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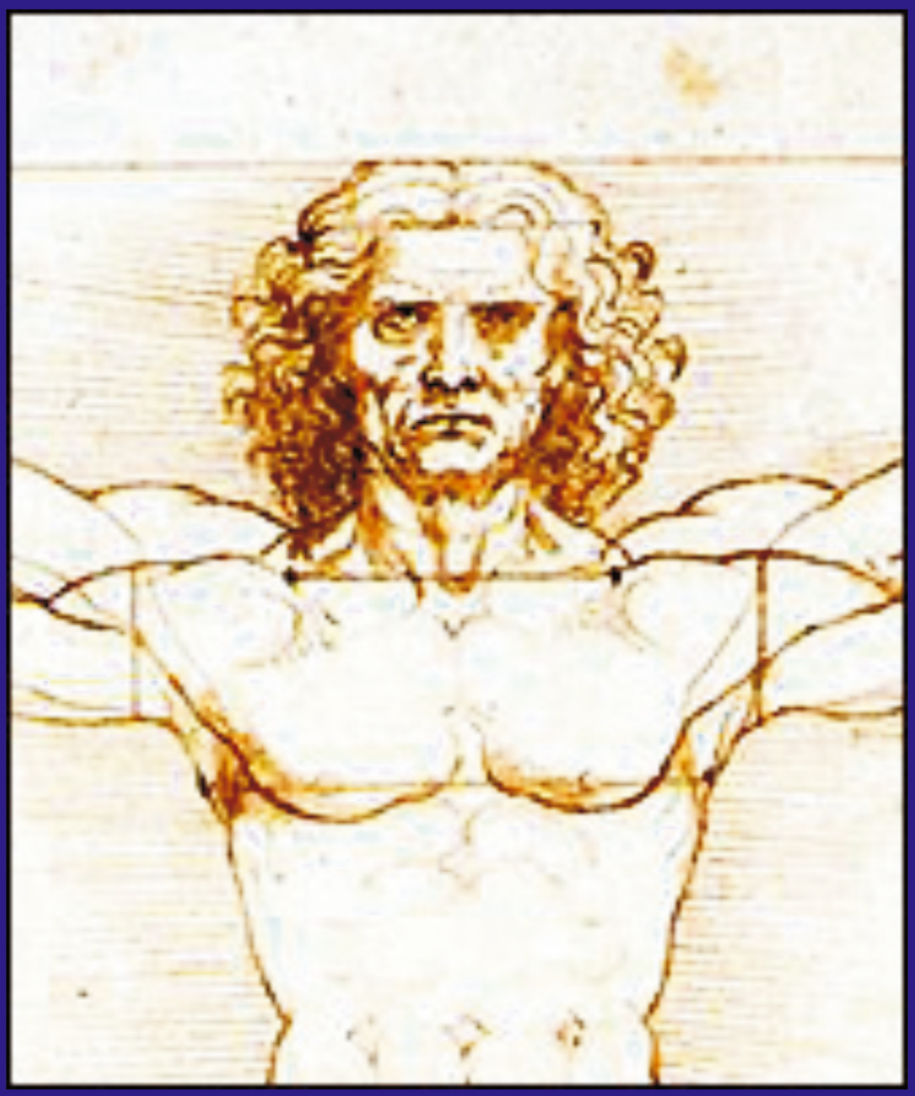

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SADRŽAJ

A word from the guest editor

I would like to express my deep gratitude to the Editorial Board of the Medical Journal Sanamed, especially the Chief Editor Avdo Ceranic and the Deputy Editor Dzemail Detanac for giving me the privilege of inviting me to be a Guest Editor of July's issue. I would also like to acknowledge the high professionalism of the whole Editorial Board of Sanamed in proposing inspiring ideas, as well as, having considerable skills in finalizing the manuscripts for publication in this project.

Hereby, I would like to express my appreciation for Sanamed's expanding initiative, which allows promoting, as well as, sharing the professional and scientific knowledge of medicine.

I hope that I have successfully accomplished my task, as Guest Editor, in promoting Sanamed as a Medical Journal both in my midst and internationally. I had a special privilege to encourage colleagues, physicians, researchers and alumni from our Alma mater, the Medical Faculty of the University "Sts Cyril and Methodius" in Skopje, to submit their papers, which provided a wide spectrum of interesting and intriguing contents for the Journal's audience. The following disciplines have been included: human genetics, neurology, psychiatry, cardiology, gastroenterohepatology, traumatology, gynecology and obstetrics, orthopedics. The communication with authors was in appropriate manner and the relation provided by the Guest Editor of the Editorial Board was supportive and very cooperative. I also hope that Editorial Board shares the authors' pleasure of the mutual collaboration. After the preparation period of the current Sanamed issue, collaborators and myself, are profoundly satisfied that we have already joined the international group of

authors, who have been contributing to the same cause - publishing in this Journal. At last, I would like to emphasize the benefit, that doctors, professionals and scientists from Macedonia, will have by taking part in such impressive and inspiring scientific project.

I owe my compliments to the Doctors Society of Novi Pazar, that did both the initiation and the foundation, as well as, the prosperous persistence of Medical Journal Sanamed.

Regards,

Kostandina Korneti Pekevska, MD PhD
Full Professor of Anatomy
Medical Faculty
University "Sts Cyril and Methodius"
(Svv. Kiril i Metodij)
Skopje, Republic of Macedonia

Reč gostujućeg urednika

Ovim putem želim da se zahvalim Uredništvu časopisa „Sanamed“, posebno glavnom i odgovornom uredniku Avdu Ćeraniću i zameniku glavnog urednika Džemailu Detancu, na privilegiji koju su mi ukazali pozivom da budem gostujući urednik u julskom broju. Takođe bih da istaknem i visoki profesionalizam celog Uredništva časopisa „Sanamed“ u predlaganju inspirativnih ideja, kao i značajnu umešnost u finalnoj obradi radova objavljenih u ovom broju.

Pohvalila bih i njihovu inicijativu koja širi mogućnost promovisanja, kao i razmene stručnih i naučnih dostignuća iz oblasti medicine.

Kao gostujući urednik, nadam se da sam uspešno ispunila zadatak u promovisanju „Sanamed“-a kao medicinskog časopisa, kako u mojoj sredini tako i šire u međunarodnim vodama. Imala sam posebnu privilegiju da ohrabrim svoje kolege, lekare, istraživače sa Medicinskog fakulteta Univerziteta „Ćirilo i Metodije“ u Skoplju, da prilože svoje radove koji pružaju širok spektar interesantnih i intrigantnih sadržaja za čitaoce časopisa. Sledeće medicinske discipline su zastupljene: humana genetika, neurologija, psihijatrija, kardiologija, gastroenterologija, traumatologija, ginekologija i akušerstvo i ortopedija. Komunikacija sa autorima je bila na odgovarajućem nivou, a odnos između gostujućeg urednika i Uredništva časopisa „Sanamed“ je bio veoma kooperativan i pun podrške. Nadam se da i Uredništvo deli isto zadovoljstvo zbog uzajamne saradnje.

Nakon perioda pripreme ovog broja, saradnici i ja smo iskreno zadovoljni što smo već ušli u grupu

internacionalnih autora koji su doprineli istom cilju — objavljivanju u ovom časopisu. Na kraju, istakla bih korist koju će doktori, stručnjaci i naučnici iz Makedonije imati učestvujući u ovako impresivnom i inspirišućem naučnom projektu.

Dugujem komplimente i Udruženju lekara „Sanamed“ za inicijativu i postavljanje temelja prosperitetnom opstanku časopisa „Sanamed“.

S poštovanjem,

Prof. dr Kostandina Korneti Pekevska,
Profesor anatomije
Medicinski fakultet Univerziteta
„Sv. Ćiril i Metodije“ (Svv. Kiril i Metodij)
Skoplje
R. Makedonija

SANAMED

Riječ urednika

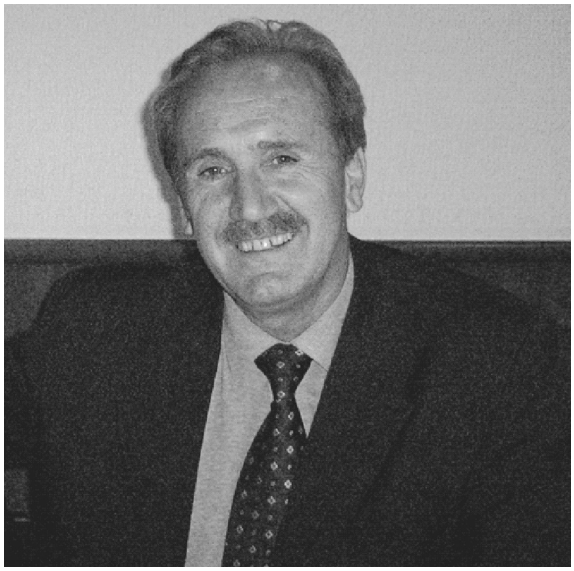
Poštovani,

Radujem se što u ovoj jubilarnoj, desetoj godini našeg „SANAMED"-a mogu da zaključim da krivulja kvaliteta ima stalno uzlaznu putanju. Vjerujem da i naši najbliži saradnici i svi drugi koji sa nama rade na podizanju kvaliteta časopisa imaju isti osjećaj. Svi novi članovi koji se javljaju sa željom da postanu deo velikog tima imaju takođe isti zaključak. Ono što je dobro je i to da u svom dosadašnjem trajanju naš tim se uvećava i ni kod jednog člana nismo osjetili da nema volju da pruži svoj doprinos za bolji kvalitet kada je to bilo potrebno.

Poseban entuzijazam, moram da iznesem, primjetio sam kod gostujućih urednika koji kroz prijateljski i ljudski pristup srdačno ulažu trud u razvoj kvaliteta časopisa kao da je njihov matični. Po tome smo čini mi se jedinstveni među časopisima barem u našoj zemlji.

Ovog puta bih se osvrnuo i na orginalnost naučnih radova, te podsjećam sve autore, one dosadašnje kao i one koji namjeravaju da šalju radove, da stoje iza svog potpisa kao garanta originala i da poštuju međunarodne standarde o načinu citiranja. Uredništvo časopisa ozbiljno radi na sprečavanju mogućnosti publikovanja plagijata. Naša iskrenost i objektivnost je u očima autora ponekad preoštra i žao nam je zbog toga, ali mi ćemo i dalje ostati dosledni razvoju kvaliteta i bićemo sve zahtevniji kako bi stigli do vrha.

Dragi i poštovani saradnici, cijenjeni čitaoci, uvaženi autori, još jednom želim da vas pozdravim i da vam poželim dobro zdravlje, sa željom da nastavimo saradnju i doživimo novi jubilej — dvadeset



godina publikovanja. Do tada, pozivam posebno sve one mlade ljude kojima je želja da stvaraju, da se udruže sa iskusnim stručnjacima i da koriste njihovo iskustvo, da se sami uključe u naučni rad i da pišu. Vrijeme sve brže protiče kroz sve brži razvoj društva, tako da ono što je danas aktuelno sutra je zastarelo.

U ovom broju objavljujemo trinaest radova. Nijesmo mogli da objavimo sve radove koji su pristigli iako su prošli recenzije i prihvaćeni za objavljivanje, te stoga molim autore za strpljenje do sledećeg broja.

Srdačan pozdrav,

Prim. dr Avdo Ćeranić
glavni i odgovorni urednik

A word from the editor

Dear readers,

I am very glad that in this jubileeyear, the 10th anniversary of "SANAMED" publishing, I can proudly state that the curve of quality has a constant upward trajectory. I believe that our close associates and other co-workers, who are industriously working on improving the quality of journal have the same feeling. All new members, who had expressed the desire to become a part of our great team, also had a same primary idea. What is good is the fact that our team is still increasing, and there is not even one member who is not willing to contribute to a better quality when it is needed.

I have noticed a special enthusiasm among the guest editors, who have warmly invested in development of the journal'sl quality, with friendly and committed approach.

This time I would like torefer to the originality of scientific papers, and remind all authors, those current and those who intend to submit their papers, to stand behind their signature as the guarantor of the originality and to follow international scientific citation standards. Editorial is seriously working to prevent the possibilities of publishing plagiarism. Our sincerity and objectivity is sometimes too harsh in the eyes of the author and we are sorry for that, but we will remain true to the development of quality and we will be more demanding in order to reach the top.

Dear and respected colleagues, dear readers, distinguished authors, once again I want to welcome you and wish you a good health, with a desire to

continue cooperation and experience new jubilee, twenty years of publication. Until then, I urge on, especially, those young people who want to create, to join experienced professionals and use their experience to get yourself involved in scientific work and to write. Time passes very quickly, so what is current today, tomorrow is out of date.

This issue includes thirteen papers. We were unable to publish all received papers, although they passed reviews and are accepted for publication. Therefore, we ask authors for patience until the next issue.

Yours faithfully,

Prim. dr AvdoCeranic
Editor in chief

Čitaj da shvatiš

Piši da preneseš

Uradi da te pamte

* * *

Read to understand

Write to impart

Work to be remembered

Avdo Ćeranić

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RADIAL ARTERY ANOMALIES IN THE MACEDONIAN POPULATION DURING TRANSRADIAL ANGIOGRAPHY PROCEDURES

Zafirovska Biljana, Petkoska Danica, Antov Slobodan, Vasilev Ivan, Jovkovski Aleksandar, Kalpak Oliver, Kostov Jorgo, Spiroski Igor, Pejkov Hristo, Bosev Marjan, Taravari Hajber, Kitanoski Darko, Kedev Sasko

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Abstract: **Objective:** To assess the incidence of arterial anomalies of the radial artery in the Macedonian population registered during transradial access (TRA) angiography procedures in a large series of patients.

Background: Transradial angiography (TRA) is now the recommended access for percutaneous coronary intervention, but technically is a more challenging approach for angiography procedures mostly due to the anatomic anomalies on the radial artery, which may influence the success rate of transradial angiographic procedures.

Methods: All consecutive 19292 patients from our Center, in the period from March 2011 until December 2014 were examined. Preprocedural radial artery angiography was performed in all patients. Clinical and procedure characteristics, type and incidence of vascular anatomy variants and access site complications were analyzed.

Results: Anatomical variants were present in 1625 (8.8%) patients. The most frequent was high-bifurcating radial artery origin from the axillary and brachial arteries in 1017 (5.5%) patients, 227 (1.2%) had extreme radial artery tortuosity, 176 (0.95%) had a full radial loop, 32 (0.17%) with hypoplastic radial artery and 173 (0.9%) had tortuous brachial, subclavian and axillary arteries. Radial artery spasm was very common in patients with present radial artery anomalies.

Conclusion: Radial artery anomalies are very common in the general population. Knowing the anatomy of the radial artery helps the interventional cardiologist in successfully planning and performing this procedure. Radial artery angiography is strongly encouraged in every patient before the begining of the transradial angiography procedures.

Keywords: TRA (Transradial artery access), RA (Radial artery), TFA (Transfemoral artery access), Vascular anatomy variants.

INTRODUCTION

Trans radial access (TRA) is now the preferred access site for percutaneous cardiovascular interventions in experienced radial centers (1).

Radial artery anomalies are frequently found in the general population. Autopsy studies of upper limbs have found arterial anatomical variations in between 4% and 18.5%, (2, 3) while arteriography studies reported percentages between 7.4% and 22.8% (4-7, 8, 9).

Multiple studies support transfer from femoral artery access to radial access for all angiographic diagnostic and interventional procedures mostly due to decreasing access site bleeding and vascular complications without sacrificing procedural success (10, 11, 12, 13). The radial approach improves patient comfort and satisfaction, allows rapid ambulation and is associated with reduced cost and hospital stay (10, 11, 12, 13).

Patients with increased risk of bleeding and vascular complications have a particular benefit from TRA as opposed to transfemoral approach (TFA): female gender, elderly, obesity, low weight, hypertension, renal failure, low platelet count and anemia (10, 11, 12, 13).

Transradial approach as opposed to transfemoral approach is a technically more challenging approach mostly due to the present radial artery anatomic anomalies, which may influence the success rate and procedure time of transradial angiographic procedures (4, 5, 6, 7). Prior studies have reported that radial arterial anomalies can influence the success of transradial access and are cause for access crossover from TRA to other access sites (4, 5, 6, 7).

It is important that interventionalists learning the transradial technique while performing angiography procedures become familiar with common anatomic

radial artery anomalies and learn how to navigate through them.

Most experienced transradial operators in high volume transradial centers can overcome these anomalies and successfully perform their procedures without prolonging procedure time.

In this study we evaluate the incidence of these variations in the Macedonian population during transradial approach angiography procedures in a large cohort of patients from a national PCI (percutaneous coronary interventions) referral center.

MATERIALS AND METHODS

Patient population

This was a prospective single center study including all patients from March 2011 to December 2014 referred for coronary or peripheral angiography to a large volume tertiary referral center at the University Clinic of Cardiology, Skopje, Macedonia.

Table 1. *Arterial access*

Clinical Variables	Total N of Patients N = 19292
TRA	18417 (95.4%)
TUA	812 (4.2%)
TFA	53 (0.3%)
TBA	10 (0.05%)

* TRA — Transradial access; TUA — transulnar access; TFA — transfemoral access; TBA — transbrachial access

All procedures were performed by experienced transradial operators (> 500 diagnostic TRA procedures and > 300 PCI procedures per year). Radial artery angiography was performed in all patients to evaluate the presence of any anatomic variation of the arteries. Total number of procedures done in that period was 19292. Transradial access was performed in 95% (18417), transulnar access with 4,2% (812), transfemoral 0,3% (53) and transbrachial access in 0,05% of all procedures (Table 1).

Radial artery puncture and cannulation

After local anesthesia with 1ml lidocaine 2%, radial artery (RA) puncture was performed with a sheath set, including a 20 gauge 2-piece needle, 0.025 inch straight wire and a 16-cm 6Fr or 5F sheath. Following sheath insertion, a drug cocktail consisting of verapamil (5mg) and heparin (3000 U) was administered through the sheath sidearm.

In case of interventional procedures weight adjusted Heparin (100 U/kg) was administered through the sheath before the start of the procedure.

Retrograde radial arteriography was performed after administration of the arterial vasodilatator to define the radial artery anatomy from mid forearm to ulnobrachial anastomosis and to delineate ulnar artery anatomy as well, generating a roadmap for the intervention. A solution of 3ml of contrast (Ultravist 370) diluted with 7 ml of blood was injected through the cannula or through the side arm of the sheath under fluoroscopy in AP position. If anomalous anatomy was identified, the operator planned the procedure on that basis. Retrograde arteriography is of particular importance when there is some resistance in guidewire advancement and in patients after previous transradial interventions. If the operator identified a possible anomaly in brachial, axillar or subclavian arteries, an arteriogram higher up the arm was obtained.

In case of radial access failure, transfer was done to ipsilateral ulnar artery or to the left radial artery or transfemoral artery depending on operator preference. Only 3 cases with anomalies required transfer to femoral access.

Post procedure management: The sheath was removed immediately after the procedure, regardless of the level of anticoagulation, and a compressive dressing or closure device was applied to the wrist. In our practice we use TR band or simple compressive dressing. In order to decrease the rate of radial artery occlusion we applied patent hemostasis by using pulse oximetry to confirm the hemoglobin oxygen saturation on the punctured radial artery (> 90%), after hemostasis was obtained (during measurement UA was compressed manually). Compression was applied for approximately a 2 to 3-hour period with gradual relaxation of compression or deflation of the TR band after the 1st hour.

Aim of study

The aim of this study was to access the incidence of radial artery anomalies in the Macedonian population. Procedural time and fluoroscopy time was analysed. Complications during the procedure as radial artery spasm and haemathoma were recorded after every procedure.

Definitions

A high bifurcating origin of the radial artery was defined as the origin of the radial artery from the brachial or axillary artery proximal to the upper border of the cubital fossa.

Radial artery loop was defined as presence of a full 360 degrees loop of the radial artery, with or without the presence of a remnant radial artery (Figure 1).

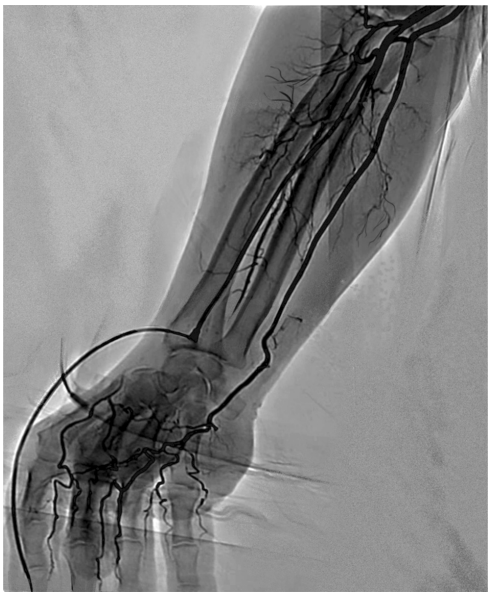

Figure 1. *Radial artery loop*

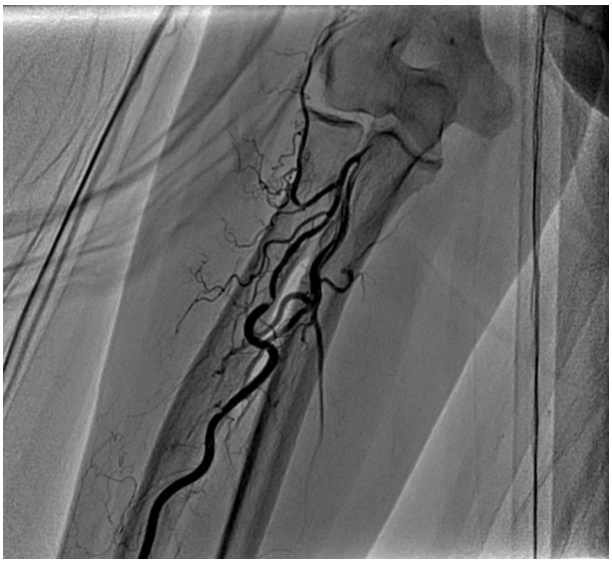

Figure 2. *Radial artery tortuosity*

Radial, brachial and subclavian artery tortuosity was defined as presence of a curve of more than 45 degrees in the vessel (Figure 2).

