права у оквиру Мађарске, односно Аустријског царства чији је Мађарска била део. У хронолошком следу до сада пронађених података, први податак односи се тек на 1842. годину. Ладислав Сивак наводи да је те године Кико као окружни лекар Тренчинског округа описао изворе минералних вода бање Белушка слатина [4]. Будући да је Кико тек три године касније одбранио докторску дисертацију на пештанском Медицинском факултету, може се претпоставити да је дужност обављао као апсолвент медицине. Поменути опис минералних вода Белушке слатине у ствари је само један део обимне студије под насловом „Тренчински крај, са посебним осврtом на лековите воде", коју је 1842. године објавио у часопису Атенеум [5]. У њој је, на основу сопствених истраживања у преко 30 села, описао физичке и хемијске карактеристике вода и њихове изворе, као и начине на које их локално становништво користи. Својом студијом желео је да скрене пажњу јавности на занемарено природно богатство Тренчинског краја. ИзИкове заинтересованости за природу проистекла је и његова поменута дисертација под насловом „Кратак приказ са листом биљака које спонтано расту у Тренчинском округу" (*Brevis adumbratio comitatus Trenchiniensis cum enumeratione plantarum hic sponte crescentium, Pestini, Typis Josephi Beimel*, 1845) (Слика 1).

Након одбране дисертације и стицања звања доктора медицине јула 1845, Кико је остао у Будимпешти и започео приватну лекарску праксу. У то време бавио се и магнетотерапијом, електротерапијом помоћу галванских струја, а такође и „животињским магнетизмом" – месмеризмом [6]. Свим тим методама изазвао је пажњу у медицинским круговима и у јавности. На позив др Пала Бугата (*Bugát Pál*, 1793–1865), оснивача и председника Краљевског мађарског природословног друштва,



BREVIS ADUMBRATIO

COMITATUS TRENCHINIENSIS

cum

ENUMERATIONE PLANTARUM

HIC SPONTE CRESCENTIUM.

DISSERTATIO

INAUGURALIS MEDICA,

QUAM ANNUENTE

INCLYTA FACULTATE MEDICA

PRO

DOCTORIS MEDICINAE LAUREA

IN REGIA SCIENTIARUM UNIVERSITATE HUNGARICA RITE OBTINENDA DISQUISITIONI SUBMITTIT

CAROLUS KIKO.

In theses disputabitur in palatio Universitatis majore die Mensis Julii 1845.

PESTINI.
TYPIS JOSEPHI BEIMEL.

Слика 1. Насловна страна докторске дисертације Карла Кика (извор: http://disszertaciok.orvostortenet.hu)
The cover page of the doctoral dissertation of Karol Kiko (source: http://disszertaciok.orvostortenet.hu)

Кико је на састанку Друштва 21. октобра 1845. године, којем је присуствовао као гост, прочитао свој есеј о магнетотерапији и месмеризму и приказао два болесника која је тим начинима лечио [7]. У часопису *Orvosi Tar* штампан му је затим приказ случаја девојке коју је излечио од афазије и глувоће [8]. За редовног члана Друштва изабран је на седници одржаној 4. новембра 1845. године [9]. Лист Орао татрански (*Orol Tatránski*), литерарни додатак Словачких народних новина (*Slovenských národných novín*), које је покренуо и уређивао Људовит Штур, с поносом је објавио чланак о Киковом успеху и избору за члана Друштва у рубрици *Славјанске вести*: „Наш земљак, др Карло Кико, практични лекар у Пешти, изазвао је велику пажњу својим магнетичким начином лечења. Излечио је такве болеснике, које ни један лекар није могао излечити..." [10]. Вест из Орла татранског пренела је и Даница Људевита Гаја [11].

У другој половини четрдесетих година Кико је био активан и на националном пољу. Као припадник групе „Пештанских Словака – љубитеља словачког језика", био је потписник апела подршке „штуровском језику" – новом књижевном словачком језику који је увео Људовит Штур[4] [12]. Поред тога, у политичком листу

[2] Људовит Штур је био кореспондентни члан Друштва српске словесности (изабран 7. августа 1844).

[3] Школска кућа и данас постоји и знаменита је по томе што су у њој рођени Људовит Штур, и век касније Александар Дубчек.

[4] За разлику од панслависта Колара (*Ján Kollár*, 1793–1852) и Павла Шафарика (*Pavel Jozef Šafárik*, 1795–1861), који су Чехе и Словаке сматрали једном нацијом и залагали се за усвајање заједничког, чехословачког језика, Штур је заступао став о посебном националном

Пријатељ народа (*Priateľovi ľudu,* 1848–1849) објавио је један просветитељски чланак под насловом „Савети за дом и домаћу економију" (*Rady pre dom a hospodárstvo*) [13]. У то време већ је имао и породицу – био је ожењен Борбалом Шефт (*Borbala Scheft*), а у Будимпешти му је рођена ћерка Малвина (*Malvina Alojsia Josefa Kiko*), која је крштена 10. маја 1846. у католичкој цркви [14].

По избијању Мађарске револуције марта 1848, Кико се прикључио Мађарској националној гарди, што је иначе била обавеза свих виђенијих људи у Будимпешти. Прво је био лекар 4. чете IV пештанског батаљона [15], а затим шеф санитета Хуњади – корпуса (касније 50. Хонведски батаљон) под командом генерала Мора Перцела (*Perczel Mór*, 1811–1899). Новембра 1848, због неких сукоба са официрима желео је да дâ оставку на то место [16], али је на дужности остао и даље – јануара и фебруара 1849. године био је шеф Војне болнице у месту Карцаг [17, 18]. За сада остаје непознато да ли је Кико био у Перцеловим трупама и за време њиховог похода у Војводини. Током пролећа и лета 1849. године Перцелове трупе су нападале српска села, сукобљавале се са српском добровољачком војском и починиле злодела над цивилним становништвом – убијено је између четири и пет хиљада људи и попаљено више села [19]. Јуна 1849. године Кико је од Лајоша Кошута (*Kossuth Lajos*, 1802–1894) затражио постављење за штаб-доктора (главног војног лекара), али исход те молбе није познат [17]. У молби за запослење коју је поднео Министарству унутрашњих дела Кнежевине Србије 29. јануара 1858. године, Кико, међутим, не наводи чиме се бавио између 1846. и 1850. године. То би могло да значи да је податак о учешћу у Мађарској револуцији изоставио намерно, због могућег негативног утицаја на одлуку српских власти о његовом ангажовању. Кико је молбу упутио из Сремске Митровице, где је тада био приватни лекар. У њој је навео следеће:

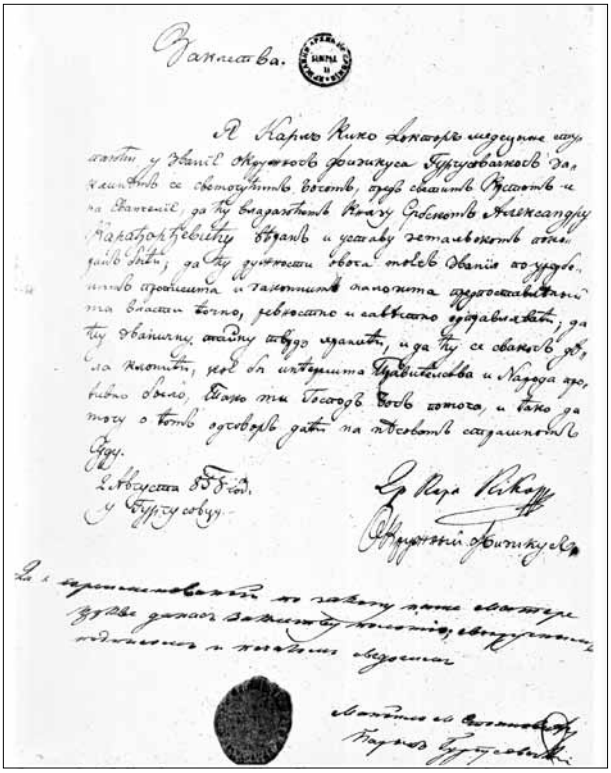
– Године 1845, као „суплирајући професор Невристичне Терапије", предавао је у Пешти „ову Науку" (што потркепљује са два сведочанства издата од стране Краљевског мађарског природословног друштва);
– Од 1851. до 1853. био је „Царско-краљевске фамилије лекар спахилука названог Рацкеве и Промонтор" (што потврђује посебан документ у прилогу);
– Од 1854. до 1856. био је „лекар трговаца Ковиначки, од ови нарочито тога ради позват. У исто време, од 1854. до 1856, док је у Ковину био, испуњавао је и дужности Полковског и Ротског лекара, осим тога по налогу високославне Државе испуњавао је и дужности Санитетског референта код Ковинског растељанства" (што потврђују два документа у прилогу) [20].

Осим поменутих сведочанстава, приложио је и копију докторске дипломе. У последњој тачки молбе навео је да „осим ови у речи познати језика[5] јесте и у Турскому и Дакороманском говору и писању искусан". Подаци о познавању језика, посебно српског, били су увек тражени од оних који аплицирају за запослење у Србији. Кико, дакле, није навео да зна српски језик, иако је молба писана на српском. У једном допису Министарства унутрашњих дела Државном савету наводи се, међутим, да он „говори и пише српски" [20]. У сваком случају, ако и није знао српски језик, Кико га је брзо савладао.

ЖИВОТ И РАД ДР КАРЛА КИКА У КНЕЖЕВИНИ СРБИЈИ

Физикус Округа књажевачког

Кикова молба односила се конкретно на место општинског лекара у Неготину, за које је, како је написао, „дознао да ће се ускоро установити". Решењем министра унутрашњих дела од 28. маја / 9. јуна 1858. он је то место добио, али је пре ступања на дужност Министарству упутио нову молбу (6/18. јула 1858), овог пута за место окружног физикуса у Округу гургусовачком. Указом кнеза Александра Карађорђевића од 23. јула / 4. августа 1858, постављен је за физикуса Округа гургусовачког, а у дужност је уведен 5/17. августа, након полагања заклетве и потписивања уговора [20] (Слика 2). Тако је Кико, уместо да постане први градски лекар у Неготину, постао први физикус



Слика 2. Копија заклетве др Карла Кика при ступању у службу физикуса Округа гургусовачког (извор: Архив Србије, МУД – С, 1858, V, 1)
The copy of the oath Dr. Karol Kiko had taken before undertaking the duties of the physician of the Knjaževac (former Gurgusovac) County (source: Archives of Serbia, MUD – S, 1858, V, 1)

идентитету Словака и о посебном словачком језику. За основу новог словачког књижевног језика узео је централно-словачки дијалект.
[5] Словачки, мађарски, немачки и латински језик.

Округа гургусовачког.[6] Наиме, Округ гургусовачки је био један од округа који је због недовољног броја доктора медицине у Србији уместо окружног *физикуса* (доктора медицине) имао *окружноī лекара* – лекара нижег медицинског образовања (магистра хирургије). Министарство унутрашњих дела, међутим, желело је да лекарско место у Гургусовцу „преобрати у физикат", а један од важнијих разлога је било постојање „добро уређене окружне болнице" у тој вароши [20].

Из сачуваних архивских извора види се да је Кико с вољом прионуо на нови посао. Поред бројних редовних дужности, трудио се да уведе корисне новине како у окружној болници, за коју је такође био задужен, тако и у искорењивању сифилиса који је у источној Србији, а посебно у том округу, био ендемски распрострањен. Управо због великог броја оболелих од сифилиса, као прва окружна болница у Србији, 1851. године била је установљена књажевачка болница. Кико је убрзо по ступању на дужност изнео предлог да се за болницу ангажује један свештеник из округа „из узрока тога: што се у болници и такови болестници примају, о којима се не зна какав ће конац болест њиова имати, за који случај добро би било, да се такови болестници молитвом и совјетом пастирским подкрепе". Дужност свештеника била би и да болесницима објашњава да је неопходно да се придржавају лекарских савета, посебно у погледу прописане дијете. Дијета је нарочито наглашена због тога што је, „као и сами лекови, необходимо нуждна", а често се „са правилима наше Цркве несложи". Ту је свакако мислио на време поста, којег се народ строго придржавао чак и у болести. Предлог, који су подржали и Начелство и Министарство унутрашњих дела, упућен је Министарству просвете и црквених дела на решење. Вероватно је био и одобрен, тим пре што је Министарство унутрашњих дела одредило да се то ванредно ангажовање свештеника плаћа из окружног болничког фонда [21]. У то време ни Београдска болница још није имала свештеника.