Clinical radial artery spasm (RAS) was classified as grade I: minimal local pain and disconfort; grade II: significant local pain and discomfort, not precluding procedure completition; grade III: severe local pain and disconfort necessiting cross over and grade IV: catheter entraptment with severe local pain and disconfort (14, 15).

Vascular access site complications were defined as the occurence of an aneurysm, fistula, hematoma, loss of radial pulse or radial nerve injury.

Hematoma was classified into five grades (grade I: local hematoma, superficial < 5 cm; grade II: hematoma with moderate muscular infiltration; grade III: forearm hematoma and muscular infiltration, below the elbow; grade IV: hematoma and muscular infiltration extending above the elbow; grade V: ischemic threat - compartment syndrome) (16).

Statistical analysis

Simple descriptive statistics was used. For normally distributed numeric variables, data was expressed as mean ± standard deviation and for continuous variables not fitting a normal distribution as median (minimum-maximum). Percentages were used to express categorical variables. Chi-square test was used to compare categorical variables and student's t-test was used to compare differences between two groups. A P-value of < 0.05 was considered statistically significant. Statistical analysis were performed with SPSS 17.0 for Windows (SPSS Inc. Chicago, ILL).

RESULTS

From 19292 consecutive transradial procedures, anatomical variants were present in 1625 (8.8%) patients. From baseline caracteristics 66% of patients with present anomalies were male, with medium BMI of 23 (19-43). Diabetes was present with 19% and hypertension with 67%. 22% of patients with STEMI (acute myocardial infarction procedures with ST segment elevation) had RA anomalies. There was no significant difference in procedure or fluoroscopy time of patients with anomalies compared to the general population.

Patients with RA anomalies in the Macedonian population had median age of 62 (27-90) higher than the median age of the general population without RA anomalies which was 52 years (18-91) (Table 2).

Table 2. *Baseline characteristics of patients with TRA*

Clinical Variables	Total N Patients (N = 18417) (95,4%)	Patients with RA anomalies (N = 1625)(8,8%)
Age (years)	52 (18-91)	62 (27-90)
Male	12750 (70%)	1076 (66%)
Female	5667 (30%)	503 (31%)
BMI (kg/m^2)	25 (19-47)	23 (19-43)
CAD risk factors		
Hypertension	13704 (74%)	1086 (66,8%)
Diabetes mellitus	4422 (24%)	312 (19,2%)
Dyslipidemia	5010 (27%)	372 (22,9%)
Smoking	5535 (30%)	453 (27,8%)
PCI	8965 (48,6%)	768 (47,2%)
CAS	2467 (13,3%)	235 (14,4%)
STEMI PCI	3495 (18,9%)	356 (22%)
Prior TRA	1-88 (min)	0-80 (min)
Fluoroscopy time	10-300 (min)	10-180 (min)
Procedure time		

* CAD — Coronary artery disease; PCI — Percutaneous coronary intervention; STEMI — ST segment elevation myocardial infarction; CAS — Carotid artery stenting

Most frequent radial artery anomaly was the high-bifurcating radial artery originating from the axillary and brachial arteries found in 1017 (5.5%) patients. Full radial loop was present in 176 (0.95%) patients and 227 (1.2%) patients had extreme radial artery tortuosity, 32 (0.17%) had hypoplastic radial artery, 173 (0.9%) had tortuous brachial, subclavian and axillary arteries, which is shown in Table 3.

Table 3. *Anatomical variants among patients with TRA*

Anatomical variants	Incidence
Total Number of patients with present anomalies	1625 (8,8%)
High bifurcating origin of the radial artery from the brachial or axillary arteries	1017 (5,5%)
Radial artery loop (360°)	176 (0,95%)
Radial artery tortuosity	227 (1,2%)
Hypoplastic radial artery	32 (0,17%)
Loop of the brachial/axillary/subclavian artery	173 (0,9%)

Table 4. *Secondary outcomes based on present RA anomalies*

	RA anomalies group N = 1625 (8,8%)	RA without anomalies N = 16790 (91,2%)	P value
Clinical radial artery spasm	206 (12,6%)	471 (2,5%)	< 0,001
Access site bleeding complications	133 (8,2%)	1290 (7, 7%)	

* RA — radial artery

Table 5. *Access site complications*

Access site complications	%
Clinical radial artery spasm	206 (12,6%)
Grade I	40/1625 = 2,5%
Grade II	84/1625 = 5,2%
Grade III	67/1625 = 4,1%
Grade IV	15/1625 = 0,9%
Access site bleeding complications	133 (8,2%)
Haemathoma grade 1	43/1625 = 2,6%
Haemathoma grade 2	56/1625 = 3,4%
Haemathoma grade 3	20/1625 = 1,2%
Haemathoma grade 4	11/1625 = 0,7%
Haemathoma grade 5	3/1625 = 0,2%
Major vascular complications	0%

* RA — Radial artery

Clinical radial artery spasm was significantly more frequent in cases with present anomalies 12%, compared to cases without present anomalies 2.5% respectively ($p < 0,001$). In 82 cases high grade IV and V clinical spasm was present (5%), which is shown in Table 4. Access site bleeding complications were similar in both groups with 8,2 and 7.7% respectively.

Haematoma grades IV and V were present in 14 cases which resolved without clinical consequences. None of the patients needed vascular repair of the puncture site, which is shown in Table 5.

DISCUSSION

We can conclude that radial artery anomalies are very common in the Macedonian population with a 8.8 percentage registered in our study in a large patient cohort. These results were analysed from the data of the the largest national center for percutaneous angiography procedures in Macedonia in the period of 4 years. Our PCI center has 98% take of all angiography procedures performed in our country. 95% of all angiography procedures in our center were performed with transradial artery access, with 4.2% using transulnar artery access. Only 0.3% of all procedures in this period were performed using transfemoral approach.

Considering the recognition given by the European cardiology panel consensus document (1) that the transradial approach should be the default approach for PCI in experienced transradial centers, it is important to understand any issues that could influence success of TRA percutaneous interventions. Even in peripheral interventions transradial approach is starting its momentum. Insufficient devices for peripheral radial artery stenting still limit its use in peripheral angiography interventions (17-23). The reported overall failure in transradial procedures is between 1% and 7% (16).

It is highly likely that radial artery anomalies influence the success of transradial agiography procedures.

Knowledge of present radial artery anomalies with pre-procedural radial artery angiography can help the interventionalist to evaluate the present anomaly and plan the angiography procedure without sacrificing procedure time or success.

We strongly encourage the use of radial artery angiography before the beginning of every transradial procedure giving the operator a chance to identify present anomalies and plan the procedure accordingly, making TRA failure less likely.

Study limitations

The definition of clinical radial artery spasm was subjective, made by presence of clinical signs. Also the hemostasis technique was not uniform.

CONCLUSION

Radial artery anomalies are very common in the general population. Knowing the anatomy of the radial

artery helps the interventional cardiologist successfully plan and perform the angiography procedure. Most of the present obstacles in TRA anomaly cases can be successfully overcome by experienced radial operators. Radial artery angiography is strongly encouraged in every patient before the begining of transradial angiography procedures.

Conflict of interest

Nothing to declare.

Source of Funding

There were no external funding source for this study.

Abbreviations

TRA — Transradial approach
RA — Radial artery
TFA — Transfemoral approach
TUA — Transulnar approach

Sažetak

ANOMALIJE RADIJALNE ARTERIJE U MAKEDONSKOJ POPULACIJI TOKOM TRANSRADIJALNIH ANGIOGRAFSKIH PROCEDURA

Zafirovska Biljana, Petkoska Danica, Antov Slobodan, Vasilev Ivan, Jovkovski Aleksandar, Kalpak Oliver, Kostov Jorgo, Spiroski Igor, Pejkov Hristo, Bosev Marjan, Taravari Hajber, Kitanoski Darko, Kedev Sasko

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Cilj: utvrditi učestalost anomalija radijalne arterije registrovanih kod makedonske populacije tokom angiografija sa transradijalnim pristupom (TRA), na velikom uzorku pacijenata.

Uvod: Transradialna angiografija (TRA) je sada preporučen pristup za perkutane koronarne intervencije, ali tehnički je još uvek više izazovan pristup za angiografiju, uglavnom zbog anatomskih anomalija na radijalnoj arteriji, što može uticati na uspešnost transradijalnih angiografskih procedura.

Metode: od marta 2011. do decembra 2014.godine, u nasem Centru pregledano je ukupno 19292 uzastopnih pacijenata. Preproceduralna radijalna angiografija je sprovedena kod svih bolesnika. Analizirane su kliničke i proceduralne karakteristike, vrsta i učestalost vaskularnih anatomskih varijanti i komplikacije.

Rezultati: Anatomske modifikacije su bile prisutne kod 1625 (8,8%) pacijenata. Većinom se radilo o visokoj-bifurkaciji radijalne arterije od aksilarne i brahijalne arterije i to kod 1017 (5,5%) pacijenata, 227 (1,2%) pacijenata je imalo izuzetnu zakrivljenost radijalne arterije, 176 (0,95%) je imalo pun radijalni luping, 32 (0,17%) je bilo sa hipoplastičnom radijalnom arterijom i 173 (0,9%) je imalo tortuozne brahijalne, subklavijalne i aksilarne arterije. Spazam radijalne arterije je bio vrlo čest kod pacijenata s prisutnim anomalijama radijalne arterije.

Zaključak: Anomalije radijalne arterije su vrlo česte u opštoj populaciji. Poznavanje anatomije radijalne arterije pomaže interventnim kardiolozima u uspešnom planiranju i izvođenju ovog postupka. Angiografija radijalne arterije se preporucuje kod svakog pacijenta pre izvođenja transradijalne angiografije.

Ključne reči: TRA (transradijalni arterijski pristup), RA (radijalna arterija), TFA (tranfemoralni arterijski pristup), vaskularne anatomske varijacije.

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EVALUATION OF TWO SURGICAL TREATMENTS OF PRIMARY VESICOURETERAL REFLUX AMONG CHILDREN: A 15 YEARS EXPERIENCE

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Abstract: **Aim:** aim of the study was to evaluate the efficiency of two different surgical treatments of vesicoureteral reflux (VUR) on succesfull rate and patient outcome.

Methods: Retrospective study on children with primary VUR and their surgical treatment from 1999 to 2014 in the University Clinic for Pediatric Surgery in Skopje. A total of 76 children (114 ureters) with VUR ranging from second to fifth grade were treated surgically, 44 patients (67 ureters) with an open surgical technique and 32 patients (47 ureters) with endoscopic treatment "STING" procedure. The following parameters were analyzed: duration of the intervention, duration of the hospitalization, the need for antibiotics and analgesic therapy and the need for blood and blood derivatives transfusion. The result of the surgical treatment was also validated. A good result was considered when reduction of VUR by 2 degrees with the endoscopic method or by 3 degrees in the open surgical technique was noticed.

Results: Using open surgical technique, patients were hospitalized for an average of 9 days (range from 5 to 13 days). All children received double antibiotic therapy. The need for analgesics lasted for 3 to 4 days. 90% of treated children needed blood and/or blood derivatives transfusion. Success rate with this method was 93.8%. Endoscopic procedure was performed as a one-day surgical procedure. The average duration was 15 minutes. Single, prophylactic dose of antibiotic was ordinated. There was no need for blood and/or blood derivatives transfusion. The overall success of the treatment was about 70%.

Conclusion: Open surgical procedure is used for more complicated cases, VUR grade IV-V or by previously failed. Endoscopic, "STING" procedure was commonly used for patients with VUR grade greater than 2, after previously failed conservative treatment, febrile urinary infection despite antibiotic prophylaxis and/or emergence of new scarring in the renal parenchyma. Patient assessment and decision for what method will be used must always be done individually for each child.

Key words: children; primary vesicoureteral reflux; surgical treatment, endoscopic treatment.

INTRODUCTION

Vesicoureteral reflux is one of the most common pathologies seen in pediatric patients. This treatment requires a multidisciplinary approach, starting from an accurate diagnosis based on heteroanamnestic data, pre-clinical, radiological, radio isotopic and laboratory investigations. Selecting the correct treatment, further control and follow-up of the affected child should be individualized (1, 2, 3).

The term vesicoureteral reflux (VUR) represents a retrograde flow of urine from the bladder to the proximal parties of the urinary tract. The ureter is normally attached to the wall of the bladder in tilted position, passing through detrusor muscle, continuing between the mucosa of the bladder and detrusor muscle as submucosal channel before entering into the lumen of the bladder. Upon contraction of the detrusor muscle, ureter lumen collapses between the mucosa and the detrusor muscle, creating thereby a valve mechanism that

prevents reflux of urine from the bladder to the ureter. Reflux occurs in cases where the channel between the submucosa and the detrusor muscle is short, or it is absent, or there is weak support from the detrusor muscle (4, 5, 6). This situation is due to disturbed/ decreased proportion of the length of the ureters' submucosal tunnel to the diameter of the ureter, which is normally in the range from 4:1 to 5:1. The decrease in this ratio implies that the submucosal tunnel is short, the urethra has wider diameter and the ureters' insertion is lateralized to the normal trigone of the bladder. This means that the physiological valve mechanism that prevents reflux is incomplete. Usually its weight corresponds to the size of the degree of deformity of the uretero-vesical junction. The incidence of the occurrence of VUR in the pediatric population is 0.4-1.8% (7).

Depending on the factors that have caused, VUR can be primary and secondary. Primary VUR is a congenital anomaly of the insertion of the ureter into the bladder, the majority of cases are with primary VUR, which tends to spontaneous resolution after maturation of the uretero-vesical circuit, especially in male children older than 5 years. There is a strong genetic correlation with disease appearance in certain families. VUR can be isolated or can be associated with other abnormalities of the genitourinary tract (6).

Secondary VUR is a result of an organic or functional obstruction of the evacuation of the urine from the bladder. As a result, there is an abnormally high pressure in the bladder (e.g. rear valve ureter, neurogenic bladder, myelomeningocele, spine injuries, double ureter, ectopic ureter, sub vesical obstruction etc.) (4).

Diagnosis is made through heteroanamnestic data, clinical investigations and the following diagnostic methods: prenatal ultrasound diagnostics, voiding cystourethrogram (golden standard) - standard investigation which gives accurate anatomical detail and gradation of the reflux, direct radioisotope voiding cystography and echo tomography (The American Urological Association, 1997). Additional diagnostic methods that can help in evaluating the severity of VUR are CT, MRI, radioisotope methods (DMSA static scan and dynamic DTPA renal scan), urodinamic examinations (8).

Aim of the study was to evaluate the efficiency of two different surgical treatments of VUR on succesfull rate and patient outcome.

METHODS

Patients

Grading the severity of reflux in all patients was made according to the International Reflux Study Committees in 5 groups. The degree of the reflux is estimated after a voiding cystourethrogram is made. It defines the

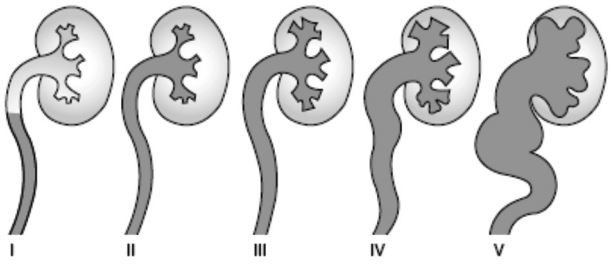

Figure 1. *Displaying the urinary tract in the presence of VUR - I, II, III, IV, V degree*

extent of the reflux, the appearance of the ureter, renal pelvis and calyces (Figure 1) (5, 9).

Gr. I: VUR limited to the ureter

Gr. IIa: VUR in the ureter and/ or pelvis

Gr. IIb: VUR to the calyces, but without their dilation

Gr. III: Moderately dilated ureter and pelvis, with blunting of the fornices

Gr. IV: Moderately dilated ureter and pelvis, with blunting of the fornices, but there is dilation of the entire collection system of the kidney

Gr. V: Pronounced dilatation and ureteral tortuosity, with enormous dilation of the pelvis and calyces and loss of renal parenchyma.

Generally accepted indications for surgical treatment were the following: high grade reflux, increasing of the existing lesions and/ or occurrence of new scars in renal parenchyma, recurrent pyelonephritis, urinary infections with febrile episodes while receiving antibiotic prophylaxis and finaly failure or lack of cooperation on the conservative treatment (3).

In the preoperative period biological samples were taken for laboratory tests, such as: urine culture, blood test, blood group determination, C-reactive protein in serum, degradation products (urea and creatinine), examination of urinary sediment (color, odor density, proteinuria, leukocituria, and bacteriuria). The obtained results, together with other medical history of the patients were crucial for forming a general picture of health condition of the patient and evaluation of anesthesiology risk of surgery.

RESULTS

At the Clinic of Pediatric Surgery in Skopje in the period from 1999 to 2014, 76 children (114 ureters) with symptomatic primary VUR diagnosed with prenatal ultrasound diagnostics, voiding cystourethrogram or direct radioisotope voiding cystography were surgically treated. The treatment was made with "STING" endoscopic procedure or an open surgical procedure. 44 patients (67 ureters) were treated with an open surgical technique. Of those, 30 were female (average age of 6 years)

Table 1. *Characteristics of the study group*

study group	open surgical treatment		endoscopic treatment	
	male	female	male	female
number of patients	14	30	7	25
age (mean value)	4.7	6	4.7	6
total number of ureters	67		47	
children with unilateral reflux	33		17	
children with bilateral reflux	17		15	
children with II grade of reflux	0		3	
children with III grade of reflux	0		15	
children with IV grade reflux	13		10	
children with V grade reflux	31		4	
hospitalization in days (average)	9		1.5	

and 14 were male (average age of 4.7 years). Reflux was diagnosed on the right ureter in 20 patients, 13 children had reflux on the left ureter and 17 children had bilateral reflux. VUR grade IV was determined in 13 patients. The number of children with VUR grade V was 31. All children were treated with intravesical and extavesical reinplantation of the reflux ureter into the bladder wall. Politano-Leadbetter access was used. The average time of hospitalization for these patients was 9 days (Table 1).

32 patients (47 ureters) were treated with endoscopic treatment with submucosal injection of copolymer dextranomer/ hyaluronic acid at the junction of reflux ureter with the bladder – "STING" procedure. 25 patients were female (average age of 6.1 years) and 7 were male (average age of 4.7 years). This study included only children which were applied to monitoring for the overall protocol. Reflux was diagnosed on the right ureter in 7 patients, 10 children had reflux on the left ureter and 15 children had bilateral reflux. Of these, three were grade II, 15 were grade III, 10 had grade IV and 3 children had grade V VUR. One patient with grade IV VUR of the left ureter was diagnosed with hypoplasia of the left kidney. The average time of hospitalization for these patients was 1.5 days.

Open surgical technique

Open surgical technique was used to increase the length of intravesical ureter. All patients were treated with intravesical reinplantation of the ureter into the bladder wall. Politano-Leadbetter access was used. The average time of the intervention was about 90 minutes in unilateral reflux and in bilateral, surgery lasted 120 minutes. During the operation, nearly all patients were given at least one unit of blood and/ or blood derivatives.

After the open surgical technique all patients received double antibiotic therapy. The need for analgesics lasted for 3 to 4 days. Hematuria was noted also in all children. Its duration was 3 to 5 days. The majority of children were given an additional unit of blood and/ or blood derivatives. Urinary catheter is extracted in the sixth postoperative day. Retrovesical drain is extracted the next day. Ureteric stent was extracted in average the eighth postoperative day. After removing the stents, control ultrasonography was performed. Complete blood count, by examining the renal function: degradation products (urea and creatinine), examination of urinary sediment was made every second day.

The final result in these patients meant a reduction of 3 degrees of the initial degree of VUR, mostly Grade V to grade II or I. Average time of hospitalization for these patients was 9 days (from 5 to 13 days).

One act surgery was used in 33 patients with VUR of the left or right ureter, and bilateral VUR was present in 17 patients. 12 cases were treated preliminary with uretero–cutaneo–stoma. In bilateral uretero–cutaneo–stomas, reimplantation was done in two consecutive acts, separately for each ureter.

Treatment in two acts was indicated because of the existence of extreme expansion of the diameter of the lumen of the ureter, severe hydronephrosis or poor general health of patients.

Desired result represented the achievement of proportion for the length of the submucosal tunnel of the ureter to the ureter - 4-5:1. With the open surgical tehnique 62 ureters showed lowering the rate of VUR by two or more grades. In 5 ureters the results were not satisfying, due to progressive rising of VUR grade after the surgery (3), VUR on the contralateral ureter (2).