Убрзо потом Кико је директно Министарству, што је било мимо уобичајене процедуре, која је подразумевала да се дописи упућују преко окружних начелстава, поднео „повремено известије" о стању окружне болнице. У кратком садржају дописа забележеном у Деловодном протоколу Санитетског одељења стоји да Кико „излажући у исто време и препоне неке које му се од стране окружног казначеја у уређењу истог полажу, моли да се те уколне" [22]. Као што ће се видети, он је са званичницима Начелства и касније имао проблема, а током целе 1859. године Министарству је своје „повремене извештаје" слао директно. Други Киков предлог, који се односио на искорењивање сифилиса, садржао је две мере. Прва је била забрана венчавања уколико и младић и девојка немају потврду окружног физикуса о стању свог здравља, а друга увођење обавезе болничког лечења свих лица код којих се примете знаци сифилиса [23]. Прва мера била је сасвим налик на забрану венчавања невакцинисаних лица која је већ постојала као једна од противепидемијских мера за велике богиње. Колико је познато, ове мере нису биле усвојене. У погледу вакцинације становништва против великих богиња, Кико је у свом округу очигледно постигао значајан успех. Познато је да су вакцинација, а поготово ревакцинација, у 19. веку углавном спровођене с великом муком због отпора у народу. Из извештаја о вакцинацији 1858. године, коју је обавио Киков претходник – окружни лекар Јосиф Вардијан, види се да је број вакцинисаних лица био свега 2349, од којег је само једно лице било ревакцинисано. Кикова примедба у извештају била је да је протокол вакцинације био „врло хрђаво вођен" [24]. Међутим, идуће године десило се нешто за оно време необично: народ књажевачког округа долазио је сам на вакцинисање „и не само да је децу доводио, но су и средовечни људи па и стара лица скупљала се и молила да им се богиње прекаламе". Као посебан куриозитет истакнуто је да су вакцинисане и 74 ромске породице, за које се знало да увек избегавају вакцинацију [25]. О томе су писале Српске новине на основу једног од Кикових „повремених" извештаја Министарству. Тај извештај је у Министарству оцењен као интересантан не само због успеха вакцинације већ и због других података које је садржао, те су неки његови делови представљени у поменутом чланку. Кикова запажања односила су се на стање сеоских школа, које је оценио као „врло занемарене". Запазио је и да деца много страдају од шуге, али да се лекарска помоћ не тражи. Пажњу је обратио и на „старине" описавши неколико цркава од којих су неке биле разрушене, као и један напуштени „рудокоп". На крају, писао је и о природним ресурсима, који су га некада, док је био у Словачкој, посебно занимали. У селу Ргошту пронашао је извор минералне воде која садржи јод, а у Шербановцима је запазио „гомилу кристалисаног гипса, брусова и глимер-шифера" [25].

Током 1859. године Кико је Министарству поднео чак 17 „повремених известија о стању здравља у Округу књажевачком и о стању окружне болнице" [26]. Подстакнут признањем Министарства, извештаје је преточио у студију под насловом „Кратко топографско-историско описаније Округа књажевачког" и послао је Друштву српске словесности [27]. У свом Гласнику Друштво српске словесности је до тада објавило три студије о округзима, од којих су две написали лекари – др Аћим Медовић („Окружије Пожаревачко са земљевидом државописно (и по већој части) повестно описано", 1852) и др Андрија Ивановић („Описаније окружија Крајинскога", 1853). Кикова студија, као ни сами извештаји, није сачувана, али се о њеном садржају понешто може сазнати из рецензије коју је урадио др Јосиф Панчић. Садржала је пет поглавља: I – Величина и границе округа; II – Природна својства округа; III – Природни производи (флора, фауна, руде); IV – Житељство и V – Статистика, археологија и повестница. Кико је уз њу израдио и приложио карту Књажевачког округа и четири скице на којима су при-

[6] Наредне, 1859. године, по одлуци Милоша Обреновића, који је на Светоандрејској скупштини (1858) поново изабран за владара Србије, Гургусовцу је назив промењен у Књажевац, а према томе је и назив округа промењен у Округ књажевачки.

казане неке „стародревне“ грађевине и Суводолски водопад. Међутим, Панчић, који је прегледао прва три поглавља и карту, пронашао је у њима бројне пропусте па и понеки нетачан податак. Свеукупна његова оцена „природописа“ била је да је „одвише површан“, да „ствари тамо наведене – осим поместних имена личе на свако окружје Србије и на ма који брдовити предјел овог света“ те да се њиме „познавање наше земље нимало повећати неће“ [28]. После такве оцене, Друштво је одлучило да дело врати писцу.

Кико се у Књажевцу није дуго задржао – већ наредне године од Министарства је затражио премештај. Томе је вероватно допринео и сукоб који је имао са помоћником Начелства Јованом Протићем. Против Протића Кико је поднео тужбу Министарству наводећи да он „неке хећиме из Турске доводи и лечење им дозвољава“. Протић се бранио навевши да је само једног лекара из Турске, из Ниша, позвао ради лечења своје жене. Закључак Министарства био је да је Кико преувеличао ствар и предмет је стављен у акта [29]. Иако је такав поступак једног званичника нарушавао и ауторитет самог лекара, Кико је првенствено поступао у складу са законом јер је сузбијање надрилекарства била једна од прописаних дужности окружних лекара и физикуса.

Лекар Општине београдске

Баш када се све то догађало, београдска општина је остала без свог лекара др Ђорђа Малаћа, који је душевно оболео и убрзо преминуо [30]. За новог општинског лекара крајем године изабран је Карло Кико, а његов избор Министарство је потврдило 20. децембра 1859 / 1. јануара 1860. године [31]. Главна дужност лекара београдске општине било је лечење болесника у Београдској болници. Осим тога, колико му је време дозвољавало, он је обављао и јавну службу у граду (лечење грађана, вакцинација, послови санитетске полиције, сузбијање надрилекарства и др.) која је иначе била у надлежности градског лекара – физикуса Управе вароши Београда. У то време, Београдска болница, основана 1841. године, још увек није имала прописана правила рада, а и само управљање том институцијом било је доста комликовано. Општина је, као оснивач и власник, водила бригу о Болници, доносила одлуке у вези са унапређењем њеног рада и постављала болничке старатеље, али је последњу реч у свему имало Министарство унутрашњих дела, које је преко свог Санитетског одељења управљало свим болницама у земљи, па и београдском. С друге стране, финансијска питања била су у домену Министарства просвете, чији су задаци били обезбеђивање добротворних фондова за болнице, прикупљање прилога и надзор над коришћењем финансијских средстава [32]. Болница је била финансирана из Болничког фонда, чија се каса до оснивања Управе фондова 1862. године налазила код Београдског примирителног суда. Старатељи су водили рачуне болничких прихода и расхода, спроводили лицитације за набавке и вршили исплате по рачунима. Непосредан надзор над радом болнице вршила је Управа вароши Београда. За сва питања у вези с Болницом, Општина и старатељи обраћали су се преко Примирителног суда Управи вароши, која је њихове дописе и извештаје, уз своје мишљење, слала поменутим министарствима, према њиховим надлежностима. Надзор над радом општинског лекара вршио је градски физикус. Његовим извештајима о стању здравља у граду прикључивани су извештаји општинског (болничког) лекара, те су заједно подношени Управи вароши и прослеђивани Министарству. Кико је био београдски општински лекар скоро четири и по године, а за све то време градски физикус је био др Јован Машин (*Jan Mašín*, 1820–1884).

Иако је постојала готово две деценије, Болница је почетком шездесетих година, дакле у време када је Кико преузео дужност њеног лекара, била установа са бројним проблемима. Још увек смештена у изнајмљеној приватној кући која није одговарала болничкој намени, оскудевала је у разним потребама, а персонал је био малобројан, нестручан и углавном немаран према свом послу. Баш уочи Киковог доласка, због немарности је отпуштен дотадашњи надзиратељ, чије су дужности иначе биле надгледање болесника, набављање потрепштина и чување болничких ствари. У извештају о Болници упућеном Управи вароши Београда 5/17. новембра 1859. године Београдски примирителни суд пише како су Суд и Општина имали „доста прилике наслушати се и известити, како се тамо бедно болесници негују, па ово рђаво надгледање заједно са нечистоћом, не лечи и’, но управо сатире и упропашћује тако, да је већ болница наша кужном називати се почела“ [33]. Болница је била намењена првенствено сиромашним Београђанима и житељима Београдског округа које није имао ко да негује у случају болести, али је примала и становнике других округа Србије, као и странце. У њој су лечени болесници различитог пола, животног доба и вероисповести, који су, осим ретких изузетака, потицали из нижих друштвених слојева. Трошкови њиховог лечења у највећем броју случајева подмиривани су из Болничког фонда. Болница је, такође, примала и амбулантне пацијенте. У то време имала је капацитет од 26 постеља, али је током једног месеца лечено и до седамдесет лица. Према врстама болести, нешто већи број болесника лечио се од „унутрашњих“ него од „спољашњих“ болести. Поред мањих хируршких интервенција као што је „пуштање крви“, понекад су вршене и неке веће операције – Кико наводи да је у јулу 1860. извршио операцију код болесника са експлозивним повредама шаке, а да је у новембру исте године извршио „три знатне операције“. У болницу су примани и душевни болесници, што је изазивало негодовање и жалбе болничког лекара и градског физикуса.[7] ИзИкових и

[7] Упуте за лечење у Болници издавала је полиција (старешине градских квартова који су били чиновници Управе града), а болесници су понекад такође примани по налогу Министарства унутрашњих дела. Прва душевна болница – Дом за с’ ума сишавше, основана је 1861. године у Београду, али су душевни болесници и након њеног оснивања понекад примани у Београдску болницу.

Машинових месечних извештаја с почетка 1860. године види се да је стање у Болници било нешто побољшано после жалби које је Суд изнео у поменутом извештају. У извештају за фебруар Кико, на пример, пише како „болница ове вароши сасвим напредује само да би се још главне таблице и диеталне прописе скорим у ред доводили". О повољном стању у то време извештава и Машин: „Варошка болница снабдевена је сада прилично свим потребама и у овој се обдржава пожелателни ред и чистоћа". Али позитивна мишљења која су очигледно била и плод ентузијазма лекара након малих побољшања, крајем године замениле су све оштрије критике. У извештају за септембар Кико пише да је „од почетка ове варошке болнице, економическа управа или никака или најгора била", да се „њени трошкови месечно показују и опет болница сасвим оскудева" и да су „сви предлози и докази остали безуспешни и остаће све тако докле Правитељство сâмо њену управу на себе не преузме" [34]. Три месеца касније износи још детаљније замерке: „Овде се то не пропушта приметити и тим пре што се година текућим месецом скончава, да болница вароши Београда до сад без мерне у име ране болесника прави трошкове, и при свем том како рана тако и послуга у највећој неуредности налазе се. Диеталне цедуље или наредба диетална бадава се преписивала, јер сваки дан једна се кувала чорба и по глави болесника по оке леба се рачунало, при тако неуредне економије, не може се сходно лечење болесника закључевати. Надамо се да концем ове године и почетком нове године и уредна економија болницу нашу за цело увећа [34]". До значајних промена у Болници није, међутим, дошло још неколико година, и поред свих жалби њеног лекара и молби које су Министарству унутрашњих дела упућивале београдска општина и Управа вароши. О проблемима болничког живота, али и о Киковим ставовима према њима, сведоче и документа о једном догађају из времена турског бомбрадовања Београда 1862. године. Наиме, један рањеник, Ј. Д., при отпусту из Болнице добио је одобрење од Кика да остале рањенике почасти ракијом. Томе се, међутим, у Киковом одсуству, успротивио надзорник Болнице Јован Поповић, који је, према жалби коју је Ј. Д. поднео Управи вароши, овога ошамарио, опсовао му оца и мајку и одузео му ракију. Ј. Д. је истом приликом оптужио Поповића за нахат у вршењу дужности навевши да су „две девојке ономад умрле јошт у вече без свеће, а он је сутра дан чак у 6 сати нашо мртве и ненадгледане". Поповић је позван на саслушање у Управу вароши, а од Кика је такође затражена изјава о целом догађају. У њој Кико износи и следеће: „Оно што имам приметити, то: да се у ововарошкој болници, распусни и гадниви болесници налазе, који никаковых закона, и никакове власти не припознају; (...) опет се свима наредбама противе и против раде, тако да и најбоље нарави Човек, увиђајући неуредност оваку, мора се разбеснити и огорчити, тим пре, што види свој труд, и негу у залуд бачену. То се само тим пре опростити може надзиратељу болнице, што он каткад и изванредно, са таковима поступати мора, кад он – надзиратељ, дан и ноћ са овима посла има (...) кад ја, као управитељ ове болнице више пута, од таковых болестника, и визиту прекинути морам, власт у помоћ звати, принуђен сам. Истина, да је то погрешно било, кад ови надзиратељ Ј. ударио био, и опет из горенаведени узрока, а особито зато, што надзиратељ тачно своја дјела извршава – чистоћу набљудава, и моје наредбе извршавати се усиљава – може се оправдати. Што се тиче ове две девојке, лако се догодити може, да се час умирања не зна, или заборави, а то је тим пре могућно, кад у једној собици, девет женски опасно болујући лица скупљена леже, а у другим собама 40 болујући лица, само два служитеља негују" [35]. Да је Кико и у таквим околностима ревносно радио, види се из дописа којим му је августа исте године Управа вароши, као старешини болнице[8], изразила признање и захвалност за стручно и пожртвовано лечење рањених у поменутом сукобу са Турцима [36].

У војној служби

После четири године очигледно напорног рада у Београдској болници Кико је желео да промени службу. Крајем 1863. године конкурисао је за место професора судске медицине на Великој школи, али га није добио, јер је програм предмета који је поднео Академском савету Велике школе оцењен као „више удешен за медицинаре" и тиме неодговарајући за катедру Правног факултета [37]. У марту 1864. године дао је оставку београдској општини и ступио је у војну службу као хирург београдске Војне болнице. Али војна служба није била његов превасходни избор – исте године је Министарству унутрашњих дела подносио молбе за постављење на упражњена места физикуса Управе вароши Београда, односно физикуса Округа крагујевачког [38]. Без обзира на то, на новој дужности је био не само савестан већ се, као и раније у Књажевцу, трудио да новинама унапреди службу. Самоиницијативно је започео стручну обуку болничара, несумњиво се користећи искуством стеченим у мађарској војсци. Исте године одржао је први курс за болничаре по програму који је сачинио под насловом „О науци за болничаре и дужности болничара у време рата". Курс је похађало 23 болничара, који су на крају полагали испит пред штабним официрима. Кико је од министра војног био посебно похваљен „за показану ревност у служби". Како је, међутим, боловао од астме, а стање му се с јесени погоршало, одређено је да га надаље у тој дужности замени др Стеван Недок [39]. Када су 1864. године, по Закону о устројству војске, војни лекари подељени у класе, Кико је добио звање хирурга I класе (1865) [40]. Иако су класе војних лекара у рангу одговарале официрским чиновима[9], лекари их у то време нису имали те су фактички били подређе-

[8] У време тих догађаја сви грађански лекари били су привремено примљени у војну службу, те је на тој основи Кико био постављен за старешину болнице.