Endoscopic treatment

32 patients (47 ureters) were treated with endoscopic treatment with submucosal injection of copoly-

mer dextranomer/ hyaluronic acid in the mouth of the reflux ureter, - "STING" procedure.

In endoscopic treatment, there was no need for postoperative antibiotic therapy or analgesics. There was no need to ordinate blood and/ or blood derivatives. Antibiotic prophylaxis was given before treatment. Patients receiving anticholinergics continued with their therapy.

The final result in these patients meant a decrease of 2 degrees of the initial degree of VUR, usually from grade IV to grade II or I.

The evaluation of the results of the treatment was done mainly according to the following criteria: reduced grade of reflux, maintaining renal function, absence of urinary infection and postoperative complications (contralateral reflux, ureteral obstruction, additional disorders, and dysfunctional bladder).

After discharge from our department, all patients were monitored with ultrasonography review 7 days after surgery (to verify the presence of a bolus) and six weeks after the intervention (to determine the extent of possible hydronephrosis). Radio isotopic cystography was performed 6 months after surgery. In cases where the finding was inconclusive, voiding cystourethrogram was performed.

Out of all treated 76 children, 56 (80 ureters) conducted over the whole monitoring protocol. The reduction of 2 levels with VUR endoscopic procedure or 3 degrees in open surgical technique and absence of postoperative complications is accepted as a good result (3). In open surgical technique, 40 ureters (93.8%) achieved a good result.

Endoscopy definitely solved the problem in 34 ureters or 70% of the patients. VUR has been detected again on the 13 operated ureters or more often on the contralateral ureter. They were successfully treated with re-endoscopy.

DISCUSSION

Treatment of children with reflux tends to prevent kidney infection, kidney damage and complications caused by kidney damage. Treatment includes pharmacotherapy, surgical treatmant and monitoring. Greenfield and Wlaker united several general principles for the treatment of children diagnosed with VUR (3). Spontaneous resolution of VUR in about 70% is common in children younger than 5 years and in lower grade reflux (gr. 1, gr. 2), grade 3 have spontaneous resolution of 50%, and less likely in children over 5 years. It is unlikely that expressed reflux will spontaneously withdraw. Sterile reflux generally does not lead to reflux nephropathy, long-term antibiotic prophylaxis in children is safe and surgery that corrected VUR is highly successful (10, 11).

Drug therapy with antibiotic prophylaxis is considered successful if the child does not get an infection; do not develop kidney damage and scarring in the parenchyma and VUR spontaneously quit (4).

Anticholinergic and bladder training can ameliorate the symptoms of dysfunctional voiding and reduce the risk of infection.

Open surgery involves modification of dysfunctional uretero-vesical circuit, which creates a ratio of 4: 1 to 5:1 in length for intramural ureter to the diameter of the ureter (6).

Endoscopic correction of VUR is injection of natural or synthetic substances in the posterior muscle wall of the uretero-vesical circuit. Subsequent swelling suppresses and elevates the urethral lumen so that it prevents reflux.

Depending on sex, age of the patient, grade of reflux, the changes in the renal parenchyma, systemic changes that can note in the presence of VUR will decide which type of treatment would be an appropriate choice for a particular patient. Each treatment is indicated in varying degrees of development of the disease (9).

Although statistics shows that open surgical technique is superior to "STING" procedure, however endoscopy proved better in terms of time of verticalization of the patients, the need to receive additional drug therapy, blood loss during operation and the duration of the operation (11). But we cannot favor any operational method because we believe that both methods have their indicational area in appropriate developmental stage of VUR (10).

CONCLUSION

Open surgical procedure is reserved for more complicated VUR cases (grade IV-V), and for patients with previously failed endoscopic procedure. This surgical method is superior in terms of satisfactory end results. This is relatively inexpensive method, but the time of verticalization of the patients, the need to receive additional drug therapy, long time of operation and anesthesia, grow up the cost.

Endoscopic treatment ("STING" procedure) can be applied in patients with VUR grade greater than 2, but with previously failed conservative treatment and other conditions. Deflux product is expensive, but the one-day surgery, short time of operation and anesthesia reduces the hospital costs. Patient assessment and decision on which method will be used should always be made individually for each child.

Conflict of interest

All authors agreed for this paper to be published, and report no conflict of interest.

Sažetak

EVALUACIJA DVE HIRURŠKE PROCEDURE U LEČENJU PRIMARNOG VEZIKOURETERALNOG REFLUKSA KOD DECE: PETNAESTOGODIŠNJE ISKUSTVO

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Cilj: Cilj studije je bio procena uspešnosti dva različita hirurška tretmana vezikoureteralnog refluksa (VUR), kroz stopu uspešnosti i ishod lečenja.

Metode: Retrospektivna studija o deci s primarnim VUR-om i njihovo hirurško lečenje od 1999. do 2014. godine, na Univerzitetskoj Klinici za dečiju hirurgiju u Skoplju. Ukupno 76 dece (114 uretera) s VUR-om, u rasponu od drugog do petog stepena, je lečeno hirurški. Od toga 44 pacijenta (67 uretera) je lečeno otvorenom hirurškom tehnikom, a 32 pacijenta (47 uretera) je endoskopski lečeno "Sting" procedurom. Analizirani su sledeći parametri: trajanje intervencije, trajanje hospitalizacije, potreba za korišćenjem antibiotika i analgetika u terapiji i potreba za transfuzijom krvi i krvnih derivata. Rezultat hirurškog lečenja je takođe praćen. Dobrim rezultatom se smatra smanjenje VUR-a za 2 stepena upotrebom endoskopske metode ili 3 stepena kod pacijenata lečenih otvorenom hirurškom tehnikom.

Rezultati: Pacijenti lečeni otvorenom hirurškom procedurom, bili su hospitalizovani u proseku 9 dana (raspon od 5 do 13 dana). Sva deca su dobila dvostruku antibiotsku terapiju. Potreba za analgeticima trajala je od 3 do 4 dana. 90% tretirane dece imalo je potrebu za transfuzijom krvi i / ili krvnih derivata. Stopa uspeha ove metode je 93,8%. Endoskopska procedura je izvedena po tipu jednodnevnog hirurškog zahvata. Prosečno trajanje je bilo 15 minuta. Jedna, profilaktička doza antibiotika je ordinirana. Nije bilo potrebe za transfuzijom krvi i / ili krvnih derivata. Ukupna uspešnost lečenja ovom metodom je oko 70%.

Zaključak: Otvorena hirurška procedura se koristi za složenije slučajeve, VUR IV-V stepena ili ranije neuspešno lečenih. Endoskopska "Sting" procedura se najčešće koristi kod pacijenata s VUR stepenom većim od 2, nakon prethodno neuspešnog konzervativnog lečenja, infekcije mokraćnih puteva praćene febrilnošću uprkos antibiotskoj profilaksi i/ili kod pojave novih ožiljaka u bubrežnom parenhimu. Procena pacijenata i odluka o izboru metode lečenja uvek mora biti individualna za svako dete.

Ključne reči: deca, primarni vezikoureteralni refluks, hirurško lečenje, endoskopsko lečenje.

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ANALYZES OF ANTIPLATELETS AND ANTICOAGULANTS UTILIZATION IN PATIENTS TREATED IN CARDIOVASCULAR REHABILITATION CENTER FROM CROATIA

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Abstract: **Purpose:** Discordance with the guidelines and underutilization of pharmacotherapy for secondary prevention frequently exists in clinical practice. Aim of our study was to assess the prescription routine and drug utilization patterns for antiplatelets and peroral anticoagulants in tertiary medical center specialized for cardiovascular rehabilitation.

Methods: study included 96 consecutive patients scheduled for cardiovascular rehabilitation in period 1-6 months after the acute treatment for ischemic 87 (80.2%) and valvular heart disease 18 (19.8%). Patients were divided according to etiology of heart disease and type of acute cardiovascular treatments (conservative, percutaneous coronary interventions (PCI) and surgery).

Results: Dual antiplatelet therapy was the most commonly applied regimen in 84 (87.5%) of conservatively treated myocardial infarctions, 47 (61.9%) of percutaneous coronary interventions (PCI) and 13 (58.9%) of surgically treated group ($p > 0.05$). Among studied group of patients significant differences in utilization were found for warfarin, or combinations of antiplatelets with warfarin ($p < 0.001$), as well as studied etiologies of heart disease ($p < 0.001$), whilst there were no differences for those groups for studied antiplatelets drugs ($p > 0.05$). All four of patients that received triple therapy (4.17%) were from surgical group. Underutilization of antiplatelets in ischemic heart disease was at 11 (14.3%) what was congruent with the developed industrial nations.

Conclusions: Acute cardiovascular treatment type, but not heart disease etiology, had significant influence on subsequent prescription routine. Decreased use of pharmacological agents for secondary prevention in surgical patients was revealed. Drug utilization analyzes can offer improvement in optimizing medical treatments, quality of care and decrease unnecessary polypragmasia, as well as improve economical efficiency of medical management.

Key words: drug utilization (DU) review; antiplatelets (AP); anticoagulants; warfarin; cardiovascular rehabilitation; ischemic heart disease; valvular heart disease.

INTRODUCTION

Antiplatelets (AP) and oral anticoagulants (OA) make inevitable components of successful long term management of various atherosclerotic born diseases (1). Named groups are among the most frequently prescribed therapy in prolonged course worldwide, thanks to efficiency in prevention of thrombogenic complications through primary, secondary or tertiary settings (2). However, occurrence of re-thrombosis is still not completely diminished by monotherapeutic approach, even with optimally selected dosage and treatment duration (3). Dual antiplatelet therapy using acetylsalicylate and thienopyridine considerably improves those outcomes, in terms of rate of major cardiovascular complications (4). Overall risk for developing major thrombotic complications on the other hand is becoming excessively increased, due to multifaceted relations. Complex associations include growth in number of population with earlier cardiovascular treatments, burden of more than a few of chronic comorbidities, di-

sease chronicity, as well as the ageing of population. The triple drug regimens, comprising from anticoagulant and two antiplatelets, were introduced for secondary and tertiary prevention of casuistic with prominent pro-thrombotic risk (5). Although the antithrombogenic effect of triple combination is more powerful, at the same time the prevalence of clinically important bleedings is unpleasantly increased. Triple antithrombotic therapies are dominantly matter of debates in regard to ideal combinations of drugs, dosage titrations or duration.

Costs of health care for advanced atherosclerotic process (including cerebrovascular and ischemic heart disease) tend to be additionally increased, and of reverse relation with the continuous adherence to established preventive measures (2). Underutilization of pharmacological secondary prevention is frequently found in clinical practice; moreover it is responsible for differences in prevalence of cardiovascular diseases, morbidity or mortality, which are found between various nations (6). There is a relative lack of data in studies concerning applying of secondary preventive measures from transitional European countries. The aim of our study was to assess drug utilization patterns for antiplaelets and peroral anticoagulants in tertiary medical center specialized for cardiovascular rehabilitation from Croatia. Additionally, combined effects of antiplatelet-anticoagulant therapy were studied in relation with cardiovascular risk factors, comorbities and clinical diagnostics.

PATIENTS AND METHODS

This was phase IV, open, not randomized and not controlled investigation, having one treatment arm. It included patients scheduled for cardiovascular rehabilitation subsequent to treatment for ischemic or valvular heart disease. Indications coverage included patients after implantation of stent for acute coronary syndrome or chronic ischemic heart disease, as well as those with surgical revascularization for coronary artery disease, and patients with valvular surgery (primary procedure, or as combined procedure with surgical revascularization. Procedures included implantation of prosthetic valves (animal or synthetic), valvuloplastic (using ring, artificial cordes or other). Study timeline included period from 1-6 months after the acute treatments. Patients were examined by team of experienced specialists including internists, cardiologists and psychologist prior to inclusion. Diagnostics included medical history (evaluation of underlying chronic conditions, cardiovascular risk factors and relevant comorbidities), transthoracic echocardiography, anthropometrics, laboratory and electrocardiography. Medical history included evaluation of underlying chronic conditions, cardiovascular risk factors and relevant comorbidities. Population was analyzed through groups of cardiovascular acute treatments and structure of antiplatelets and anticoagulant therapy.

Patients with severe acute illness or chronic conditions considered as contraindications for cardiovascular rehabilitation were not included. Those namely were: unstable angina (acute and chronic of Canadian Cardiac society-CCS III to IV grade), hemodynamically significant pericardial effusion, decompensated heart failure (New York heart association-NYHA III and IV grade), hemodynamic instability, significant disorders of rhythms (ventricular fibrillation, sustained ventricular tachycardia, significant bradycardia in need for pacemaker), decompensated diabetes (untreated hyperglycemia, hypoglycemia, ketosis), thyroid disorders (untreated hyperthyreosis, hypotyreosis), significant acid base misbalance (acidosis or alkalosis), advanced or end stage respiratory disease (chronic obstructive disease of Global Initiative for Chronic Obstructive Lung Disease-GOLD III and IV grade, untreated asthma, pulmonary hypertension, pulmonary embolism, pleural effusion, pneumonia, active tuberculosis), acute febrile illnesses (sepsis, flu, urinary infections), end stage renal disease (in need for dialysis), malignant disease (untreated, being in remission for less than 2 years, metastatic cancer), edema (peripheral, ascites or anasarca), severe hematologic or rheostatic disorders (severe anemia, patients that had transfusion after the first postoperative week, pronounced increase or decrease of any type of blood cells i.e. leucopenia and leucosis, as well as others) and those with significant early postoperative surgical complications (wound dehiscence, renal failure, surgery scission-related bleeding, infection/sepsis).

Main outcome measures

Drug utilization analyzes: Prescription analyzes included prevalence of proton pump inhibitor, ACE-inhibitor/sartan, beta blocker, calcium antagonists, loop diuretic, antidiabetics, acetylsalicylate/thienopyridine and peroral anticoagulant i.e. warfarin. While quoted drugs use was assessed as therapeutic group, and there were no additional individual analyzes, the rate of specific antiplatelets, peroral anticoagulant and their combinations were analyzed. Psychoneuromodulatory therapy was not included in analyzes (anxiolytics, hypnotics).

Anthropometrics: Measurements of body weight were given in kilograms, height in meters and body mass index (BMI) calculated (kg/m^2). Waist and hip circumferences (WC, HC) and ratios (WHR) were presented in centimeters.

Laboratory diagnostics: Samples were taken in morning hors 07:30-08:30 AM in fasting patients. Routine comprised from: Complete blood count (CBC) with number of erythrocytes (ERC) multiplied by 10^{12}, hematocrit (HCT) in L/L, mean corpuscular erythrocyte volume (MCV) in fL, number of platelets (PLT) multiplied by 10^{9}; leukocyte count (LKC) multiplied by 10^{9}. Biochemical analyzes comprised of alanine aminotransferase (ALT) in IU/L at 37'C, aspartate aminotransferase (AST) in IU/L at 37'C, gamma glutamyltransferase (GGT) in IU/L at 37'C, serum glucose in mmol/L, total cholesterol (CHOL) in mmol/L, low density lipoprotein (LDL) in mmol/L, high density lipoprotein (HDL) in mmol/L, triglycerides (TG) in mmol/L, creatinine (CR) in μmol/L, urea in mmol/L, uric acid (UA) in μmol/L and thyroid stimulating hormone in mIU/L.

Cardiovascular risk: assessment included prevalence of hypertension, hypercholesterolemia, chronic renal disease (CRD), treated diabetes mellitus, glucose intolerance, smoking history, chronic obstructive pulmonary disease, any disturbance of psychological profile (DPP), known atherosclerotic process and thrombosis (medical history of clinically overt peripheral artery disease, cerebrovascular stroke, carotid artery stenosis and pulmonary artery embolism), atrial fibrillation, past myocardial infarction, preserving of systolic function of the left ventricle (cutoff point set at 50%).

Echocardiography: Transthoracic echocardiography assessments were done by two experienced cardiologists on Toshiba "Artida" equipped with 3 MHz cardiology probe, following general recommendations by American Society for Echocardiography and European Association of cardiovascular imaging[7].

Ethical issues: Study was approved by ethical committee of the University Hospital "Thalassotherapia Opatija" in line with the good clinical practice guidelines. Patients were included upon signing of written informed consent. There were no financial compensations, supports or grants for patients and authors engaged in the study. Study was not performed on behalf of any other parties than presented.

Statistical analyses: Population and groups were studied with descriptive statistic and presented as means and standard deviations. Population demographic, comorbidities, and nutritional risk screen was tested for differences with Chi square tests accordingly. Data on anthropometrics, laboratory, echocardiography and remainder numeric data were analyzed for differences by Mann-Whitney U test or Kruskal-Wallis ANOVA by ranks. Correlation of the anticoagulant or antiplatelets therapy with clinical diagnostics and outcomes was done by Spearman Rho. P value less than 0.05 was considered significant. Statistical analyses were done by experienced statistician using Statistica 10 for Windows and IBM-SPSS12 v20.

Table 1. *Characteristics of the patient sample (n = 96) and studied groups*

		Total	Treatments			Kruskal Wallis ANOVA by ranks	Disease		Chi square
		N = 96	Conservative	PCI	Surgery		Ischemic	Valvular	
		N (%)	N (%)	N (%)	N (%)		N (%)	N (%)	
Age group	< 44	5 (5.2%)	0 (0.0%)	1 (2.4%)	4 (8.7%)	0.161	2 (2.6%)	3 (15.8%)	0.063
	45-65	44 (45.8%)	3 (37.5%)	26 (61.9%)	15 (32.6%)		37 (48.1%)	7 (36.8%)	
	> 65	47 (49.0%)	5 (62.5%)	15 (35.7%)	27 (58.7%)		38 (49.4%)	9 (47.4%)	
BMI grade	< 25	19 (19.8%)	3 (37.5%)	6 (14.3%)	10 (21.7%)	0.020	13 (16.9%)	6 (31.6%)	0.316
	25-30	56 (58.3%)	5 (62.5%)	21 (50.0%)	30 (65.2%)		45 (58.4%)	11 (57.9%)	
	30-35	15 (15.6%)	0 (0.0%)	11 (26.2%)	4 (8.7%)		13 (16.9%)	2 (10.5%)	
	> 35	6 (6.3%)	0 (0.0%)	4 (9.5%)	2 (4.3%)		6 (7.8%)	0 (0.0%)	
Nicotine history	Non-smoker	16 (16.7%)	1 (12.5%)	6 (14.3%)	9 (19.6%)	0.264	10 (13.0%)	6 (31.6%)	0.139
	Active smoker	35 (36.5%)	3 (37.5%)	22 (52.4%)	10 (21.7%)		30 (39.0%)	5 (26.3%)	
	Former smoker	45 (46.9%)	4 (50.0%)	14 (33.3%)	27 (58.7%)		37 (48.1%)	8 (42.1%)	
Chronic obstructive pulmonary disease		32 (33.3%)	2 (25.0%)	15 (35.7%)	15 (32.6%)	0.834	25 (32.5%)	7 (36.8%)	0.717
Arterial hypertension		86 (89.6%)	8 (100.0%)	41 (97.6%)	37 (80.4%)	0.020	73 (94.8%)	13 (68.4%)	0.001
Hyperlipoproteinemia		94 (97.9%)	8 (100.0%)	41 (97.6%)	45 (97.8%)	0.910	77 (100.0%)	17 (89.5%)	0.004
Chronic renal disease		43 (44.8%)	1 (12.5%)	14 (33.3%)	28 (60.9%)	0.058	30 (39.0%)	13 (68.4%)	0.021
Diabetes mellitus		25 (26.0%)	3 (37.5%)	10 (23.8%)	12 (26.1%)	0.724	25 (32.5%)	0 (0.0%)	0.004
Glucose intolerance		34 (35.4%)	4 (50.0%)	15 (35.7%)	15 (32.6%)	0.639	27 (35.1%)	7 (36.8%)	0.885
Metabolic syndrome		63 (65.6%)	5 (62.5%)	28 (66.7%)	30 (65.2%)	0.972	55 (71.4%)	8 (42.1%)	0.016
Known coronary artery disease		79 (82.3%)	8 (100.0%)	42 (100.0%)	29 (63.0%)	< 0.001	77 (100.0%)	2 (10.5%)	< 0.001
Past myocardial infarction		62 (64.6%)	8 (100.0%)	42 (100.0%)	12 (26.1%)	< 0.001	60 (77.9%)	2 (10.5%)	< 0.001
Atherothrombotic disease		34 (35.4%)	1 (12.5%)	11 (26.2%)	22 (47.8%)	0.040	30 (39.0%)	4 (21.1%)	0.144
Atrial fibrillation		5 (5.2%)	0 (0.0%)	1 (2.4%)	4 (8.7%)	0.328	4 (5.2%)	1 (5.3%)	0.990
Preserved systolic function (LVEF > 50%)		66 (68.8%)	5 (62.5%)	25 (59.5%)	36 (78.3%)	0.157	51 (66.2%)	15 (78.9%)	0.284

PCI — percutaneous coronary intervention; **CABG** — coronary artery bypass surgery; **VS** — valvular surgery; **LVEF** — left ventricle ejection fraction

RESULTS

Patients

Mean age of patient was 63.1 years, with range 23-86. There was more of male patients, 70 (72.9%), than female 26 (27.1%). Patients were scheduled for cardiovascular rehabilitation in the timeline 1-6 months after heart surgery; median period at inclusion was 2.4 months. There were 77 patients (80.2%) with acute treatment for ischemic heart disease and 18 (19.8%) for valvular heart disease; with total of 46 (47.9%) surgical treatments; 42 (43.8%) percutaneous coronary interventions and 8 (8.3%) of conservatively treated myocardial infarctions. Coronary artery bypass surgery (CABG) was performed in 28 patients (29.2%), of which combined operation with valvular surgery (VS) was performed in 1 (1.1%). Results of cardiovascular diagnostics among studied groups of patients are presented in the Table 1.