[9] Звање главног лекара I класе одговарало је чину потпуковника; главног лекара II класе – чину мајора; лекара I класе – чину капетана I класе; лекара II – чину капетана II класе.

ни официрима. Овакво стање било је извор великог незадовољства лекара и многих сукоба између њих и официра. Горчину тог подређеног положаја искусио је и Кико 1865. године, када је неколико пута казнио несавесне болничаре. Болничари су, међутим, били подређени комесару Болнице, који је дефакто био њен управник. Да би се осветили Кику, оклеветали су га код комесара, навевши да он болеснике назива стоком. Комесару није много требало да Кика тужи министру војном и затражи његово кажњавање [41].

Упоредо са званичним дужностима, Кико је у Београду обављао приватну лекарску праксу. Посебно се бавио лечењем венеричних болести. У једном огласу у Српским новинама наводи да „застареле, тајне, и све спољашње болести лечи особитим, на више годишњем искуству основаним начином" [42]. Године 1866, када се у склопу четврте пандемије колере ова болест појавила и у Србији, Управа вароши је позвала све београдске лекаре са приватном праксом да се ангажују у лечењу оболелих. Кико се такође одазвао позиву, а када се епидемија завршила, испоставило се да је од свих лекара он учинио највећи број визита болесницима (398). За свој труд, лекари су били плаћени и награђени на основу указа кнеза Михаила Обреновића од 19/31. октобра 1866. године. Новчане надокнаде одређене су према броју учињених визита, па је Кико добио највећи износ – 53 дуката цесарска и један цванцик. Поред тога, награђен је са 50 дуката [43]. Исте године био је послат и у Лозницу да лечи тамошње житеље оболеле од колере, али се на дужности разболео па је по молби враћен у Београд [44].

Две године касније, у политички турбулентним околностима које су настале након убиства кнеза Михаила, Кико се нашао у једној незавидној ситуацији. Познато је да је као главног виновника злочина тадашња власт окривила кнеза Александра Карађорђевића, а известан број њему блиских људи као саучеснике. Кнез, којем је суђено у Будимпешти, ослобођен је оптужби услед недостатка доказа, али је у Србији, по одлуци Преког суда, погубљено и осуђено на робију више људи. Један од оптужених за саучешће био је и Андра Вилотијевић, надзорник имања кнеза Александра у Србији. Вилотијевић је, као и остали оптужени, у затвору подвргнут тешком мучењу. До тада потпуно здрав, толико је оронуо да је постојала бојазан да неће доживети пресуду. Пошто су у граду већ кружиле приче о мучењима у затвору, Варошки суд је одредио Кика и др Ђорђа Клинковског, физикуса Управе вароши, да прегледају Вилотијевића и утврде од чега болује. Прегледом који су извршили 5/17. јула 1868. нашли су код Вилотијевића „по целом телу на кожи тамно-мрке пегице велике као сочиво" и поставили дијагнозу скорбута [45]. Несумњиво је да су своје мишљење донели под притиском власти.

Вероватно су тај догађај и несигурне прилике које су завладале у земљи били главни разлози за Киково опредељење да коначно напусти Србију. О његовој намери сведочи један запис у дневнику Бењамина Калаја (*Benjamin Kallay*, 1839–1903), тадашњег аустро-угарског изасланика у Србији: „16. новембар 1868. Дошао је к мени Кико, тренутно војни лекар, који би желео да поново ступи у хонведску војску, у којој је раније служио, уколико се она оформи. Обећао сам му да ћу то издејствовати ако икако буде могуће и замолио га да ми са своје стране даје обавештења о одељењу војног санитета, што је и прихватио" [46]. У Калајевом дневнику Кико се даље не спомиње. Да ли је предузимао неке шпијунске активности и да ли је Калају достављао тражена обавештања, за сада није познато. Хонведска војска је у Аустроугарској монархији формирана 5. децембра 1868. године, али Кико није у њу ступио. Преминуо је 6. новембра 1869. године у Београду, после „краће болести" [47].

ЗАКЉУЧАК

Карло Кико је у Србију дошао са богатим искуством које је стекао радећи у Аустријском царству као цивилни, војни и приватни лекар. И после више од петнаест година службе, у средовечном животном добу, и даље је био радозналог и предузимљивог духа. У Србији се поново, као у младости, бавио истраживањем природних појава и ресурса, начина живота и обичаја становништва, старина... Поново је писао, предлагао и уводио новине у служби. За своју стручност, иницијативност и савесно обављање дужности више пута је похваљиван. Али с друге стране, бројне околности биле су извори његових проблема и узроци незадовољства. Због тадашњег начина организације здравствене службе, као окружни физикус делом је био потчињен полицијској власти (Начелству округа), а као лекар Војне болнице официру – комесару Болнице. Нису успела његова настојања да се уздигне на друштвеној лествици – место професора Велике школе није добио, а студија о Књажевачком округу, која је могла да му отвори врата за пријем у Друштво српске словесности, негативно је оцењена. У тешким политичким приликама након убиства кнеза Михаила Обреновића очигледно је био принуђен да делује против своје савести и лекарске етике. На крају, узбурканој Србији која није испунила његова очекивања и чији држављанин никада није постао, Кико није сматрао да дугује лојалност.

ЗАХВАЛНОСТ

Аутор се најсрдачније захваљује госпођама Рожи Маринковић и Жужани Болић (*Zsuzsanna Bolits*) за превод текстова са мађарског језика; др Роберту Херману (*Hermann Róbert*), председнику Мађарског историјског друштва (*Magyar Történelmi Társulat*), за објашњења у вези са ангажовањима др Карла Кика током Мађарске револуције (1848/49) и за помоћ у истраживању, др Зорану Вацићу за уступљени превод књиге Емериха П. Линденмајера „Serbien, dessen Entwicklung und Fortschritt im Sanitätswesen, mit Andeutungen über die gesammten Sanitätsverhältnisse im Oriente".