There were no patients with clinically overt acute gastrointestinal hemorrhage. There were no reports on dyspeptic symptoms within medical history, no recorded reflux esophagitis (verified by endoscopy).

Cardiovascular diagnostics

Differences in diagnostics among studied groups of acute treatment and etiologies of heart disease are presented in the Table 2, including the appraisal of clinical relevance.

Antiplatelet and anticoagulant therapy

Significant differences were found in use of antiplatelets (any AP agent) and previous treatments ($p < 0.001$); in 36 (85.7%) patients with PCI, 7 (87.5%) of patients with conservative treatment and 30 (65.2%) of surgically treated. Peroral anticoagulant (warfarin) therapy was used only in surgical patients, with prevalence of 24/46 (52.5%). Significant difference was found on basis of heart disease etiology for prevalence of warfarin 8 (10.4%) vs. 16 (84.2%); ($p < 0.001$) for ischemic and valvular backgrounds respectively. There

Table 2. *Clinical diagnostics within studied groups of treatments and etiology of heart disease*

	Total	Treatments			Kruskal Wallis ANOVA by ranks	Disease		Mann Whitney U test
	N = 96	Conservative	PCI	Surgery		Ischemic	Valvular	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
n (coronary risk factors)	6.2 ± 1.6	6.8 ± 0.9	6.8 ± 1.2	5.7 ± 1.9	0.018	6.7 ± 1.2	4.3 ± 1.9	< 0.001
Age (years)	63.6 ± 11.5	70.0 ± 11.5	62.0 ± 8.7	64.0 ± 13.4	0.080	64.2 ± 9.8	61.0 ± 16.8	0.971
Height (m)	1.70 ± 0.10	1.66 ± 0.10	1.67 ± 0.08	1.72 ± 0.10	0.024	1.69 ± 0.09	1.72 ± 0.11	0.639
Weight (kg)	80.3 ± 13.0	73.2 ± 12.8	80.5 ± 12.1	81.2 ± 13.7	0.338	81.0 ± 12.1	77.4 ± 16.3	0.153
BMI (kg/m^2)	27.9 ± 3.7	25.9 ± 2.5	28.9 ± 3.9	27.3 ± 3.5	0.028	28.3 ± 3.7	26.2 ± 3.0	0.012
Waist circumference (cm)	100.7 ± 9.1	97.5 ± 6.8	101.9 ± 9.8	100.1 ± 8.7	0.348	101.6 ± 8.8	96.8 ± 9.5	0.065
Hip circumference (cm)	101.9 ± 11.4	99.9 ± 6.3	104.0 ± 6.6	100.3 ± 14.8	0.146	103.1 ± 6.4	97.1 ± 21.8	0.242
VHR (n/n)	1.0 ± 0.1	0.98 ± 0.08	0.98 ± 0.07	0.98 ± 0.07	0.995	0.99 ± 0.07	0.95 ± 0.07	0.035
Erythrocytes count (n*1012)	4.39 ± 0.60	4.45 ± 0.56	4.55 ± 0.53	4.23 ± 0.64	0.021	4.41 ± 0.57	4.31 ± 0.73	0.459
Hematrocryte (n/n)	0.39 ± 0.05	0.40 ± 0.04	0.41 ± 0.04	0.37 ± 0.05	0.005	0.39 ± 0.05	0.37 ± 0.06	0.104
Mean corpuscular volume (fL)	88 ± 11	91 ± 4	88 ± 10	87 ± 13	0.498	88 ± 12	89 ± 6	0.937
Leukocytes (n*1012)	7.93 ± 2.47	7.46 ± 2.12	7.87 ± 2.35	8.06 ± 2.66	0.896	8.06 ± 2.43	7.37 ± 2.63	0.208
Platelets (n*109)	302 ± 136	278 ± 113	259 ± 81	346 ± 165	0.060	305 ± 141	287 ± 114	0.797
Glucose (mmol/L)	6.5 ± 1.2	6.7 ± 0.9	6.5 ± 1.4	6.5 ± 1.1	0.635	6.7 ± 1.3	5.9 ± 0.4	0.008
Creatinine (μmol/L)	114.1 ± 49.6	100.8 ± 28.5	111.1 ± 58.4	119.1 ± 43.6	0.032	114.5 ± 54.5	112.2 ± 21.2	0.187
Triglycerides (mmol/L)	1.4 ± 0.8	1.52 ± 0.70	1.28 ± 0.61	1.59 ± 0.98	0.264	1.39 ± 0.63	1.68 ± 1.35	0.861
Cholesterol (mmol/L)	4.3 ± 1.2	3.76 ± 0.73	3.93 ± 1.23	4.70 ± 1.21	0.002	4.07 ± 1.13	5.14 ± 1.32	0.001
HDL-cholesterol (mmol/L)	0.9 ± 0.4	0.89 ± 0.30	0.95 ± 0.32	0.88 ± 0.52	0.526	0.88 ± 0.34	1.04 ± 0.67	0.390
LDL-cholesterol (mmol/L)	2.2 ± 1.1	1.69 ± 0.75	1.96 ± 1.18	2.60 ± 0.92	0.001	2.10 ± 1.08	2.84 ± 0.88	0.002
AST (IU/L at 37'C)	29.3 ± 81.1	21.63 ± 8.02	22.21 ± 6.46	37.07 ± 117.19	0.203	20.82 ± 7.07	63.58 ± 181.63	0.254
ALT (IU/L at 37'C	36.9 ± 52.3	28.00 ± 13.95	32.05 ± 17.46	42.93 ± 73.44	0.896	31.64 ± 16.50	58.37 ± 112.61	0.613
GGT (IU/L at 37'C	52.7 ± 54.7	35.38	43.21 ± 31.08	64.33 ± 70.99	0.100	51.74 ± 53.19	56.47 ± 61.96	0.626
LVEDd (mm)	52.4 ± 4.8	52.0 ± 6.4	52.1 ± 4.3	52.8 ± 5.0	0.903	52.3 ± 4.6	52.8 ± 5.7	0.723
LVEF (%)	50.7 ± 8.5	47.5 ± 12.0	49.1 ± 9.2	52.8 ± 6.6	0.102	50.0 ± 8.8	53.6 ± 6.6	0.067
AV PG (mmHg)	14.7 ± 11.1	12.3 ± 5.5	10.9 ± 10.2	18.4 ± 11.5	0.001	12.4 ± 10.3	23.7 ± 9.6	< 0.001
e/a (n/n)	1.1 ± 0.5	1.1 ± 0.7	1.0 ± 0.5	1.2 ± 0.5	0.372	1.1 ± 0.5	1.3 ± 0.5	0.051

SD — standard deviations; **PCI** — percutaneous coronary intervention; **CABG** — coronary artery bypass surgery; **CS** — clinically significant difference; **NS** — clinically not significant difference; **BMI** — body mass index; **ALT** — alanine aminotransferase in IU/L at 37'C, **AST** — aspartate aminotransferase in IU/L at 37'C, **GGT** — gamma glutamyltransferase in IU/L at 37'C, HDL — high density lipoprotein; **LDL** — low density lipoprotein; **LVEDD** — left ventricle end diastolic dimension; **LVEF** — left ventricle ejection fraction; **AV PG** — aortic valve peak flow gradient.

Table 3. *General cardiovascular drugs*

		Treatments			Kruskal Wallis ANOVA by ranks	Disease		Chi square
		Conservative N (%)	PCI N (%)	Surgery N (%)		Ischemic N (%)	Valvular N (%)	
Angiontensinogen-convertase inhibitor/sartan		7 (87.5%)	35 (83.3%)	17 (37.0%)	< 0.001	51 (66.2%)	8 (42.1%)	0.053
Beta blocker		7 (87.5%)	40 (95.2%)	34 (73.9%)	0.023	68 (88.3%)	13 (68.4%)	0.032
Calcium antagonist		3 (37.5%)	8 (19.0%)	4 (8.7%)	0.086	14 (18.2%)	1 (5.3%)	0.165
Loop diuretic		4 (50.0%)	8 (19.0%)	13 (28.3%)	0.171	20 (26.0%)	5 (26.3%)	0.976
Statin		8 (100.0%)	40 (95.2%)	22 (47.8%)	< 0.001	66 (85.7%)	4 (21.1%)	< 0.001
Omega-3/fibrate		3 (37.5%)	26 (61.9%)	3 (6.5%)	< 0.001	31 (40.3%)	1 (5.3%)	0.004
Nitrate (sublingval and peroral)		4 (50.0%)	30 (71.4%)	4 (8.7%)	< 0.001	38 (49.4%)	0 (0.0%)	< 0.001
Trimetazidine		5 (62.5%)	3 (7.1%)	1 (2.2%)	< 0.001	9 (11.7%)	0 (0.0%)	0.117
Proton pump inhibitor		7 (87.5%)	10 (23.8%)	30 (65.2%)	< 0.001	36 (46.8%)	11 (57.9%)	0.384
Oral antidiabetics		2 (25.0%)	8 (19.0%)	5 (10.9%)	0.432	15 (19.5%)	0 (0.0%)	0.036
Insuline		1 (12.5%)	3 (7.1%)	2 (4.3%)	0.649	6 (7.8%)	0 (0.0%)	0.209
Acetilsalycilate (ASA)		7 (87.5%)	36 (85.7%)	36 (78.3%)	0.610	64 (83.1%)	15 (78.9%)	0.670
Thienopyridine (T)		7 (87.5%)	27 (64.3%)	28 (60.9%)	0.351	49 (63.6%)	13 (68.4%)	0.696
Warfarin		0 (0.0%)	0 (0.0%)	24 (52.2%)	< 0.001	8 (10.4%)	16 (84.2%)	< 0.001
AP-combinations	None	1 (12.5%)	5 (11.9%)	9 (19.6%)	0.369	11 (14.3%)	4 (21.1%)	0.552
	Acetilsalycilate	0 (0.0%)	10 (23.8%)	9 (19.6%)		17 (22.1%)	2 (10.5%)	
	Clopidrogel	0 (0.0%)	1 (2.4%)	1 (2.2%)		2 (2.6%)	0 (0.0%)	
	Dual AP	7 (87.5%)	26 (61.9%)	27 (58.7%)		47 (61.0%)	13 (68.4%)	
Warfarin + AP-combinations	None	8 (100.0%)	42 (100.0%)	22 (47.8%)	< 0.001	69 (89.6%)	3 (15.8%)	< 0.001
	Warfarine	0 (0.0%)	0 (0.0%)	6 (13.0%)		3 (3.9%)	3 (15.8%)	
	Triple	0 (0.0%)	0 (0.0%)	4 (8.7%)		2 (2.6%)	2 (10.5%)	
	Warfarine + AP	0 (0.0%)	0 (0.0%)	14 (30.4%)		3 (3.9%)	11 (57.9%)	

		Mean ± SD	Mean ± SD	Mean ± SD	Kruskal Wallis ANOVA by ranks	Mean ± SD	Mean ± SD	Mann Whitney U test
	N (drugs)	8.1 ± 2.0	6.5 ± 1.5	4.8 ± 1.3	< 0.001	6.2 ± 1.7	4.6 ± 1.5	< 0.001
	Antiplatelts (%)	11.8 ± 5.4	16.4 ± 5.0	13.4 ± 10.8	0.308	16.3 ± 6.7	7.4 ± 10.8	0.001
	Warfarin (%)	0.0 ± 0.0	0.0 ± 0.0	11.5 ± 12.1	< 0.001	1.8 ± 5.5	20.4 ± 11.0	< 0.001
	AP+Warfarin (%)	0.0 ± 0.0	0.0 ± 0.0	8.7 ± 16.2	0.001	3.3 ± 10.7	7.8 ± 16.1	0.146

SD — standard deviations; **n** — number; **CABG** — coronary artery bypass surgery; **VS** — valvular surgery; **AP** — antiplatelets; **ASA** — Acetylsalicylate acid; **T** — Thienopyridine

were no differences in studied platelets regimens for studied groups of treatment and disease etiology, while regimens that included peroral anticoagulant therapy showed significant differences in both studied categories.

Drug utilization analyzes for common cardiovascular group of drugs was studied in connection with type of previous cardiovascular treatment (percutaneous coronary interventions or surgery-coronary artery bypass graft and/or valvular surgery) and etiology of heart disease (ischemic or valvular). According to type of cardiovascular treatment, there were significant differences for angiontensinogen-convertase inhibitor/sartan; beta blockers, antilipid drugs, antianginals and warfarin. On the other hand, when etiology of heart disease was studied, significant differences were found for beta blockers, nitrates, antilipid drugs, peroral antidiabetics and warfarin.

Relative shares of specific representatives and drug combinations of all studied group of drugs and their combinations are shown in the Table 3.

During the study course, we did not have any case of clinically significant bleeding (intracerebral, pericardial, pleural, abdominal, and gastrointestinal) and no blood transfusions. Cases of bleeding associated with surgical treatment complications (early complications, in first postoperative week) that had to be managed by surgery were not included in the study.

DISCUSSION

Current study for the first time systematically analyzed utilization of antiplatelets and anticoagulant group in patients with secondary prevention and rehabilitation from Croatia. Share of antiplatelets agents was in range from 10-17%, while peroral anticoagulants made about 12% of total prescriptions. Relative portions of antiplatelet and anticoagulant group were greater in the postsurgical group, which in part represents suspected underutilization of antilipemics, beta blockers and angiotensin-convertase inhibitors/sartans; pa-

rallel with decrease in total number of drugs per patient (8). Consumption of antiplatelets was greater in the group of patients with ischemic heart disease, conversely to the warfarin which was more commonly used with valvular operations. Additional factor that favored peroral anticoagulants was presence of atrial fibrillation which was pounded more frequently in surgical patients, especially ones with ischemic heart disease. Interestingly, there were no differences in consumption of antiplatelets or their combinations within studied groups of cardiovascular treatment or the etiology of heart disease. Warfarin and its combinations showed to be plentifully related with cardiovascular treatment, as well as through etiology of heart disease. Relations of anticoagulant therapy with laboratory parameters seem to represented acute treatments backgrounds i.e. greater prevalence of surgical treatments, than the effects of therapy *per se*.

Consumption of acetylsalicylate acid varied from 87.5% of conservative treatments down to 78.3% in surgical and was of similar ranges between the ischemic heart disease and valvular. Rate of underutilization for acetylsalicylates was 13% for the ischemic group. Low dose acetylsalicylic acid (ASA) (75-100 mg) acts as irreversible inhibitor of the cyclooxygenase-1 (COX-1) in platelets (9). Additional mechanisms that might exhibit the cardiovascular protection include anti-inflammatory and tissue remodeling/reparation effects by inhibition of the expression of inducible nitrous oxidase (INOS), inhibition of activation of nuclear factor kappa-beta (NF-kB), with initiation of acute phase response and inhibition of neutrophil activation (10, 11). Large scale meta-analysis reported on beneficiary effects of acetylsalicylic acid in primary prevention of serious adverse atherothrombotic complications, pointing out the prevalence of first non-fatal myocardial infarction, stroke, cardiovascular death (12). Furthermore, owing to conceptualization shift to preventive actions in the "cardiovascular continuum" ASA is now-days recommended therapy by evidence based merits for patients that did not survive the cardio-cerebro-vascular or peripheral artery event, nonetheless bear the increased scores of 10-years cardiovascular hazard due to prevalence of combined risk factors or chronic comorbidities, particularly diabetes (13, 14). Over and above, the group of individuals with arterial hypertension of high risk grade also showed long-term benefits in preventive therapy with acetylsalicylate acid (15). Secondary prevention considers the lifelong therapy with antithrombotic agent, outlining only the importance for remaining short and long term patency of the implanted intracoronary stent or coronary bypass grafts (16, 17). Despite the predictable complications, dominantly in terms of gastric and enteric mucosal lesions, nephropathy and salicylism in the adults, underutilization of acetylsalicylate acid is commonly found in clinical practice (18). The latter was predicted to save up to 10.000 of lives each year in the population of 350 million, if the theoretical sustained coverage would be equal to entire set of patients surviving the acute coronary syndrome (19). Another important problem is around acetylsalicylate acid lesser treatment efficiency i.e. aspirin resistance, which could be of clinical and laboratory types. Latter could happen in relation with patients' characteristics (alternation in platelets production or function, genetic alternations in metabolism of drugs, diabetes mellitus, nicotinismus, some food and beverages as grape juice or alcohol), and drug-drug interactions (with non-steroidal anti-inflammatory drugs, some type of statins, and proton pump inhibitors) (20, 21, 22, 23). Similar scenarios occur with other antiplatelet drugs, as well as their combinations (24, 25).

Dual antiplatelet therapy consisting of ASA and Clopidogrel was the most commonly used antiplatelet modality in our patients, making 62% in ischemic heart disease, and of nearly equal ranges among studied groups of cardiovascular treatments (26). Clopidogrel is irreversible thienopyridine blocker of P2Y12 protein, adenosine diphosphate (ADP) chemoreceptor on platelet cell membranes (27). Drug is used for prevention of thromboembolic events such as cerebrovascular stroke, peripheral artery disease or acute coronary syndrome, as well as for improvement of the short and long term patency of implanted intracoronary stents (28, 29). Increased consumption of dual antiplatelet combinations in 57% of surgical patients and 68% of valvular, might be prominently explained through prevalence of atherothrombotic disorders and atrial fibrillation in these groups. Benefits of dual antiplatelet therapy in remaining of the bare metal stent patency beyond the period of 6-12 months are less evident; however future studies comprising of populations with surgical revascularization, prevalence of comorbidities and the extent of atherosclerotic process would be valuable in order to increase the cost-efficiency (30).

Position of peroral anticoagulant therapy with antagonist of the K vitamin in secondary prevention of cardiovascular diseases is still matter of consultations due to unanimous conclusions (31). Studies showed lack of coherence in evidences about net benefit in major cardiovascular events versus bleeding which was mainly corresponding with the dosing regiments i.e. attained levels of international normalized ratios (INR) (32). Supplementary controversies of vitamin K antagonists could be found in the reported advancement in atherosclerosis or thrombus stability through inhibition of matrix Gla-protein (MGP) and subsequent vascular calcification (32, 33). The triple combination also

brings certain challenges and questions in terms of legislative. Although some professional societies recommend triple therapy in some instances, the labeling directives of drugs, produced by various companies do not imply preferring the use of such combinations due to similar safety concerns (bleeding risk).

Although the study settings represent the non-randomized cohort of patients on cardiovascular rehabilitation, most of the comorbidities were found to be of similar national prevalence within earlier reports (33, 34). Most of risk factors from the modifiable cluster were still found to be of high prevalence, particularly continuous nicotine abuse in 36% of patients. In addition, 23% of patients were obese and 58% overweight, diabetes 26%, glucose intolerance 35%, metabolic syndrome 66%, and chronic renal disease 45% (6,35).

In conclusion, utilization of acetylsalicylate acid therapy was found to be of similar range in compare with the most developed industrial nations. Dual antiplatelet therapy was the most common prescription routine. Triple therapy was used to less degree, in patients of secondary or tertiary prevention, mostly ones with atrial fibrillation. Acute settings cardiovascular treatment was shown to influence the prescription routine, apart from heart disease etiology, raising concerns about the decreased use of available pharmacological agents in secondary prevention of the post-surgical patients.

Conflict of interest:

None declared

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Abbreviations:

AP — antiplatelets
COPD — chronic obstructive pulmonary disease
AC — anticoagulants
CRD — chronic renal disease
ASA — Acetylsalicylate acid
LVEF — left ventricle ejection fraction (%)
T — Thienopyridine
ERC — eritrocytes
PCI — percutaneous coronary intervention
HCT — hematocrit
CABG — coronary artery bypass surgery
MCV — mean corpuscular volume of erythrocytes
VS — valvular surgery
LKC — leukocytes
BMI — body mass index (kg/m2)
PLT —platelets
WC — waist circumference (cm)
GLC — serum glucose
HC — hip circumference (cm)
CREAT — creatinine
WHR — waist-hip ratio
CHOL — cholesterol
HDL — high density lipoprotein
LDL — low density lipoprotein

Sažetak

ANALIZA KORIŠTENJA ANTITROMBOCITNIH LEKOVA I PERORALNE ANTIKOAGULANTNE TERAPIJE KOD BOLESNIKA NA STACIONARNOM PROGRAMU BOLNIČKE KARDIOLOŠKE REHABILITACIJE

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Uvod: Neslaganje sa smernicama i neoptimizacija farmakoterapije u sekundarnoj prevenciji često postoji u kliničkoj praksi. Cilj istraživanja bio je proceniti obrazac propisivanja i utilizacije antitrombocitnih lekova i peroralne antikoagulantne terapije u tercijarnom medicinskom centru specijalizovanom za kardiovaskularnu rehabilitaciju.

Metode: u studiju je uključeno 96 uzastopnih bolesnika zakazanih za kardiovaskularnu rehabilitaciju u razdoblju od 1 do 6 meseci nakon akutnog lečenja zbog ishemijske bolesti srca (80,2%) i bolesti srčanih zalistaka (19,8%). Bolesnici su podeljeni prema etiologiji bolesti srca i akutnim oblicima lečenja.

Rezultati: Dvojna antiagregaciona terapija bila je najčešće korišćeni režim kod 87,5% konzervativno lečenih infarkta miokarda, 61,9% perkutane koronarne intervencije (PCI) i 58,9% kod hirurški tretirane grupe ($p > 0,05$). Profil utilizacije nije bio značajno različit za

antitrombocitne lekove ($p > 0,05$); Obrnuto, utilizacija varfarina, ili kombinacije koje su uključivale varfarin, značajno su se razlikovale prema ispitivanim grupama lečenja ($p < 0.001$) i etiologiji bolesti ($p < 0,001$). Sva četiri bolesnika koja su primila trostruku terapiju (4,17%) bila su u grupi hirurški lečenih pacijenata. Neadekvatna utilizacija antitrombocitnih lekova u ishemijskoj bolesti srca iznosila je 14,3%, što je u skladu sa razvijenim industrijskim zemljama.

Zaključak: Vrsta akutnog kardiološkog lečenja u značajnoj je meri određivala naknadno korišćenje lekova, nasuprot etiologiji bolesti srca. Zapaženo je suboptimalno korišćenje lekova sekundarne prevencije kod grupe hirurških bolesnika. Analiza potrošnje lekova može pomoći kod optimizacije terapije, unapređenja kvaliteta zdravstvene nege, smanjenja polipragmazije, te poboljšanja ekonomske efikasnosti medicinskog lečenja.

Ključne reči: analiza utilizacije farmakoterapije; antitrombocitna terapija; antikoagulantna terapija; varfarin; kardiovaskularna rehabilitacija; ishemijska bolest srca; bolesti srčanih zalistaka.

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THE EFFECT OF PLASMA PREPARATION RICH IN GROWTH FACTORS ON PATELLAR STABILITY AFTER MEDIAL PATELLOFEMORAL LIGAMENT REEFING

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Abstract: **Introduction:** Although more than 100 operative procedures have been described for the treatment of patellar instability, there is no single universally successful procedure. For the most patients with lateral patellar instability medial patellofemoral ligament (MPFL) reefing is recommended. When we perform MPFL reefing we are not aware of the quality and strength of the MPFL tissue. In the presence of recurrent patellar instability, the quality and strength of MPFL tissue is often compromised and it disturbs patellar stability after MPFL reefing. Biomedicine development, recognizing the ligament healing process show us that autologous blood products, particularly PRP can enhance healing in soft tissue injuries.

Purpose: The purpose of this study was to determine the potential effect of Plasma preparation rich in growth factors on patellar stability after MPFL reefing.

Material and methods: Plasma preparation rich in growth factors was produced from a unit of autologous whole blood using Arthrex ACP double syringe system.Platelet gel was prepared by adding bovine thrombin and 10% solution of calcium chloride.The platelet gel was applied locally into the place where suturing of the MPFL was performed. In this prospective, randomized and double blind study12 patients were included:6 patients in the PG group who received platelet gel and 6 patients in the control group who were not treated with platelet gel. Patellar stability was evaluated before surgery and 3 months after surgery with Axial stress radiographs.

Results: The calculated 3 month improvement was 12.67 ± 2.51 in the control group and 17.33 ± 1.52 in the PG group, ($p = 0.064$). Although there was greater improvement in patellar stability in PG group comparing to the control group, the difference was not statistically significant ($p > 0.05$). The main reason for this was probably the small number of patients included in the study.

Conclusion: Results showed that growth factors from the plasma preparation rich in growth factors have positive effect on patellar stability after MPFL reefing.We believe that they stimulate and accelerate physiological healing and reparative tissue processes in ligament healing. More studies should be made, including more patients, if we want to get more relevant results.

Keywords: patellar instability, medial patellofemoral ligament reefing, plasma preparation rich in growth factors, clinical results.

INTRODUCTION

Patellar instability is a complex problem for orthopedic surgery especially when a specific operative treatment should be chosen. Although more than 100 operative procedures have been described for the treatment of patellar instability, there is no single universally successful procedure. The multifactorial etiology is probably the main reason for those treatment dilemmas. For the patients with patellar instability who have normal tibial tubercle-trochlear groove (TT-TG) dis-

tance, normal patellar height and no marked trochlear dysplasia, medial patellofemoral ligament (MPFL) reefing or reconstruction is recommended. In patients who have increased TT-TG distance or patella alta, distal realignment procedures are used. Trochleoplasty is rarely indicated in patients with marked trochlear dysplasia. Because studies have shown that MPFL is the most significant passive stabilizer of the patella (1), and because they have shown that MPFL heals and is elongated in majority of patellar dislocation cases (2), most of the authors recommend reefing or reconstruction of MPFL for the treatment of patellar instability. With MPFL reefing similar to capsulorrhaphy for treating shoulder instability, plication of the redundant tissue of the elongated MPFL is done. The procedure is performed by suturing with PDS sutures under arthroscopic control. The result of this procedure is MPFL tightening and obtaining a normal position and normal tracking of the patella.

When we perform MPFL reefing we are not aware of the quality and strength of MPFL tissue. The MPFL has approximately 12 N of strength and a load to failure of approximately 208 N. In the presence of recurrent traumatic lateral patellar instability, this relatively frail structure has been torn many times over, not only in its mid substance, but often at its attachment points (3). So, sometimes there is a question if to repair the tissue that has already failed many times over.

Recently, advances in biomedicine and biotechnology have shown the use of cell therapy, tissue engineering, and autologous blood concentrates to enhance healing in bone and soft tissue injuries (4). One of these methods used to biologically augment healing in the fields of orthopaedic surgery and sports medicine includes the use of autologous blood products, particularly, platelet rich plasma (PRP). Platelet rich plasma (PRP) is a portion of plasma fraction from autologous blood with platelet concentration above baseline (5). It is produced from a patient's peripheral vein and centrifuged to achieve a high concentration of platelets within a small volume of plasma. There are numerous protocols and commercial systems for producing PRP. Traditionally, two centrifugation steps are used to isolate the erythrocyte fraction from the buffy coat (plasma containing platelets, leukocytes, and clotting factors). The second step separates the platelet-poor plasma from the platelet-rich fraction. Single-step systems are also available. Once activated, platelets begin to secrete many growth factors, chemokines, cytokines, and inflammatory mediators. Platelets begin to secrete these growth factors within 10 minutes after clothing, 95% of growth factors are secreted within 1 hour and they continue to secrete during their life (5 to 10 days) (6). They have an influence on many aspects of ligament healing (7) (Table 1).

During PRP production it is important to keep the platelet activation on minimum, because secreted proteins will be released earlier and they might be lost and not transferred to the right surgical place. During centrifugation platelet activation and fragmentation can be avoided by use of acid citrate dextrose anticoagulant and low gravity forces (8). Platelet activation and platelet gel production can be achieved by adding calcium chloride and thrombin to PRP (9). The thrombin directly activates platelets and calcium ion replenishes the calcium that was previously bound with anticoagulant citrate dextrose.

There are a lot of studies that describe the clinical use of PRP in orthopedic practice. Some of them describe the effect of PRP on medial collateral ligament healing (10), other the effect of PRP on graft healing after ACL reconstruction (11), or donor site morbidity after ACL reconstruction with BTB graft (12). Many studies show the use of PRP in patient with cartilage damage (13), plantar

Table 1. *Synopsis of growth factors present in PRP by Peter AM Everts (7)*

Platelet growth factor	Function
Transforming growth factor β (TGF-β)	Stimulates mesenchymal cell proliferation; regulates endothelial, fibroblastic, and osteoblastic mitogenesis; regulates collagen synthesis and collagenase secretion;stimulates endothelial chemotaxis and angiogenesis
Platelet-derived growth factor (PDGF)	Mitogenetic for mesenchymal cells and osteoblasts; stimulates chemotaxisand mitogenesis in fibroblast; regulates collagenase secretion and collagen synthesis; stimulates macrophageand neutrophile chemotaxis
Basic fibroblast growth factor, BFGF	Promotes growth and differentiation of chondrocytes andosteoblasts; mitogenetic for mesenchymal cells, chondrocytes and osteoblasts
Epidermal growth factor, EGF	Stimulates endothelial chemotaxis/angiogenesis; regulates collagena sesecretion; stimulates epithelial/mesenchymal mitogenesis
Vascular endothelial growth factor, VEGF	Increases angiogenesis and vessel permeability, stimulates mitogenesis for endothelial cells
Connective tissue growth factor, CTGF	Promotes angiogenesis, cartilage regeneration, fibrosis and platelet adhesion

fasciitis (14), epicondylitis (15, 16, 17), jumpers' knee (18, 19). In current data bases we have not found studies that describe the effect of PRP on MPFL healing after its reefing in patients with patellar instability.

Our study was designed to determine the potential effect of locally applied plasma preparation rich in growth factors on patellar stability after MPFL reefing.

PATIENTS, MATERIALS AND METHODS

Patient selection

Twelve patients between 12 and 33 years of age were included in our study. They were operated on, in the period from March 2013 to March 2014 in the University Clinic for Orthopedic Surgery in Skopje, Macedonia. Patellar instability in all of them was diagnosed preoperatively with accurate history, physical examination and imaging studies. Patients with inflammatory diseases, malignant diseases, diabetes mellitus, renal diseases, thrombocytopenia, immunological diseases, knee osteoarthritis and previous knee surgery were excluded from the study. Patients with patellar instability who had marked trochlear dysplasia, patella alta or TT-TG distance more than 20 mm were also excluded from the study because MPFL reefing is not a suitable operative procedure for treating these patients. Patients were divided into two groups: PG group and the control group. The PG group had 6 patients in whom plasma prepared platelet gel was locally applied during the operative procedure (MPFL reefing). The control group had 6 patients and they did not receive platelet gel during the same operative procedure. Randomization was performed with closed envelopes, with number 1 for PG group and number 2 for control group. In all patients the same operative procedure (MPFL reefing) was performed. All patients were operated by the same surgeon (A. A.), and in all of them the same rehabilitation protocol was performed by the same physiotherapist. RTG evaluation was made by an independent radiologist in a blinded fashion. The study was prospective, randomized and double blind.

Surgical technique

The operative procedure started with routine arthroscopy, where inspection of the knee and assessment of patellar position and patellar tracking was made. In patients with marked lateralization of the patella MPFL reefing was performed. Skin incision 1-1.5 cm long was made near the medial patellar border. We use two needles: needle with free end suture and needle with suture loop (PDS 1 suture). We inserted the free end suture needle through the periosteum of the medial patellar facet. The needle with suture loop was inserted 2-5 cm medially depending on the amount of reefing desired. The free end suture was then pulled outside the knee joint with the needle with suture loop. Three to five sutures were placed in this way. Patellar position was checked while tension was placed on the sutures, and if the position was correct, the sutures were tied with the knee in extension (Figure 1). In patients from the PG group, platelet gel was applied in the place where the sutures were tied (Figure 2).

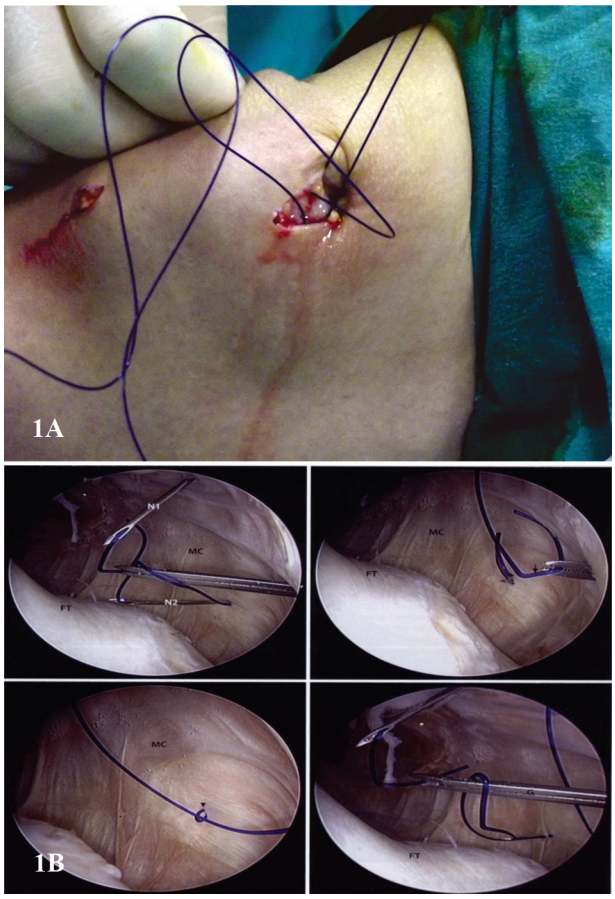

Figure 1. *MPFL reefing operative technique.* ***A:*** *View outside knee joint;* ***B:*** *Arthroscopic view inside knee joint*

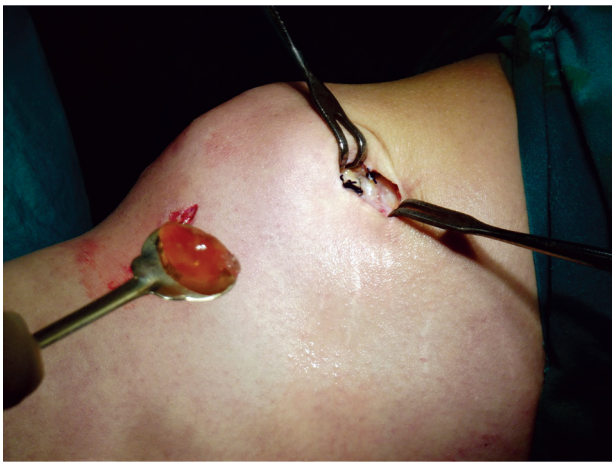

Figure 2. *Medial patellar incision where the platelet gel is applied*

Platelet gel preparation

Platelet rich plasma was produced using Arthrex double syringe system. For that purpose 15 ml of patient's whole blood was drawn and centrifuged on 1500 prp for 5 minutes. When centrifugation was finished three layers were formed: the bottom layer consisting of red blood cells, the middle layer consisting of platelets and white blood cells, and the top plasma layer. With the other smaller syringe about 3 ml plasma with platelets and white blood cells was then drawn from the bigger syringe. Platelets activation and platelet gel formation was performed by adding a solution of 1000 units of topical bovine thrombin and 1 ml of 10% calcium chloride to the PRP. Because we got 3 ml PRP, according to the Marx et al. study (5), 0.5 ml of calcium chloride/thrombin solution were mixed with 3 ml PRP and platelet gel was prepared.

Rehabilitation

All the patients had the same rehabilitation protocol. Brace was used postoperatively for 6 weeks. Flexion of 30 degrees was allowed after the first 2 weeks postoperatively, 60 degrees flexion in the 3-rd week and 90 degrees flexion in the 4-th postoperative week. All the patients used crutches for 4 weeks and full weight bearing was allowed in the 4th postoperative week. Physiotherapy was performed after 6 weeks by the same physiotherapist.

Follow up evaluation

Postoperatively, after 3 months, all patients underwent a physical examination and Axial radiograph was performed to determine the patellar displacement.Axial view was then repeated while a medial force was applied to the patella, so stress radiographs of the patellofemoral joint were made (Figure 3). The applied force was kept constant with the use of a special *force gauge model FG-5005* instrument and the patellar displacement was measured with the technique described by Laurin et al. (20). Statistically mean value, standard deviation and standard error were calculated, and using the t-test a statistically significant difference between PG group and control group was determined.

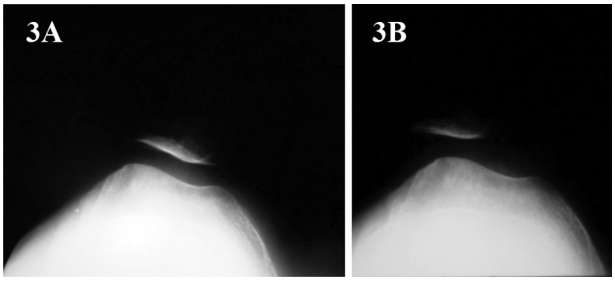

Figure 3. A: *Axial knee radiograph;*
B: *Axial stress radiograph*

RESULTS

Axial radiographs and stress radiographs were made preoperatively and 3 months postoperatively. The difference in patellar stability between PG group and control group measured with the technique described by Laurin et al. was calculated (Table 2).

Table 2. *Difference in patellar stability between PG group and control group (mm)*

	N	Mean	Std. Deviation	Std. Error Mean
Control group	6	12.67	2.517	1.453
PG group	6	17.33	1.528	0.882

The calculated 3 month improvement was 12.67 ± 2.51 in the control group and 17.33 ± 1.52 in the PG group, ($p = 0.064$). Although there was greater improvement in patellar stability in PG group comparing to the control group, the difference was not statistically significant ($p > 0.05$). The main reason for this is probably the small number of patients included in the study.

DISCUSSION

Patellar instability is the least known (the black hole in orthopedics) and the most problematic and controversial pathology of the knee. Although there are some dilemmas according to the etiology and diagnosis of the patellar instability, the biggest dilemma arises when the right operative treatment should be chosen. There are some surgeons, for example, Prof. Jeffrey Halbrecht's, who propose that MPFL reefing is the best procedure for treating patellar instability (21). According to them, MPFL reefing is indicated for the most cases of patellar instability. "It gives good clinical and radiographic stability, complications are rare, it is easy to perform, and does not cost much", writes Prof. Halbrecht. Surgeons who perform MPFL reefing have a problem because they do not know the strength and quality of the MPFL and that has large influence on MPFL healing and postoperative patellar stability when reefing of the MPFL is done. "Does it make sense to repair tissue that has failed many times before?" writes prof. Schepsis (3).

Advances in biomedicine and biotechnology show us that autologous blood products, particularly PRP, can enhance healing in soft tissue injuries biologically. Its use in the treatment of musculoskeletal injuries is described in many studies.Recognizing the ligament healing process, we become aware of the impor-

tance of platelet growth factors during this process (22). Growth factor responses at the initial inflammatory and proliferative phases of ligament healing are critical for the filling of tissue defect with neo fibrous tissue (23). That was the reason why we have decided to determine the effect of plasma preparation rich in growth factors in improving the healing process of previously damaged tissue of MPFL and in improving the patellar stability after MPFL reefing in our study.

Arthrex double syringe system was used for producing PRP. It gives up to 3-fold increase in platelet concentration over baseline. Some investigators suggest that PRP should achieve a 3 to 5-fold increase in platelet concentration over baseline (24), although the dependence of clinical benefit on platelet concentration versus total number of platelets delivered may need further investigations (25). According to Weibrich et al. (26), different individuals need different platelet concentrations to get right biological effect. We prepared platelet gel because we needed prolonged secretion of growth factors during whole platelets life on the right surgical site.

Because stress radiographs provide the only available objective measurement of patellofemoral joint instability, we have decided to use them for preoperative and postoperative evaluation of the patellar stability (27). Because patellar instability most often occurs in the first 30 degrees of knee flexion we made Axial view with 30 degrees of knee flexion with and without medial force applied to the patella to get stress radiographs. All the patients had lateral instability and that is why only the lateral displacement was measured. It was important to keep the applied force constant with special instrument and to make right measurement according to Laurin et al. (20).

CONCLUSION

Although there was not statistical significance ($p = 0.064$), the results showed that the patients from the PG group have improved their patellar stability more than the patients from the control group. That means that growth factors from the platelet gel have positive effect on patellar stability after MPFL reefing. We believe that they stimulate and accelerate physiological healing and reparative tissue processes in ligament healing.

More studies should be made, including more patients, if we want to get more relevant statistically significant results.

Conflict of interest

The authors declare no conflict of interest.

Abbreviations

MPFL — Medial Patellofemoral Ligament

TT-TG distance — Tibial Tubercle-Trochlear Groove distance

PRP — Platelet Rich Plasma

Sažetak

UTICAJ PLAZMA PREPARATA BOGATOG FAKTORIMA RASTA NA PATELARNU STABILNOST NAKON ŠIVENJA MEDIJALNOG PATELOFEMORALNOG LIGAMENTA

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Uvod: I pored toga što je opisano više od 100 operativnih procedura u tretmanu patelarne nestabilnosti, danas, još uvek, ne postoji jedinstvena uspešna univerzalna procedura. Za većinu pacijenata sa patelarnom nestabilnošću preporučuje se šivenje medijalnog patelofemoralnog ligamenata (MPFL - Medial patellofemoral ligament). Prilikom šivenja medijalnog patelofemoralnog ligamenta mi nemamo saznanje u kvalitet i čvrstoću njegovog ligamentarnog tkiva. Kod rekurentne patelarne nestabilnosti kvalitet i čvrstoća ligamentarnog tkiva su često kompromitovane i to narušava patelarnu stabilnost nakon šivenja medijalnog patelofemoralnog ligamenta. Razvitak biomedicine, poznavajući process ligamentarnog zarašćivanja, pokazuje da autologni produkt krvi, u velikoj meri plazme koja je bogata trombocitima, može stimulisati zarašćivanje mekotkivnih povreda.

Cilj: Cilj ove studije je da utvrdi potencijalni uticaj plazma preparata bogatog faktorima rasta na patelarnu stabilnost nakon šivenja medijalnog patelofemoralnog ligamenta.