ЛИТЕРАТУРА

1. Dombaiová P. Kalendár výročí osobností a udalostí v okresoch Bánovce nad Bebravou, Myjava, Nové Mesto nad Váhom a Trenčín v roku 2013 [Internet]. Trenčin: Verejná knižnica Michala Rešetku v Trenčíne; 2012. 39. Available from: http://www.vkmr.sk/buxus/docs/Kalendar_vyroci_2013.pdf.
2. Dombaiová P. Kalendár výročí osobností a udalostí v okresoch Bánovce nad Bebravou, Myjava, Nové Mesto nad Váhom a Trenčín v roku 2017 [Internet]. Trenčin: Verejná knižnica Michala Rešetku v Trenčíne; 2016. 49. Available from: http://www.vkmr.sk/dokumenty/materialy-vkmr/kalendar-vyroci-v-roku-2017.html?page_id=6253.
3. Slávnosti v Uhrovci. TnU Trendy, štvrť ročnik Trenčianskej univerzity Alexandra Dubčeka V Trenčine. 2008; VI(3):4. Available from: www.tnuni.sk/rek/trendy.
4. Sivák L. Kúpele Belušské Slatiny a ich história. Belušan – Noviny občanov Obce Beluša. 2015 júl, august; Číslo 4, 8.
5. Kikó K. Trencsin megye, különös tekintettel gyógyvizeire. Atheneum. 1842 martius 6; (28):433-439; Atheneum. 1842 martius 8;(29):449–57; Atheneum. 1842 martius 10; (30):465–72.
6. Tarjányi E. Jósika Miklós és a mesmerizmus. Irodalomtörténeti Közlemények. 1992; 96(1):54. Available from: http://epa.oszk.hu/00000/00001/00367/pdf/itk00001_1992_01_050-060.pdf
7. 1845-ik év october 21-kén tartott kis gyűlés jegyzökönyve. Orvosi Tar. 1845 Dec 7; VIII (24):384.
8. Kikó K. Tökéletes szótalanság, némaság, érczdeléjjel meggyógyítva. Orvosi Tar. 1845 Nov. 30; VIII(23):357–8.
9. A kir. magyar természettudományi társulat 1845-dik évi november hó 8-kán tartott köz gyűlésének jegyzökönyve. Orvosi Tar. 1846 Jan. 18; IX(4):64.
10. Slovanskje správi. Orol Tatranski. 1846 Jan. 23; 1(19):151.
11. Slavjanske vesti. Danica horvatska, slavonska i dalmatinska. 1846 Feb. 21; XII(8):32.
12. Kačírek Ľ. Národný život Slovákov v Pešťbudíne v rokoch 1850–1875. Békéscsaba: Magyarországi Szlovákok Kutatóintézete/Výskumný ústav Slovákov v Maďarsku; 2016, 102. and Kmeť M. Slovenské dolnozemské enklávy v reflexii Štúrových politických novín. Acta Historica Neosoliensia. 2005(8):93.
13. zlatyfond.sme.sk [Internet]. Hurban Vajanský S. Z dejín literatúry 1. Available from: http://zlatyfond.sme.sk/dielo/1622/Vajansky_Z-dejin-literatury-1/1#axzz4lzuega6S
14. https://familysearch.org/ark:/61903/1:1:XKPP-5Y4.
15. Czaga V, Jancsó É, editors. Pest-Budai nemzetőrök 1848-1849. Dokumentumok a Fővárosi Nemzetőrség történetéhez – Budapest Történetének Forrásai. Budapest: Főváros Levéltára; 2001. p. 419.
16. Hermann R. Perczel Mór első honmentő hadjárata – Zalai Gyűjtemény 36/II. Zalaegerszeg: Zala Megyei Levéltár; 1995. p. 102, 88. Available from: https://library.hungaricana.hu/hu/view/ZALM_zgy_36_2/?pg= 102&layout=s&query=kiko
17. Zétény G. A magyar szabadságharc honvédorvosai. Budapest: Egyetemi, 1948; p. 149.
18. Hermann R. Perczel Mór második honmentő hadjárata és az első szolnoki ütközet. In: Tamás F, editor. Zounuk – A Jász-Nagykun-Szolnok Megyei Levéltár Évkönyve 26. Szolnok: 2011. p. 223. Available from: https://library.hungaricana.hu/hu/view/JNSM_Ek_26/?pg=226&layout=s&query=kiko
19. Mikavica D, Lemajić N, Vasin G, Ninković N. Srbi u Habsburškoj monarhiji 1526–1918, 1. Od Mohačke bitke do Blagoveštenskog sabora 1526–1861. Novi Sad: Prometej i Radio-televizija Vojvodine; 2016. p. 443.
20. Arhiv Srbije (dalje AS), MUD – S, 1858, V, 1.
21. Arhiv Srbije, MUD – S, 1858, V, 25.
22. Arhiv Srbije, MUD – S, 1858 – Delovodni protokol, 1487.
23. Arhiv Srbije, MUD – S, 1858 – Delovodni protokol, 1795.
24. Arhiv Srbije, MUD – S, 1858, VI, 23.
25. Srbiя. Srbske novine 1859 Maj 28; XXVI(62):1.
26. Arhiv Srbije, MUD – S, 1859 – Registar.
27. Spasović IB. Društvo srpske slovesnosti, Srpsko učeno društvo i srpski narod. U: Krestić VĐ, Spasović IB. Društva svoga doba: Društvo srpske slovesnosti, Srpsko učeno društvo. Beograd: Službeni glasnik : Srpska akademija nauka i umetnosti; 2016. 99. i Arhiv Srpske akademije nauka i umetnosti (dalje ASANU), DSS, 23/1860.
28. ASANU, DSS, 47/1860.
29. Arhiv Srbije, MUD – S, 1859 – Registar; AS, MUD – S, 1860 – Delovodni protokol, 377.
30. Arhiv Srbije, MUD – S, 1859 – Registar.
31. Arhiv Srbije, MUD – S, 1860 – Delovodni protokol, 7.
32. Lindenmayr EP. Serbien, dessen Entwicklung und Fortschritt im Sanitätswesen, mit Andeutungen über die gesammten Sanitätsverhältnisse im Oriente. Temesvár: Druck und Verlag der Csanáder Dioecesan-Buchdruckerei; 1876, 129 i AS, MUD – S, 1845, F IV, 20; Istorijski arhiv Beograda, Uprava grada Beograda (dalje IAB, UGB), 1845, k. 37, F I, 66.
33. Arhiv Srbije, MUD – S, 1860, I, 37.
34. IAB, UGB, 1860, k. 454, F I, 9.
35. IAB, UGB, 1862, k. 616, F XXIII, 342.
36. IAB, UGB, 1862, k. 608, F XIX, 26.
37. Arhiv Srbije, VŠ, 1864, 6 i AS, VŠ, 1864, 117.
38. Arhiv Srbije, MUD – S, 1864 – Registar.
39. Đorđević V. Istorija srpskog vojnog saniteta. Knjiga prva, 1835–1875. Beograd: Državna štamparija; 1879. p. 783–5.
40. Zvaničnыi deo. Srbske novine 1865 April 3; XXXI(37):1.
41. Đorđević V. Istorija srpskog vojnog saniteta. Knjiga prva, 1835–1875. Beograd: Državna štamparija; 1879. p. 199.
42. Oglasi. Srbske novine 1865 Mart 27; XXXI(34): 8.
43. Arhiv Srbije, MUD – S, 1866, F V, 19.
44. Arhiv Srbije, MUD – S, 1866, Delovodni protokol, 2554, 2627.
45. Đukanović IN. Ubistvo kneza Mihaila i događaji o kojima se nije smelo govoriti. Knjiga prva: Topčiderska katastrofa. Reprint izdanje iz 1935. Beograd: Beletra; 1990. p. 155–6.
46. Dnevnik Benjamina Kalaja: 1868–1875. Radenić A, urednik. Beograd: Istorijski institut; Novi Sad: Institut za istoriju Vojvodine; 1976. p. 128.
47. Zvaničnыi deo. Srbske novine 1869 Nov. 13; XXXV(140):1.