Materijal i metode: Plazma preparat koji je bogat faktorima rasta, dobijamo od autologne krvi pacijenata koristeći *Arthrex ACP double syringe system*. Dodajući boving (goveđi) trombin i 10% rastvor calcium hlorida dobjamo trombocitni gel kojeg lokalno apliciramo na mesto gde je urađeno šivenje medijalnog patelofemoralnog ligamenta. U ovoj prospektivnoj, randomiziranoj i dvostruko slepoj studiji bilo je uključeno 12 pacijenata: 6 u takozvanoj PG grupi koji su dobili trombocitni gel i 6 u kontrolnoj grupi koji nisu bili tretirani gelom. Patelarna stabilnost bila je evaluirana pre operacije i 3 meseca posle operacije sa aksijalnim stress radiografijama.

Rezultati: Preračunato, tromesečno poboljšanje bilo je 12.67 ± 2.51 mm u kontrolnoj i 17.33 ± 1.52 mm u PG grupi. I pored toga što smo dobili veće poboljšanje u patelarnoj stabilnosti u PG grupi u odnosu na kontrolnu grupu, ipak ta razlika nije bila statistički signifikantna ($p > 0,05$). Glavni razlog za to bio je najverovatnije mali broj pacienata uključenih u studiju.

Zaključak: Dobijeni rezultati pokazuju da faktori rasta dobijeni iz plazma preparata bogatog faktorima rasta, imaju pozitivni uticaj na patelarnu stabilnost nakon šivenja medijalnog patelofemoralnog ligamenta. Mi verujemo da oni stimulišu ubrzavanje fiziološkog zarašćivanja i reparativne tkivne procese kod ligamentarnog zarašćivanja. Potreban je veci broj studija sa većim brojem pacijenata kako bi dobili relevantnije rezultate.

Ključne reči: patelarna nestabilnost, šivenje medijalnog patelofemoralnog ligamenta, plazma preparat bogat faktorima rasta, klinicki rezultati.

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REPRODUCTIVE OUTCOME, DURATION OF PREGNANCY AND MODE OF DELIVERY AFTER HYSTEROSCOPIC METROPLASTY IN PATIENTS WITH INFERTILITY

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Abstract: **Introduction:** Reproductive outcome can be negatively affected in patients with congenital uterine anomalies (CUA), increasing the number of unsuccessful pregnancies and obstetric complications. Standard, safe and minimally invasive method for the treatment of correctible types of congenital uterine anomalies is hysteroscopic metroplasty (HM).

The aim of the study was to analyze the reproductive outcome, duration of pregnancy and mode of delivery in group of patients with infertility after hysteroscopic metroplasty.

Material and methods: We analyzed 48 patients with previous history of fetal loss (abortion) to whom hysteroscopy was done in the period of 01. 11. 2009 to 01. 05. 2013 year at the University Clinic of Obstetrics and Gynecology in Skopje. In patients who were diagnosed having CUA hysteroscopic metroplasty was done. Patients and their reproductive outcome were followed for a period of at least 2 years after the intervention. Reproductive outcome was followed considering pregnancy rate, fetal loss (abortion) up to 22 gestational week, rates of preterm and term deliveries, live births and mode of delivery. Statistical analysis was performed using computer software and value for the confidence interval (± 95% CI) was considered to be statistically significant with level of $p < 0.05$.

Results: After hysteroscopic metroplasty, there was a significant decrease of the abortion rate to 13.9%, and significant increase in pregnancy rates of 86.1%. Overall pregnancy rate was 75%, and term delivery was noted in 93,6% of the patients, with spontaneus deliveries in 58,6%. There were no complications during the hysteroscopic metroplasty, nor during the deliveries.

Conclusion: Hysteroscopic metroplasty has a significant effect on the reproductive outcome, resulting in a large number of live births and no significant complication during consecutive pregnancy and delivery.

Keywords: hysteroscopy, metroplasty, reproduction, infertility, pregnancy, delivery.

INTRODUCTION

Congenital anomalies of the female reproductive system (Mullerian anomalies) represent a heterogeneous group of malformations of the genital tract, which can involve uterus, cervix, vagina and Fallopian tubes (1). Majority of reproductive system anomalies can seriously influence the reproductive and obstetric health of women depending on the specificity of the anomaly. They increase the rate of abortions, preterm deliveries, and obstetric complications. Patients with uterine malformations have decreased reproductive potential and unfavorable reproductive outcome. Overall term pregnancy rate in patients with untreated uterine malformations is around 50%. Term delivery rate in pregnant patients with untreated septate and bicornuate uterus is ~40%, and in patients with arcuate uterus reproductive outcome is slightly better, with term delivery rate of ~65% (2). Uterine septum is the most present anomaly in patients with infertility, and possibly the most prone to a surgical correction (3, 4).

Etiology of CUA is not completely explained, majority of patients having normal karyotype, and some environmental, pharmacological and genetics factors might have some influence. Most probably its origin is polygenic or multifactorial (5). Several classifications were made in order to optimize the diagnosis and treatment of those anomalies. The classification of the anomalies of the female reproductive system depending on the degree of failure of normal development, in groups of similar clinical manifestations, treatment and progno-

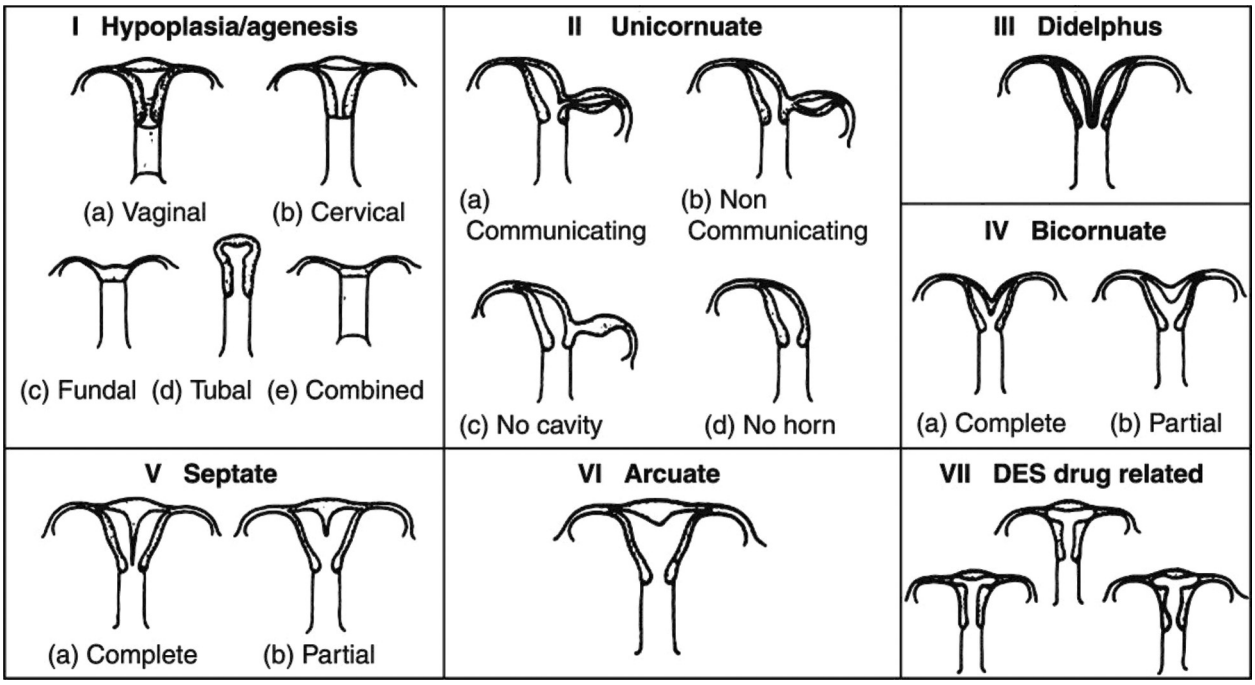

Figure 1. *Schematic presentation of AFS classification*

sis for their reproductive outcome, had the most clinical practice and was adopted by the American Fertility Society (AFS) in 1988 (6), and is used worldwide (Figure 1).

Uterine cavity abnormality is considered to be one of the factors which influence the reproductive outcome of these patients. A surgical correction by hysteroscopic metroplasty (HM) has all the benefits of a good operative treatment: decreased intra- and postoperative morbidity, short-time intervention, less analgesic requirements, shorter hospital stay, shorter interval to conception and possibility for a vaginal delivery (7).

It provides anatomically normal uterine cavity, but does not certainly result in a favorable reproductive outcome since uterine vascularization is probably involved in the uterine function. The theory which is nowadays widely accepted, states that septum is consisted of fibroelastic tissue with inadequate vascularization and changed ratio between blood vessels of the endometrium and myometrium, presenting negative effects on decidualisation and placentation (8).

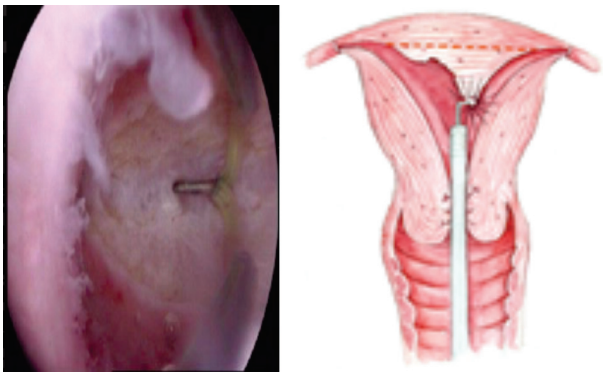

Figure 2. *Hysteroscopic metroplasty in uterus septus*

Majority of uterine malformations (> 55%) are presented with septate and arcuate uterus (type 5 and 6 according to AFS classification), which can be effectively treated by means of operative hysteroscopy. Partial reconstruction of the uterine cavity by hysteroscopy is possible in some cases of partial bicornuate uterus (type 4b). Hysteroscopic metroplasty obtains normal uterine cavity, but also resolves normal uterine function, by providing normal reproductive outcome in these patients (9, 10, 11) (Figure 2).

The results of some studies suggest that patients who underwent hysteroscopic metroplasty are at no higher risk of adverse obstetric outcome at term and during labor, comparing to the general population. (12). Several studies reported an increased incidence of premature labor in patients who underwent dilatation and curettage or conceived after a long time of infertility (13, 14). Though vaginal delivery seems to be safe, rare but serious complication reported, like uterine rupture during pregnancy or labor, should always be taken into consideration.

The aim of the study was to analyze the reproductive outcome, duration of pregnancy and mode of delivery in group of patients with infertility after hysteroscopic metroplasty.

MATERIAL AND METHODS

We analyzed 48 patients with infertility to whom hysteroscopic metroplasty (HM) was performed at the University Clinic of Obstetrics and Gynecology in Skopje, during the period between 01. 11. 2009 to 01. 05. 2013. Inclusion criteria for the study was diagnosis of uterine malformation of correctible types (4b, 5a, 5b and

6), according to the AFS classification, and exclusion criteria were existence of other intrauterine pathology (submucous myoma, polyp, etc.). Patients and their reproductive outcome were monitored during a two-year period and the same group served as a control group for themselves, taking into account their previous reproductive history. Hysteroscopic metroplasty was done after the patient previously signed informed consent.

Intervention was done with endoscopic equipment (Olympus and Storz types), using a rigid hysteroscope of 5.5 mm and a resectoscope of 8 and 9 mm, in general anesthesia and sterile conditions. A mixed solution Ispirol® (solution of 2.7% sorbitol and 0.54% manitol) or NaCl 0,9% solution, sterile and apyrogenic served as a distension media.

Hysteroscopic metroplasty (resection of the septum) starts in the midline between the anterior and posterior uterine wall and continues cranially towards the end point. End point is the moment when the following has been achieved: hysteroscope can move freely from one to the other ostium without obstruction, when both ostia are easily visualized from the upper part of the cavity or when more intensive bleeding starts from the place of the resection as a sign of proximity to the junction between the septum and the myometrium.

The following variables associated with the reproductive outcome were monitored in our group of patients: pregnancy rate, abortion rate, preterm and term delivery rate and the way of delivery. Data were analyzed using the program SPSS for Windows, version 11.0. Statistical analysis was done using Chi-square test and p-value of 0.05 was considered to be statistically significant.

RESULTS

Comparing the number of diagnosed anomalies – the largest number of 35 (72.9%) hysteroscopic metroplasties were done in the group of patients with arcuate uterus (type 6), followed by the group of patients with partial septate uterus (type 5b) - 6 cases (12,5%) and the group of patients with complete septate uterus (type 5a) in 4 patients (8.3%). The least present anomaly was partial bicornuate uterus (type 4b) in 3 cases (6.3%), as we can see in Table 1.

Table 1. *Frequency of certain types of CUA*

Diagnosed CUA	No.	%
IVb	3	6.3
Va	4	8.3
Vb	6	12.5
VI	35	72.9
Total	48	100.0

As represented in the most of the published literature, congenital uterine anomalies most present were types 5b and 6 - partial septate uterus and arcuate uterus, represented by 85.4%.

None of the patients had complications from the procedure-during hysteroscopy and hysteroscopic metroplasty.

Table 2. *Pregnancy after hysteroscopic metroplasty and time period to subsequent pregnancy*

Pregnancy	No.	%
No pregnancy	12	25.0
0-6 months	21	43.7
7-12 months	10	20.8
13-24 months	5	10.4
≥ 24 months		
Total	48	100.0

Most of the patient become pregnant during the first 6 months after HM (43.7%), 20.8% in the period between 6-12 months, or overall during the first year 31 patients became pregnant (64.6%). During the two year period 36 patients became pregnant (75%) (Table 2).

Fetal loss up to 22 gestational week (abortion) was noted in 5 of the patients (13.9%), out of which 1 belonged to group IVb, one to group Va, and 3 to the group VI. Pregnancy continued in 31 patients (86.1%).

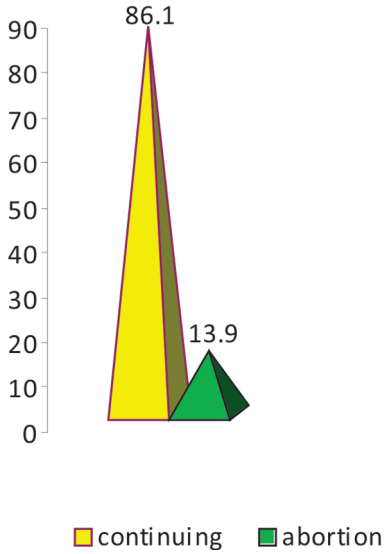

Figure 3. *Distribution according to duration of pregnancy up to 22 g.w.*

Out of 31 patients who continued their pregnancies above 22 gestational week, only 6.4% had preterm deliveries, while majority of them, 29 (93.6%) had delivery during term, as it is shown in Figure 3 and Table 1. Patients in the group of preterm deliveries belonged to the group IV b and Vb.

Table 3. *Distribution according to the gestational week of delivery*

Gestational week	Delivery	
	No.	%
29-32	1	3.2
32-36	1	3.2
37-40	29	93.6
Total	31	100.0

The rate of operative delivery- caesarean section is slightly elevated in the group of term deliveries, and comprises of 12 patients (41.4%). In the preterm delivery group all the patients -2 (100%) were delivered by SC, which would be a significant difference if the numbers were not too small (Table 4).

Table 4. *Mode of delivery*

	Preterm delivery		Term delivery	
	No.	%	No.	%
Spontaneous vaginal	–	–	17	58.6
SC	2	100.0	12	41.4
Total	2	100.0	29	100.0

DISCUSSION

Hysteroscopic metroplasty is surgical intervention for treatment of CUA that are hysteroscopicaly correctible, which are types 4b (partial bicornuate), 5a (complete septate), 5b (partial septate) and 6 (arcuate uterus).

One of the first published scientific papers made on this topic by Acien in 1993 (15) compared the reproductive outcome in 173 patients with untreated uterine malformation who had 383 pregnancies, and a second group of 28 patients with normal uterus and 47 pregnancies. Abortion rate in patients with uterine malformations was 36%, and preterm delivery rate was 18%, which was significantly higher ($p < 0.01$) than the rate of abortions of 8% and preterm delivery rate of 6% in patients with normal uterus. Term delivery rate in patients with uterine malformations was 44% and live birth rate of 53%, which was lower and statistically significant ($p < 0.001$) from the group with normal uterus where term delivery rate was 85% and live birth rate of 89%.

Analyzing the results from previous studies of Raga, Buttram and Heinonen (3, 16, 17) in a systematic review in 2001, Grimbizis found that in 102 patients with untreated arcuate uterus and number of 241 pregnancies, the abortion rate was 25.8% and prematurity rate was 7.5%. The rates for term delivery and live birth were 62.7% and 66%, respectively. In the group with untreated septate uterus he found an abortion rate of 44.3% and a preterm delivery rate of 22.4%. After performing hysteroscopic metroplasty, a significant decrease in rates of abortions and preterm delivery was reported in treated patients. Abortion rate decreased to 16.4%, while preterm delivery rate decreased to 6.4%, while a significant rise of term deliveries and live birth was reported (76.3% and 83.2%), in comparison with the rates before the HM that were lower (33% and 50.1%, respectively) (7).

Study of Sendag in 2010 (18) analyzed 30 patients with different degrees of septate uterus, who after one year following hysteroscopic metroplasty had a total of 20 pregnancies. Of these, 11 (55%) were carried to term, two (10%) ended in preterm delivery, seven (35%) ended in spontaneous abortion.

In a study of Nouri in 2010 (19), reproductive outcome was evaluated after hysteroscopic metroplasty in 64 women with septate uterus and primary infertility. Complete follow-up was available for 49/64 (76%) patients, with overall pregnancy rate after HM was 69% (34/49) and overall life birth rate was 49% (24/49).

Roy et al. (20) in the published study in 2011 have analyzed 170 cases with HM during the period of 8.5 years where a significant decrease of unsuccessful pregnancies rate was noted, from 91.5% before metroplasty to 12.5% after metroplasty, and an increase in term delivery rate from 2.5% to 79.5%.

The analysis of our material also showed a significant improvement in the reproductive outcome, which was in agreement with the published medical literature. There was a significant decrease of abortion rate to 13.9%, and a term delivery rate was 93.6%, which is comparable to patients with normal uterus.

There was not an increase of the premature delivery rate in the study group (6.5%). The preterm delivery rate in general population varies between 12 to 13% in the USA and 5 up to 9% in other developed countries (21).

In most of the cases there was a spontaneous vaginal delivery, even though the increase in the rate of caesarean sections was influenced by demand of the patient, or because of the patients previous reproductive history (prolonged period of infertility, previous abortion and operation etc.).

Complications which are published in the literature like rupture of the uterus were not noted in our group of patients (22, 23).

This is a confirmation of the fact that obtaining normal uterine cavity in cases with congenital uterine malformations who have been hysteroscopically corrected, is successfully preparing the uterus for uncomplicated continuation of the pregnancy to term delivery.

CONCLUSION

Congenital uterine anomalies, even minor types of anomalies with small defect of the uterine cavity, have been pointed in several published scientific papers as a uterine factor for a bad reproductive outcome. After treatment with hysteroscopic metroplasty in patients where surgically correctible congenital uterine anomaly exists, a significant improvement of the reproductive outcome in these patients has been reported, without notable complications during pregnancy or delivery period.

Conflict of interest

Nothing to declare.

Abbreviations

CUA — congenital uterine anomalies
HM — hysteroscopic metroplasty

Sažetak

REPRODUKTIVNI ISHOD, TRAJANJE TRUDNOĆE I NAČIN POROĐAJA POSLE HISTEROSKOPSKE METROPLASTIKE KOD PACIJENTKINJA SA INFERTILITETOM

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Uvod: Kongenitalne anomalije uterusa mogu negativno uticati na reproduktivni ishod, povećavajući broj neuspešnih trudnoća i ginekoloških komplikacija. Standardna, bezbedna i minimalno invazivna metoda za tretman korektabilnih kongenitalnih anomalija uterusa je histeroskopska metroplastika (HM).

Cilj studije je analiza reproduktivnog ishoda, trajanje trudnoće i način porođaja kod pacijentkinja sa infertilitetom, posle histeroskopske metroplastike.

Materijal i metode: Analizirali smo 48 pacijentkinja sa prethodnom istorijom abortusa, kod kojih je rađena histeroskopija u periodu od 01. 11. 2009. do 01. 05. 2013. godine, na Univerzitetskoj Klinici za ginekologiju i akušerstvo u Skoplju. Kod pacijentkinja kod kojih je dijagnostikovana urođena anomalija uterusa, rađena je histeroskopska metroplastika. Pacijentkinje i njihov reproduktivni ishod su praćeni tokom najmanje 2 godine nakon intervencije. Reproduktivni ishod je praćen uzimajući u obzir stopu trudnoća, gubitak fetusa (abortus) do 22. gestacione nedelje, stopu preterminskih i terminskih porođaja, živorođenja i način porođaja. Statistička analiza je izvedena uz pomoć odgovarajućeg programa i vrednost intervala poverenja (± 95% CI) je uzeta kao statistički značajna za $p < 0,05$.

Rezultati: Posle histeroskopske metroplastike javio se značajan pad stope abortusa na 13,9%, i značajan porast stope trudnoća na 86,1%.Ukupna stopa trudnoća je bila 75%, a terminski porođaj je notiran kod 93,6% pacijentkinja, spontani porođaj kod 58,6%. Nije bilo komplikacija tokom histeroskopske metroplastike, niti tokom porođaja.

Zaključak: Histeroskopska metroplastika ima značajan uticaj na reproduktivni ishod, rezultirajući u značajnom broju živorođenja i bez značajnih komplikacija tokom konsekutivne trudnoće i porođaja.

Ključne reči: histeroskopija, metroplastika, reprodukcija, infertilitet, trudnoća, porođaj.

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VALIDITY OF CORE NEEDLE BIOPSY IN THE HISTOPATHOLOGICAL VERIFICATION OF PAROTID GLAND LESIONS

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Abstract: **Background and purpose:** An adequate diagnosis of a parotid gland enlargement is crucial for an appropriate treatment. The aim of the study was to evaluate effectiveness and minimal invasiveness of diagnostic procedures of core-needle biopsy.

Materials and Methods: This study involved 67 patients, aged 40 to 90 years, with a tumor mass in the submandibular and parotid region. Method used for taking samples of pathological masses was BD Disposable guillotine spring-loaded needle for biopsies on soft tissues. Final diagnoses were established on the basis of surgical-pathological results in 67 cases, and on the basis of histopathological analysis of core-biopsy samples.

Results: Compared with results of surgical biopsy, core-needle biopsy had sensitivity of 100% in differentiating benign from malignant lesions and in setting up an adequate diagnosis. Its positive predictive values were 100% in diagnosing malignancy. There were found 28 non-malignant and 39 malignant lesions with fewer disadvantages for patients.

Keywords: Core-needle biopsy, surgical biopsy, parotid gland masses, validity.

INTRODUCTION

Considering localization and anatomy of parotid gland, lesions can remain indolent, as well as undiagnosed, that often happens with lesions in parapharyngeal region and deep parotid region. As a result, many parotid gland lesions have been found accidentally, on the X-ray made for other indications, such as headaches or trauma (1). Enlargements of the biggest salivary gland and associated lymph nodes represent a wide spectrum of pathological processes that are ranked from inflammation and reactive hyperplasia to benign and malignant neoplasms (2).

Many pathological processes manifest with swelling of parotid region, so it is often hard to determine the type of pathological mass only on the basis of clinical examination. Adequate diagnose is necessary, especially when surgical removal of the mass is considered, because many of the non-tumor as well as some tumor masses do not require surgery, what is specifically important when it comes to patients of risk for introduction into general anesthesia (3).

Tumors of parotid gland are present in 2-4% cases of neoplasm of maxillofacial region. They are classified in benign neoplasm, neoplasm-like masses and malignant neoplasm. 70% of salivary tumors have origin from parotid gland (4).

For adequate diagnosis of parotid gland disease, clinical examination is insufficient method, considering the fact that treatment modalities differ significantly depending on the diagnosis (2).

The least invasive method to obtain biopsy material is fine-needle aspiration (FNA), but because of significant number of samples inadequate for histopathological (HP) analysis it is considered as imprecise, and often requires additional diagnostic tests (5).

Core-needle biopsy represents a method of choice which is less invasive compared to surgical, 'opened' biopsy, and obtained material is more adequate for HP analysis than material obtained by FNA (6).

Although open-biopsy is considered gold standard, advantage of core-biopsy is avoiding general anesthesia and effectiveness of the procedure (7, 8, 9). In every day surgical praxis, because of the priority of emergencies, surgical biopsy is often delayed, so in

these cases, core-biopsy is indicated in order to diagnose disease on time (10).

Core-biopsy is described as a method for extirpation of large tissue samples from parotid gland lesions, but it has risks and limits, because it is more invasive procedure than FNA (2).

The main problem when talking of core-biopsy of parotid gland is risk of injury of facial nerve, with consequential paralysis and facial deformities, injury of vascular elements and hematoma formation, as well as seeding the tumor cells. To prevent these complications, the needle tip has to be limited to the mass before and after cutting, avoiding penetration deep into the glandular tissue (11, 12).

The aim of the study was to investigate validity of core-needle biopsy for diagnosing parotid gland lesions, comparing patho-histological results obtained by this method with patho-histological results obtained by analysis of samples after surgical removal of the mass.

MATERIALS AND METHODS

The study was conducted from January 2008 to December 2015 at the Department of Otorhinolaryngology and Maxillofacial Surgery, University Hospital Center "Zemun". The study comprised of 67 patients, aged from 40 to 90 years, with clinically and radiographically verified tumor mass in parotid and submandibular region larger than 2 cm in diameter before hospitalization.

Data were collected during hospitalization and three months after surgery. Criteria for exclusion from the study were patients whose tumor mass was not HP verified after surgical removal. All patients gave written consent to participate in the study, and used method was core biopsy, which was performed by a trained surgeon. For the implementation of the method BD Disposable guillotine spring-loaded needle for biopsies on soft tissues was used.

Core-biopsy was performed after application of a local anesthetic of 1% lidocaine with epinephrine 1: 100 000 (Xylocaine TM - Astra Pharmaceutical Products Inc., Westboro, MA), subcutaneously, with insulin needle and minimal tissue trauma. The process was repeated twice, and the resulting samples were stored in formaldehyde solution (Figure 1).

HP analysis were conducted in laboratory of University Hospital Center "Zemun". Depending on the HP findings obtained by the described method, therapeutic modalities have been as follows: resection and extirpation of the complete mass (carcinomas, adenomas and cysts), conservative treatment (toxoplasmosis, sarcoidosis, tuberculosis), representation to the Oncology board (metastatic cancer). Tumor-like lesions (sialoadenosis and lymph-epithelial lesions) were

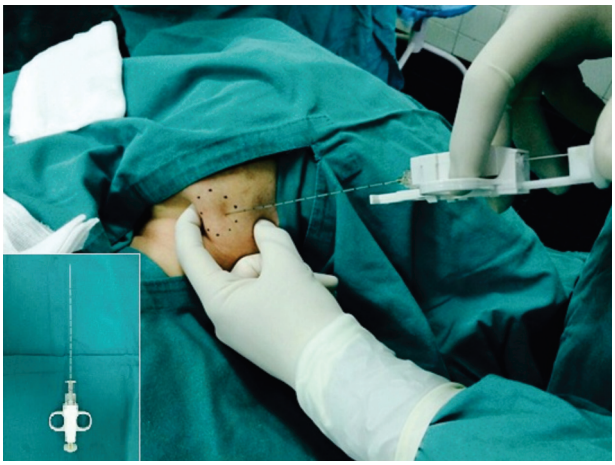

Figure 1. *A method of performing a core-biopsy*

clinically and ultrasonically controlled. Patients with verified lymphomas were treated by a hematologist at appropriate protocol and controlled by the competent doctor. After receiving HP results, the analysis included only patients who had the lesions fully surgically removed, so it would be impossible to adequately compare the findings obtained by core biopsy.

RESULTS

The study comprised of 67 patients, 41 were males and 26 were females. No patient had intraoperative and postoperative complications (injury of facial nerve with consequential paralysis and facial deformities, injury of vascular elements and hematoma formation, seeding the tumor cells, allergy to anesthetic, expressed bleeding, wound infection, intraoperative cardiac complications).

It was registered 28 malignant lesions (42.79%), 26 benign tumors (38.8%) and 13 (19.4%) non-tumor lesions (Figure 2). 16 malignant lesions were verified in male patients and 12 in female patients, while in non-malignant lesions that relation was 25 to 14.

For all lesions, HP findings obtained by core-biopsy were the same as results obtained by surgical bi-

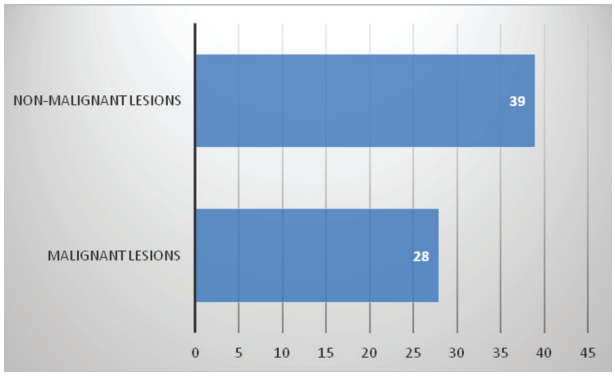

Figure 2. *The incidence of malignant and benign lesions*

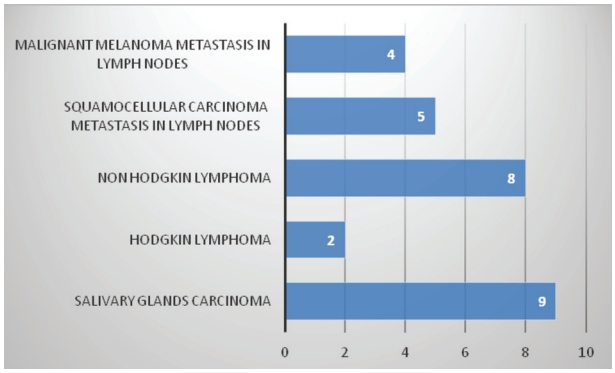

Figure 3. *Distribution of malignant lesions*

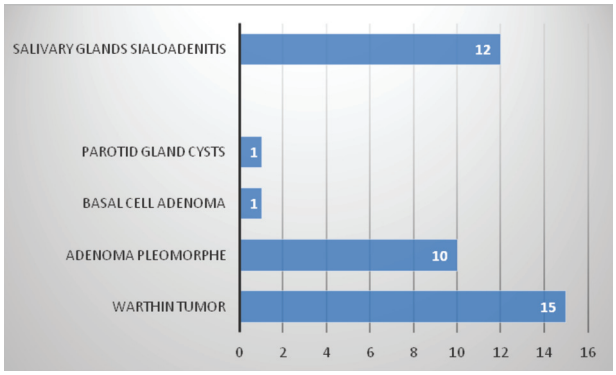

Figure 4. *Distribution of non-malignant lesions*

opsy. Based on the surgical and pathologic results of all 67 cases, core-biopsy showed sensitivity of 100% and a positive predictive value of 100% in setting up adequate diagnosis and differentiation of benign from malignant lesions.

Malignancies have had the following distribution: It was registered 9 salivary gland carcinoma, 2 Hodgkin lymphoma, 8 Non-Hodgkin lymphoma, 5 squamous cell carcinoma metastasis in the lymph nodes, and 4 malignant melanoma metastases in the lymph nodes (Figure 3).

Non-malignant lesions consisted of 15 Warthin tumors, 10 pleomorphic adenomas, 1 basal-cell adenoma, 1 cyst of the parotid salivary gland, and 12 chronic sialoadenitis of salivary glands (Figure 4).

DISCUSSION

As a result of many studies (13, 5, 14), fine-needle biopsy is not precise enough in differentiating malignancy, so that core-biopsy is proposed as a method of choice for diagnosing large masses of maxillo-facial region.

In patients who were previously exposed to the X-ray therapy, extirpation of suspected metastasis is difficult because of the scar tissue, and in these cases, core-needle biopsy is especially recommended (15, 16, 17, 18). The authors showed that the evaluation of new methods such as core-needle biopsy should be based on a comparison of HP findings obtained with the new method with PH findings obtained after surgical extirpation of the masses.

Core-needle biopsies compared to the fine-needle biopsy provide better differentiation of lymphoid hyperplasia from lymphoma, as well as better determination of subtypes and cancer grading (19). On the other hand, complications of core-needle biopsy (bleeding, infection, nerve injury) are no greater nor more frequent in relation to the complications of fine-needle biopsies (19). Regarding that for some neoplastic and non-neoplastic masses surgery extirpation is not indicated, accurate diagnosis is crucial for the adequate treatment of the patient (7). In the opinion of some authors, core- needle biopsy can lead to the spread of cancer cells into the surrounding structures (needle-track seeding), but many studies have confirmed that the spread of cancer cells rarely happens, and does not increase with the increase of the needle diameter for core-needle biopsy (3, 8, 9, 20).

In a study by Grundman et al (21), tips of needles for core-biopsy were evaluated by electron microscopy and tissue was not found on any tip, so that authors concluded that there is no seeding of cancer cells this way.

In the study where diagnostic value of core-needle biopsy and fine-needle aspiration in salivary gland lesions was compared, Novoa et al did not find any displaced tumor cells as a complication of core-needle biopsy (22). Diaz et al (23) performed excision of the region through which the needle was placed after the core-needle biopsies of breast cancer patients and showed no malignant cells in the examined region.

In the study by Kraft et al (24), needle-track seeding was found in only one sample of 75 patients. In the mentioned study, core-needle biopsy was performed with 20 gayge-sized needle, and neck dissection was performed on the same day, so it cannot be said with certainty that the cells would survive longer in the tissue after seeding. In the same study, the authors described that in masses smaller than 1 cm in diameter was hard to do a biopsy at the first time, and that it was difficult to aspirate the contents of cystic masses by core-biopsy.

Howlett et al showed the specificity, sensitivity and fluency of 100% in HP verification and detection of malignant neoplasms in the study with 135 patients in whom core-biopsy of parotid region was performed (3).

In a similar study, Screaton (7) described a sensitivity of 98% , specificity of 100% and accuracy of 99% in differentiating benign from malignant lymphadenopathies, but only 23% of 260 patients underwent opened-extirpation of lymph nodes and neck dissection, while in other cases, definitive diagnosis was confirmed by clinical and laboratory findings (8).

CONCLUSION

Based on obtained results, it can be concluded that the core-biopsy is highly specific and highly sensitive method, which is a safe alternative to open surgical extirpation of the masses of the neck. The described method is useful in all patients, due to the shorter duration of the procedure and a significantly smaller number of complications of intervention in relation to extirpation biopsy. The absence of the introduction into general anesthesia, shorter periods of hospitalization and return to normal activities, present a significant financial benefits of the core-biopsy. Based on the results of this study, we recommend core biopsy as a good and reliable diagnostic method for determining the type of parotid region lesions.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Abbreviations

FNA — fine-needle aspiration
HP — histopathological

Sažetak

VALIDNOST CORE-BIOPSIJE U HISTOPATOLOŠKOJ VERIFIKACIJI LEZIJA PAROTIDNE ŽLEZDE

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Uvod: Pravilno uspostavljena dijagnoza uvećanja parotidne žlezde je osnova za adekvatno lečenje pacijenta. Cilj ove studije bio je evaluacija efikasnosti i minimalne invazivnosti core biopsije.

Materijal i metod: U studiji je učestvovalo 67 pacijenata, od 40 do 90 godina, sa prisutnom tumorskom masom u submandibularnom ili parotidnom regionu. Korišćen metod za uzimanje uzoraka patoloških promena bio je BD Disposable guillotine spring-loaded needle for biopsies on soft tissues. Definitivna dijagnoza bila je uspostavljena na osnovu hirurško-patoloških rezultata u 67 slučajeva, i na osnovu histopatološke analize uzoraka dobijenih core-biopsijom.

Rezultati: U poređenju sa rezultatima hirurške biopsije, core-biopsija imala je senzitivnost od 100% u diferencijaciji benignih od malignih lezija i u uspostavljanju adekvatne dijagnoze. Pozitivna prediktivna vrednost u dijagnostikovanju maligniteta bila je 100%. Ovom metodom, dijagnostikovano je 28 ne-malignih i 39 malignih lezija, sa manje nelagodnosti za pacijente.

Ključne reči: Core-biopsija, hirurška biopsija, uvećanja parotidne žlezde, validnost.

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EVALUATION OF EARLY ISCHEMIC CHANGES IN STROKE PATIENTS TREATED WITH THROMBOLYTIC THERAPY

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Abstract: **Introduction:** The aim of this study is to evaluate early brain ischemic changes on CT scan in stroke patients in correlation with the clinical outcome, as well as to evaluate if there is prognostic and predictive features that can be used. **Patients and methods:** We examined 20 patients with acute ischemic stroke, from which 12 were male and 8 were female, at the age from 47 to 76 years. **Results:** The hyperdense medial artery (HMA) sign was present in 10 (50%) patients. Concerning the ASPECTS score, 5 patients (25%) had normal score of 10 points, while 7 patients (35%) had score of 7 points. 12 patients (60%) had unfavorable outcome, while 8 patients (40%) had favorable outcome. Our statistical analysis shows that age of more than 65 years, presence of 2 or more risk-factors, ASPECTS score of 7 and presence of HMA sign were all statistically significant predictors of unfavorable outcome in examined patients ($p < 0.05$ each). The presence of the hyperdense medial artery sign was the most significant single predictor for unfavorable clinical outcome ($p = 0.0042$, $p < 0.05$). **Conclusion:** The presence of HMA sign is the most significant single predictor for unfavorable clinical outcome.

Key words: stroke; hyperdense medial artery sign; outcome; thrombolysis.

INTRODUCTION

Acute ischemic stroke is characterized by the sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurologic function. Acute ischemic stroke is caused by thrombotic or embolic occlusion of a cerebral artery. This is a clinical emergency that requires prompt diagnosis and treatment (1).

Acute ischemic stroke is one of the most important causes of death and long-term disability in the world. According to the World Health Organization (WHO), 15 million people suffer from stroke worldwide each year (2). Of these, 5 million die, and around 5 million are permanently disabled. Acute ischemic stroke constitutes approximately 85% of all strokes. Contemporary and comprehensive management of ischemic stroke require prompt access to neuroimaging and thrombolytic therapy.

Neuroimaging plays a very significant role in the evaluation of patients suspected of acute ischemic stroke. Computed tomography (CT) is the first line diagnostic test for the emergency evaluation of acute stroke due to accuracy of imaging, widespread availability and its low cost (3).

There are subtle changes on non-contrast CT that can be used for prompt diagnosis of acute ischemic stroke. Those changes are hypoatenuation of areas in brain parenchyma, cortical swelling with sulcal effacement, loss of gray-white matter differentiation, as well as hyperdense medial cerebral artery sign (4).

Alberta Stroke Program Early CT score (ASPECTS) is a clinical tool that uses non-contrast CT for evaluation of early ischemic brain changes. This is a 10-point medial artery zone quantitative topographic CT scan score (5, 6). ASPECTS offers the reliability and utility of a standard CT examination with a reproducible grading system to assess early ischemic changes on pretreatment CT studies in patients with acute ischemic stroke of the anterior circulation. To compute the ASPECTS, 1 point is subtracted from 10 for any evidence of early ischemic change for each of the predefined brain regions. ASPECTS score of 10 means that there are no early ischemic changes. This score is widely recognized and used in many studies (7, 8, 9).

Another tool for evaluation of early brain ischemic changes is the hyperdense medial artery (HMA) sign (Figure 1) (10). It has been known to be an indica-

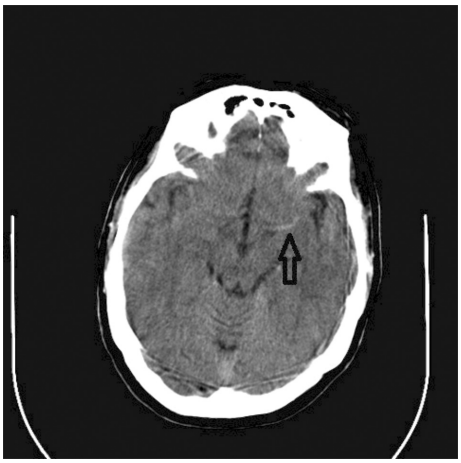

Figure 1. *Hyperdense media artery (HMA) sign*

tor of occluding clot in cases of acute ischemia on non-enhanced CT, for a long time. Additionally, it is the earliest sign, and is visible long before early parenchymal changes. HMA sign becomes visible within the onset of occlusion in a medial cerebral artery M1-segment. The histopathological analogue for the HMA sign is a thrombus occluding the vessel.

Evidence from a numerous studies suggest that early ischemic changes on non-contrast CT before the administration of intravenous thrombolysis can predict functional outcome of patients (11).

Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) has been widely accepted and used as a safe and effective treatment in patients whose onset of symptoms is within 4.5 h. Nowadays, diagnostic imaging technologies play an important role in determining which patient will have the greater benefit from administering the thrombolytic medication (12, 13).

The aim of our study was to evaluate these changes in correlation to clinical outcome of patients, as well as to evaluate if there is a prognostic and predictive features that can be used.

PATIENTS AND METHODS

In this study, we examined 20 patients with acute ischemic stroke, treated at the Clinic of neurology-Skopje, Macedonia, in the period from June to November 2015. Non-contrast CT was used to detect early ischemic changes and to exclude intracerebral hemorrhage. All patients fulfilled criteria for thrombolytic treatment and received appropriate intravenous thrombolytic therapy recombinant tissue plasminogen activator (Actilyse / rt-PA, Boehringer Ingelheim, Germany). This therapy was given using standard protocol (0.9 ml/kg; 10% in bolus, 90% in 1 hour infusion). The outcome was measured using the modified Rankin Scale (mRS) which is commonly used for measuring the degree of disability or dependence in patient with stroke (14). A 3-month follow-up status was measured by the mRS and then dichotomized into either favorable (mRS ≤ 2) or unfavorable (mRS > 2) outcome groups.

Non-contrast CT findings indicating early ischemic changes for each patients were analyzed with ASPECTS grading system as well as HMA sign.

Age and presence of risk factors (hypertension, hyperlipidemia, previous stroke or TIA, previous myocardial infarction, diabetes, smoking) as variables that can influence the outcome were also evaluated.

Standard statistical methods for descriptive statistic were used, as well as determination of correlation between examined data groups. Also, logistic regression analysis was used in order to evaluate the probability to determine the outcome. P values of < 0.05 were considered as statistically significant.

RESULTS

We examined 20 patients with acute ischemic stroke, from which 12 were male and 8 were female, at the age from 47 to 76 years (mean age 61±11 SD). 12 patients (60%) were older than 65 years. Presence of these risk-factors were evaluated: hypertension, hyperlipidemia, previous stroke or TIA, previous myocardial infarction, diabetes and smoking. The most present risk-factor was hypertension (12/60%), followed by hyperlipidemia and smoking (8/40% each). Also, from the total of 20 patients, 12 patients (60%) had 2 or more risk-factors.