Dr. Karlo Kiko (Karol Kiko, 1813–1869) – One of the Slovaks in the Serbian health service in the 19th century

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SUMMARY

Dr. Karlo Kiko was one of many doctors from the former Austrian Empire living and working in the Principality of Serbia in the 19th century. He was born in Uhrovec, Slovakia, which was then part of the Kingdom of Hungary – in itself part of the Austrian Empire. Kiko was promoted to the Doctor of Medicine in Pest in 1845. In his youth, he dealt with alternative ways of healing, he explored medicinal herbs and mineral waters and published several expert papers. He was a Fellow of the Royal Hungarian Natural Science Society. As a physician in the troupe of General Mor Percel, he participated in the Hungarian Revolution of 1848/49. Kiko spent the last 11 years of his life in Serbia working as a physician of the Knjaževac County, as a doctor of the Belgrade Municipality and a military doctor – a surgeon of the Military Hospital in Belgrade. Although he is considered a respectable person in the Region of Trenin, from which he emerged, in Slovakia it is not known that he has lived and died in Serbia. The goals of this paper are to round off Kiko's biography with his "Serbian period" and to present the personality of a worker in the Serbian health service in the past.

Keywords: Karol Kiko, physician; doctor; Slovakia; Serbian health service

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ПИСМО УРЕДНИКУ / LETTER TO THE EDITOR

Др Карло Кико – Словак у Српском Ковину

Поштовани уредниче,
С интересовањем смо прочитали рад из историје медицине Јелене Јовановић Симић „Др Карло Кико (*Karol Kiko*, 1813–1869) – један од Словака у српском санитету у 19. веку“ [1], о једном од ретких Словака који је радио као лекар у нашој земљи.

У свом раду ауторка наводи да је „у молби за запослење коју је поднео Министарству унутрашњих дела Кнежевине Србије ... 1858. године“ и коју је „упутио из Сремске Митровице, где је тада био приватни лекар“, Кико навео да је од 1851. до 1853. године био „царско-краљевске фамилије лекар спахилука названог Рацкеве и Промонтор“, те да је од 1854. до 1856. године био „лекар трговаца Ковиначки, од ови нарочито тога ради позват“ и да је „док је у Ковину био, испуњавао... и дужности Полковског и Ротског лекара... и дужности Санитетскога референта код Ковинског растељанства“. Ауторка наводи да су „подаци о познавању језика, посебно српског, били... увек тражени од оних који аплицирају за запослење у Србији“, те да „Кико, дакле, није навео да зна српски језик, иако је молба писана на српском“. Даље, да се „у једном допису Министарства унутрашњих дела Државном савету“ наводи... да он „говори и пише српски“. Ако „није знао српски језик“, онда да га је „Кико... брзо савладао“ [1], односно као да постоји дилема да ли је Кико знао наш језик.

Рацкеве, град у којем је доктор Кико боравио од 1851. до 1853.године, био је Српски Ковин, или Мали или Доњи Ковин, којег Мађари зову *Ráckeve*, односно Српски- или Киш-Кеве. Град се налази на око 40 километара јужно од Будимпеште, на Чепелској ади, на левој обали Дунава. Основали су га 1440. године Срби, избегли од турског зулума, из Ковина на Дунаву у Банату. Пошто су први пут освојили Смедерево, Турци су у два наврата прешли Дунав и упали у Ковин, па су Срби избегли на север, до Чепелске аде. Ту је ковинским пресељеницима угарски краљ Владислав уступио касноготску цркву за њихов православни храм. И данас на Чепелској ади постоји Српски Ковин, са црквом посвећеном Успењу Богородице [2]. Црква је три пута живописана, а последњи пут је у XVIII веку фреске урадио Теодор Грунтовић, Цинцар из Мосхопоља у Епиру [3]. Данас у Српском Ковину нема Срба, али црква живи као српски манастир [4].

Три године је доктор Кико провео међу Србима у Српском Ковину, на које је вероватно оставио добар утисак, па је он од трговаца „Ковиначки... нарочито... позват“ да буде међу њима још три године, све до 1856. године. Дакле, следеће три године, од 1854. до 1856. године, он је вероватно био позван од Срба из Српског Ковина да им буде лекар, а не од Срба из Ковина у Банату, тзв. Доњег Ковина. Ако је наша претпоставка тачна – да је доктор Кико шест година у континуитету био међу Србима као лекар, то онда значи да је сигурно и научио српски, па не чуди да је молба за запослење коју је упутио Министарству унутрашњих дела Кнежевине Србије – на српском. Даље, он посебно и не наводи да зна српски, јер је већ написао и поткрепио документима да је међу Србима у Српском Ковину провео шест година – довољно да научи наш језик, што се опет и наводи у једном допису Министарства унутрашњих дела Државном савету: он, Кико, „говори и пише српски“ [1]. Чини се, дакле, да доктор Кико није „брзо савладао“ [1] српски по доласку у нашу земљу, већ је у Србију дошао а да је вероватно већ добро говорио српски и то са акцентом Срба из Угарске, Срба из Српског Ковина.

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ЛИТЕРАТУРА

1. Jovanović Simić J. Dr Karlo Kiko (Karol Kiko, 1813–1869) – jedan od Slovaka u srpskom sanitetu u 19. veku. Srp Arh Celok Lek. 2017; 146(3-4):231-8.
2. Kalezić D, glav. ur. Enciklopedija pravoslavlja (Treći tom). Beograd: Savremena administracija; 2002.
3. Medaković D. Barok kod Srba. Zagreb: Prosvjeta; 1988.
4. Manastir u Srpskom Kovinu u Mađarskoj. [Accessed on September 30, 2017] Available from: www.spc.rs/sr/uspenje_presvete_bogorodice_u_manastiru_srpski_kovin_u_madjarskoj

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ПИСМО УРЕДНИКУ / LETTER TO THE EDITOR
ОДГОВОР АУТОРА / AUTHORS' REPLY

Др Карло Кико – Словак у Српском Ковину

Поштовани уреднице,

За сваког аутора подстицајно је када његов рад изазове пажњу стручне јавности и постане основа за конструктивну дискусију. Из тог разлога захвална сам колегама Слободану Николићу и Владимиру Живковићу, који су пажљиво прочитавши мој рад „Др Карло Кико (1813–1869) – један од Словака у српском санитету у 19. веку" [1] написали текст под насловом „Др Карло Кико – Словак у Српском Ковину" [2]. Николић и Живковић су за полазну тачку узели моју недоумицу у погледу питања да ли је др Кико знао српски језик када је 1858. године дошао у Србију и ступио на дужност физикуса Округа књажевачког. Основа за моју недоумицу била је чињеница да су три документа која је Кико потписао (две молбе упућене Министарству унутрашњих дела и заклетва при ступању у службу) писана, истина, на српском језику, али сваки од њих различитим рукописом. Поред тога, писмо које је Кико упутио лично др Емериху Линденмајеру, тадашњем начелнику Санитетског одељења Министарства унутрашњих дела, писано је на немачком језику (рукопис се разликује од сва три рукописа у поменутим документима) [3]. Питање Киковог знања српског језика само по себи нема велику важност, али је повезано са његовом радном биографијом и разумевањем појединих историјских чињеница које јесу значајне и због којих пишем овај текст. Наиме, у раду сам уз цитирање делова Кикове прве молбе за запослење у Србији представила његову радну биографију. Ту стоји да је Кико „од 1851. до 1853. био (је) 'Царско-краљевске фамилије лекар спахилука названог Рацкеве и Промонтор'". Даље, „од 1854. до 1856. био је 'лекар трговаца Ковиначки, од ови нарочито тога ради позват. У исто време, од 1854. до 1856, док је у Ковину био, испуњавао је и дужности Полковског и Ротског лекара, осим тога по налогу високославне Државе испуњавао је и дужности Санитетскога референта код Ковинског растељанства'". На основу изнетих чињеница, Николић и Живковић закључили су да је Кико „шест година у континуитету био међу Србима као лекар" и да је зато без сумње знао српски језик. По питању говорног, али не и писаног српског језика, углавном бих се сложила с тим мишљењем. Николић и Живковић дали су и кратак историјат Српског Ковина (Рацкеве, односно мађарски *Ráckeve*), који је свакако корисна допуна мог рада. Међутим, изнели су и становиште да је Кико „од 1854. до 1856. године"(...) вероватно био позван од Срба из Српског Ковина да им буде лекар, а не од Срба из Ковина у Банату, тзв. Доњег Ковина". Пренебрегнута је чињеница да цитиране дужности које је Кико обављао у том периоду – дужности „Полковског и Ротског лекара" и „дужности Санитетскога референта код Ковинског растељанства" недвосмислено указују да је реч о Војној крајини тадашњег Аустријског царства, односно њеном делу – Банатској војној граници формираној 1764. године, у чијем је саставу било и место Ковин. У њему је постојала *компанијска станица* као део XII Немачкобанатске регименте, чије је седиште било у Панчеву. Банатска војна граница постојала је до развојачења 1872. године [4].

Поред војне улоге, граница је имала и улогу у одбрани земље од уноса заразних болести. Осим карантина, дуж ње су постојала и трговишта – *растели*, грађена на посебан начин који је онемогућавао физички контакт између трговаца из две државе – Аустријског и Османског царства. *Растели* су дакле биле типично граничне установе.

Доказ да је Кико између 1854. и 1856. године ипак службовао у банатском а не у Српском Ковину јесу и две потврде које су

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о томе издате на немачком језику, службеном језику у банатској војној граници [3]. Прва од њих, „Certificat“ написана је 24. априла 1855. године у „Kubinu“ (немачки назив за Ковин). Друга, „Zeugnis“ (сведочанство), у којој се наводи Киков ангажман код „кубинске компаније“ од 4. августа 1854. до фебруара 1856. године, написана је 24. марта 1856. у Панчеву. Др Карло Кико, дакле, јесте провео међу Србима шест година, али у два Ковина – у Српском и у банатском.

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ЛИТЕРАТУРА

1. Jovanović Simić J. Dr Karlo Kiko (Karol Kiko, 1813–1869) – jedan od Slovaka u srpskom sanitetu u 19. veku. Srp Arh Celok Lek. 2017; 146(3-4):231-8.
2. Nikolić S, Živković V. Dr Karlo Kiko – Slovak u Srpskom Kovinu. Srp Arh Celok Lek. 2017; 146(3-4):239.
3. Arhiv Srbije. Ministarstvo unutrašnjih dela, Sanitetsko odeljenje. V: 1. 1858.
4. Spasović IB. Banatska vojna granica i njeno ukidanje 1872. godine. Pančevo: Istorijski arhiv u Pančevu; 2004. str. 16 i 113.

Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорарашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални (научни и стручни) радови, метаанализе, прегледни радови, претходна и кратка саопштења, прикази болесника и случајева, слике из клиничке медицине, видео-чланци, радови за праксу, актуелне теме, радови из историје медицине и језика медицине, лични ставови, наручени коментари, писма уреднику, прикази књига и други прилози. Оригинални радови, претходна и кратка саопштења и прикази болесника и случајева публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}*Tc*, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало

би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, метаанализу, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходно и кратко саопштење, метаанализе и прегледне радове, сажетак треба да има следећу структуру: Увод/Циљ, Методе, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh)*.

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом.

Уколико је рад у целости на српском језику (нпр. рад из историје медицине, језика медицине и др.), потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик. Сажетке и радове који су у целости на српском језику аутори из Србије треба да пишу ћирилицом.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад, метаанализа, претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор метаанализе и прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°C), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада – који чине насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, претходно и кратко саопштење, рад

из историје медицине и преглед литературе до 5.000 речи, а за приказ болесника, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3.000 речи; радови за остале рубрике могу имати највише 1.500 речи. Видео-радови могу трајати 5–7 минута и бити у формату *avi, mp4*(*flv*). У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

ТАБЕЛЕ. Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле.

Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

СЛИКЕ. Слике су сви облици графичких прилога и као „слике“ у СА се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду). Видеоприлози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *е*-издању и објављена у штампаном издању.

Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

ГРАФИКОНИ. Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета.

Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

СХЕМЕ (ЦРТЕЖИ). Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме.

Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, а у метаанализи до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публикације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да

буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примери навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био објављен у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) за годину у којој се рад предаје Уредништву. Сви домаћи аутори такође морају бити претплаћени на часопис или измирити накнаду за обраду чланака (*article processing charge*) за годину у којој се рад предаје Уредништву, у износу од 3.000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*article processing charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

Додатне информације о чланарини и претплати могу се добити путем имејла (*office@srpskiarhiv.rs*) и на интернет-страници часописа *http://srpskiarhiv.rs/en/subscription/).*

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад могу се доставити имејлом (*office@srpskiarhiv.rs*), електронски преко система за пријављивање на интернет-страници часописа (*http://www.srpskiarhiv.rs*), препорученом пошиљком или лично, доласком у Уредништво. Уколико се рад шаље поштом или доноси у Уредништво, рукопис се доставља одштампан у три примерка и нарезан на *CD* (снимљени материјал треба да је истоветан оном на папиру).

НАПОМЕНА. Рад који не испуњава услове овог упутства не може бити упућен на рецензију и биће враћен ауторима да га допуне и исправе. Придржавањем упутства за припрему рада знатно ће се скратити време целокупног процеса до објављивања рада у часопису, што ће позитивно утицати на квалитет чланака и редовност излажења часописа.

За све додатне информације, молимо да се обратите на доленаведене адресе и број телефона.

АДРЕСА:
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