The hyperdense medial artery (HMA) sign was present in 10 (50%) patients.

Concerning the ASPECTS score, 5 patients (25%) had normal score of 10 points, while 7 patients (35%) had score of 7 points. There were no patients with ASPECTS score lower than 7. According to guidelines for thrombolytic therapy, it is contraindicated to give this therapy when there are early ischemic changes over one-third of brain hemisphere (ASPECTS score < 7).

The outcome was measured using the mRS, at 3rd month after the ischemic stroke, and results where dichotomized into either favorable (mRS ≤ 2) or unfavorable (mRS > 2) outcome groups. 12 patients (60%) had unfavorable (mRS > 2) outcome, while 8 patients (40%) had favorable (mRS ≤ 2) outcome.

There was statistically significant correlation between age (especially age of more than 65 years) and presence of risk-factors (especially presence of 2 or more risk-factors), in relation to the outcome ($p < 0.05$ both). Also, there was statistically significant correlation between ASPECTS score values and the outcome ($p < 0.05$). We use Fisher's exact test when we analyzed the presence of HMA sign in relation to outcome.

Results confirmed that there is a statistically significant relationship between presence of hyperdense medial artery (HMA) sign and unfavorable outcome.

We also describe the relationship between the outcome, presented as dependent dichotomous variable of mRS [favorable (mRS ≤ 2) or unfavorable (mRS > 2) outcome] on one side, and measured independent variables (age, presence of risk factors, ASPECTS and HMA sign) on other side. For this purpose we used the logistic regression analysis. This statistical analysis shows that age of more than 65 years, presence of 2 or more risk-factors, ASPECTS score of 7 and presence of HMA sign were all statistically significant predictors of unfavorable outcome in examined patients ($p < 0.05$ each). Also, ASPECTS score of more than 7 points was found not to be significant prediction factor for favorable outcome ($p = 0.42$). The presence of the hyperdense medial artery (HMA) sign was the most significant single predictor for unfavorable clinical outcome ($p = 0.0042$, $p < 0,05$) (Table 1).

Table 1. *Clinical variables of patients with favourable or unfavourable functional outcomes*

Clinical variables	mRS ≤ 2 favourable outcome (n.of patients)	mRS > 2 unfavourable outcome (n. of patients)
Age > 65 y. Age ≤ 65 y.	2 6	10 2
Risk-factors ≥ 2 Risk-factors < 2	2 6	10 2
ASPECTS 7 ASPECTS >7	1 7	6 6
HMA sign present HMA sign absent	1 7	9 3

ASPECTS - Alberta Stroke Program Early CT Score; HMA sign - Hyperdense Medial Artery sign; mRS - modified Rankin Scale

DISCUSSION

Early brain ischemic changes can be evaluated using the non-contrast CT. This is of great importance, because it allows to get early diagnostic data of patients in acute phase of stroke. After that, appropriate therapeutic measures can be used. ASPECTS score and HMA signs are widely used CT parameters in neuroimaging. Their clinical significance is confirmed in many studies.

Prediction of outcome as guideline for further treatment is needed for all patients who are suspected of acute ischemic stroke, because treatment decision is made in the acute stage when the final diagnosis is still unclear (15, 16).

Our results confirmed that there is a good correlation between age, presence of risk-factors, and also ASPECTS score points and presence of HMA sign (17).

We have selected prediction factors that are widely available to the neurologists in the acute stage, that are very helpful in managing patients with stroke (18). Concerning the possibility of predicting the outcome, our results showed that presence of HMA sign can be used for this purpose. In our study, we confirmed that presence of the hyperdense medial artery (HMA) sign is the most significant single predictor for unfavorable clinical outcome. Also, age of more than 65 years, presence of 2 or more risk-factors and ASPECTS score of 7 can be used as predictors of unfavorable outcome in patients with acute stroke. In his work, Milosavljevic and Ivkovic examined the role of CT brain perfusion in cases of acute brain stroke following thrombolytic therapy, in which they successfully saved ischeamic penumbra in their patients. This will be our goal for future work in the field of acute stroke therapy. Our results are in concordance with several other studies (19, 20, 21, 22).

CONCLUSION

We can conclude that age of more than 65 years, presence of 2 or more risk-factors, ASPECTS score of 7 and presence of HMA sign are all statistically significant predictors of unfavorable outcome in examined patients. The presence of HMA sign is the most significant single predictor for unfavorable clinical outcome. Those prediction factors can be used for further planning appropriate measures, in order to achieve the best possible therapeutic solutions for patients with acute ischemic stroke.

Conflict of interest

The autors declare that there are no conflicts of interest.

Abbreviations

WHO — World Health Organization
CT — Computed tomography
ASPECTS — Alberta Stroke Program Early CT score
HMA — hyperdense cerebral media artery
mRS — modified Rankin Scale

Sažetak

EVALUACIJA RANIH ISHEMIJSKIH PROMENA KOD PACIJENATA SA MOŽDANIM UDAROM TRETIRANIH TROMBOLITIČKOM TERAPIJOM

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Uvod: Cilj ove studije je evaluacija ranih ishemičnih promena mozga upotrebom kompjuterizovane tomografije, kod pacijenata sa akutnim moždanim udarom, u korelaciji sa kliničkim ishodom, kao i procena pojedinih prognostičkih parametara. **Pacijenti i metode:** Ispitali smo 20 pacijenata sa akutnim ishemijskim moždanim udarom , od kojih 12 muškog, a 8 ženskog pola, starosti od 47 do 76 godina. **Rezultati:** Hiperdenzni znak medijalne cerebralne arterije je bio prisutan kod 10 (50%) pacijenata. U odnosu na ASPECTS skor, 5 pacijenata (25%) su imali normalan skor od 10 poena, dok je 7 pacijenata (35%) imalo skor od 7 poena. 12 pacijenata (60%) je imalo nepovoljan ishod, dok je 8 pacijenata (40%) imalo povoljan ishod. Statistička analiza podataka pokazala je da uzrast od preko 65 godina, prisutvo 2 ili više faktora rizika, ASPECTS skor od 7 i prisustvo hiperdenznog znaka medijalne cerebralne arterije su bili statistički signifikantni prediktori za nepovoljan ishod ($p < 0,05$ svaki). Prisustvo hiperdenznog znaka medijalne cerebralne arterije je bio najznačajniji pojedinačni prediktor nepovoljnog ishoda kod ispitivanih pacijenata ($p = 0,0042$; $p < 0,05$). **Zaključak:** Prisustvo hiperdenznog znaka medijalne cerebralne arterije jeste najznačajniji prediktor za nepovoljni klinički ishod.

Ključne reči: moždani udar, hiperdenzni znak medijalne cerebralne arterije, ishod, trombolitička terapija.

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Case report

MISTAKES IN THE DIAGNOSIS AND TREATMENT OF PRIMARY ANGLE-CLOSURE GLAUCOMA: CASE REPORT

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Abstract: Primary angle-closure glaucoma (PACG) is a leading cause of blindness globally. It is a condition that is responsible for nearly half of patients who have a bilateral blindness caused by glaucoma. PACG is highly prevalent in Asian countries, as compared with Primary open-angle glaucoma (POAG), which is reported as the predominant disease among Whites, but prevalence of PACG in Europe has been underestimated previously. Early detection by effective screening and appropriate prophylaxis and treatment may prevent blindness from angle-closure glaucoma. The purpose of this study was to present through the cases of 3 patients with PACG the importance of each phase of glaucoma: diagnosis, treatment and follow-up.

Key words: Primary angle-closure glaucoma; blindness; YAG laser iridotomy; prophylaxis; risk factors.

INTRODUCTION

There are considerable differences in the prevalence of angle closure among ethnic groups. Primary angle-closure glaucoma (PACG) is highly prevalent in Asian countries, compared with Primary open-angle glaucoma (POAG), which is reported predominant disease among Whites (1, 2). The prevalence of PACG in Europe is 0.1 % (3). However, the Egna –Neumarkt Glaucoma Study stated that the burden of PACG in Europe has been underestimated previously (4). PACG is estimated to affect 26% of people with glaucoma worldwide and is responsible for almost half the number of bilateral blindness caused by glaucoma (5). It is estimated that 21 million people worldwide will have angle-closure glaucoma in 2020 (6). The proportion of blindness caused by PACG is greater that than caused by open angle glaucoma, two to five times more, because of the greater estimated morbidity of this disease (6, 7). Quigley et al. estimated that the number of people with bilateral blindness from PACG will be 5.3 million worldwide by 2020 (6). Early detection by effective screening and appropriate prophylaxis and treatment may prevent blindness from angle-closure glaucoma. The purpose of this study was to present through the cases of 3 patients with PACG the importance of each phase of glaucoma: diagnosis, treatment and follow-up.

CASE REPORT 1

A 61-year-old women, from Vojvodina, a psychiatrist by profession, presented with pain in her left eye and left half of the head and she went to ophthalmologist in her town. She also presented blurring of vision and she was referred to the Clinic for Eye Diseases, Clinical Center in Serbia as an emergency case. In recounting her previous medical history, she complained of frequent headaches, always in one half of the head. However, the headaches “were frequent in the female line” and she did not attach great importance. She had regular medical check-ups every year as part of the institution where she works [visual activity (VA) on both eyes (BE), intraocular pressure (IOP), funduscopy] and review of glasses for near and distance in 2-2.5 years. Family history of glaucoma was positive, grandmother had glaucoma. On the examination at the Clinic for Eye Diseases, the best corrected visual activities (BCVA) were 1.0 in the right eye (RE) and 0.7 in the left eye (LE) respectively, with +2.50 diopter sphere in BE. The IOP was 12 mmHg in RE and 50 mmHg in LE measured with Goldmann aplanation tonometry (GAT). The biomicroscopy showed shallow anterior chambers in BE and in LE moderate corneal edema, moderate conjunctival hyperemia and mid-dilated pupil. Gonioscopy revealed narrow angle in RE and a 360° closed angle in LE. Fundus examination using indirect ophthal-

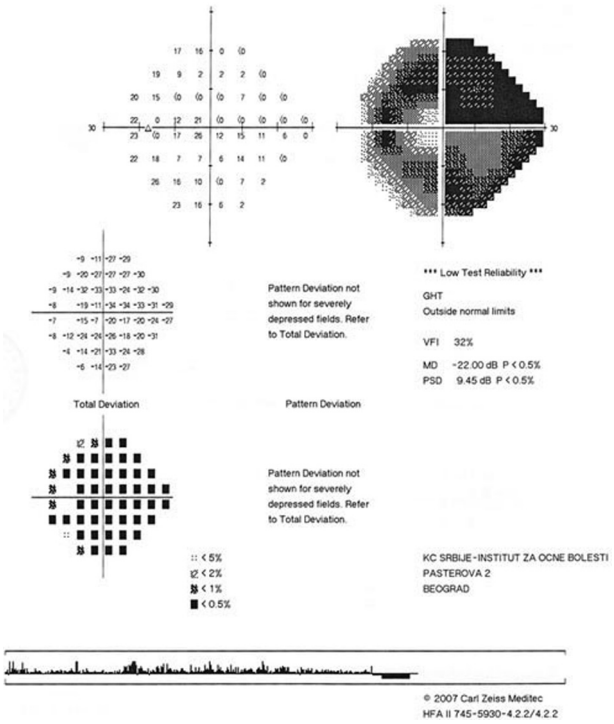

Figure 1. *Visual field result in LE was preserved central island of visual field in case 1*

moscopy with Volk Superfield lens 90D showed cup to disc ration in RE 0.4 and in LE 1.0. Beside complete ophthalmic examination we did complete diagnostic observation 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, Germany) and scanning laser ophthalmoscopy-Heidelberg retinal tomography (HRT II, Heidelberg Engineering, GmbH, Dossenheim, Germany, version 2.02). Visual field result in RE was normal and in LE was preserved central island of visual field (Figure 1). Central corneal thickness (CCT) values were measured by ultrasonic pachymeter (Alcon laboratories, OcuScan®RxP Ophthalmic Ultrasound system, Fort Worth TX) by trained ophthalmic technicians and were 587 μm in RE and 616 ìm in LE. During hospitalization an laser peripheral iridotomy (LPI) performed on LE and filtration surgery on RE. On first postoperative day IOP was 12 mmHg in RE and 10 mmHg in LE and BCVA was 1.0 in RE and 0.9 in LE.

CASE REPORT 2

A 37-year-old women, from south of Serbia, medical doctor by profession, presented with pain in her right eye and right half of the head and blurring of vision in RE and she went to ophthalmologist in her town. The local hospital diagnosis was Iridocyclitis serosa on RE and she was treated with topical corticosteroids, non-steroidal anti-inflammatory drugs, antibiotics, acyclovir, anti-glaucoma medications (timolol, dorzolamide, brimonidine and latanoprost) and oral acetazolamide. IOP in RE in that period was 26-40 mmHg. She had no family history of eye disorders. After one month, she was referred to the Clinic for Eye Diseases, Clinical Center in Serbia as an emergency case. On examination at the Clinic for Eye Diseases, the BCVA was 0.4 in RE and 1.0 in LE, respectively. She had a refractive error of 1.0 Dioptre spherical equivalent hyperopia in each eye. IOP was 44 mm Hg right and 16 mm Hg left. The biomicroscopy showed typical presentation of acute angle closure glaucoma, including edematous cornea, shallow anterior chambre, fixed dilated pupil and glaucomatous flecks of lens in RE and shallow anterior chambre in LE. Gonioscopy revealed a 360° closed angle in RE and narrow angle in LE. Fundoscop examination was normal; the optic nerve head cup-to-disc ratios of 0.3 BE. We also did 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, Germany) and scanning laser ophthalmoscopy-Heidelberg retinal tomography (HRT II, Heidelberg Engineering, GmbH, Dossenheim, Germany, version 2.02). Pachymetry measurements indicated that the CCT was 562 μm in RE and 572 μm in LE. The patient underwent placement of LPI on BE. Despite maximal medical therapy and LPI, her IOP still were very high in RE. Trabeculectomy was performed on patient's right eye. The IOP postoperatively was 14 mmHg in RE and 16 mmHg in LE and BCVA was 1.0 BE.

CASE REPORT 3

A 65-year-old women, from Belgrade, trader by profession, presented with pain in her left eye and blurring of vision and she was referred to the Clinic for Eye Diseases, Clinical Center in Serbia as an emergency case. In her previous medical history, she recounted that 7-8 years ago she had increased IOP in RE. At that time, she went to one private ophthalmology clinic where, she reported that they treated her with drops during one day and she underwent LPI on BE and ophthalmologists in that clinic told her that "she is cured glaucoma and after 2 days follow-up, other ophthalmic follow-up are not required and any further therapy". Her family history was positive, mother and grandfather had glaucoma. On the examination at the Clinic for Eye Diseases, the BCVA was 0.1 RE and 1.0 in LE, respectively, with +1.00 diopter sphere in RE and +0.75 diopter sphere in LE. IOP measured with GAT was 54 mmHg in RE and 13 mmHg in LE. On slit lamp exam conjunctiva showed hyperemia with fixed dilated pupil, subatrophy iris and peripheral iridotomy on 8.30

hours in RE (Figure 2) and shallow anterior chambers in BE (Figure 3) and peripheral iridotomy on 2.30 hours in LE (Figure 4). Gonioscopy revealed a 360° closed angle in RE ad her Shaffer angle-closure grades were 2 in LE. Funduscopy revealed cup to disc ratio of approximately 0.8 and haemorrhagia on 12 hours in

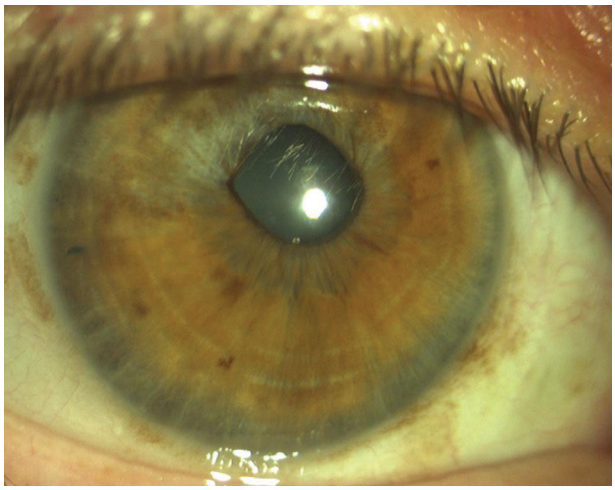

Figure 2. *Fixed dilated pupil, subatrophy iris and peripheral iridotomy on 8.30 hours in RE in case 3*

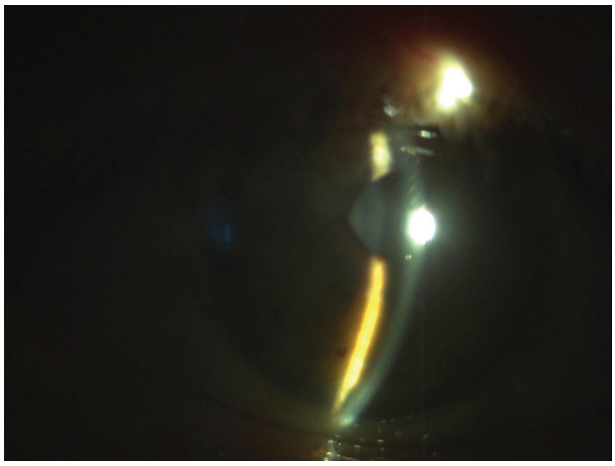

Figure 3. *Shallow anterior chamber in case 3*

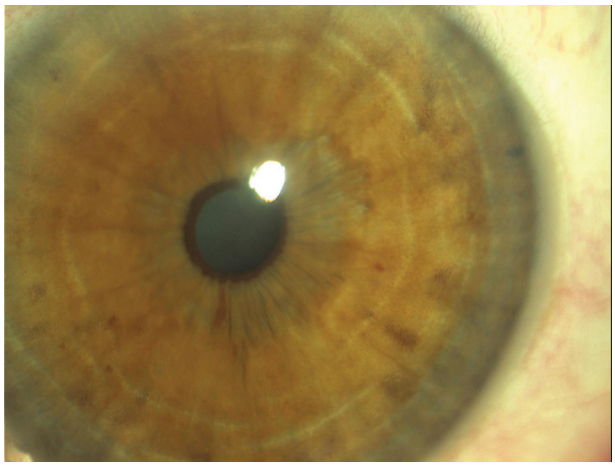

Figure 4. *Peripheral iridotomy on 2.30 hours in LE in case 3*

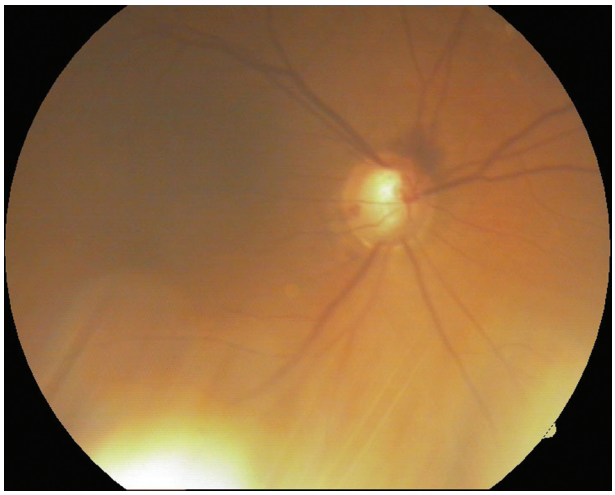

Figure 5. *Foto fundus revealed cup to disc ratio of approximately 0.8 and haemorrhagia on 12 hours in RE in case 3*

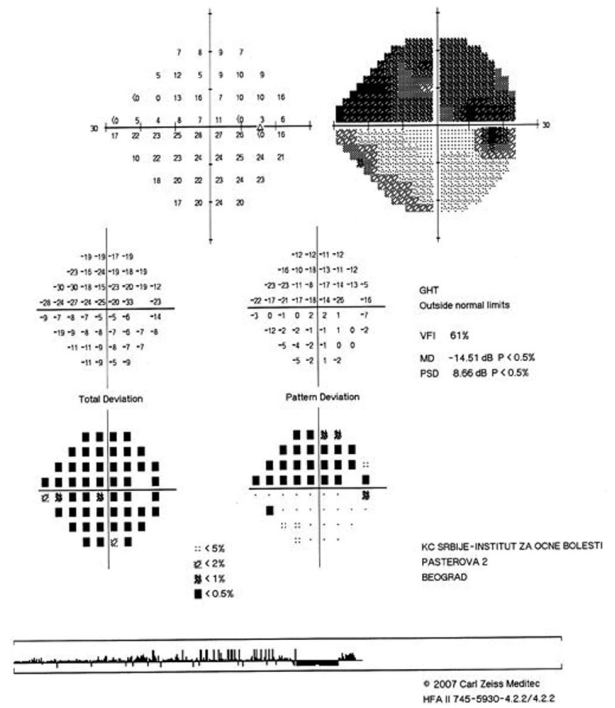

Figure 6. *Visual field result on RE was preserved loss of the upper half of the visual field in case 3*

RE (Figure 5) and 0.5 in LE. We also did scanning laser ophthalmoscopy-Heidelberg retinal tomography (HRT II, Heidelberg Engineering, GmbH, Dossenheim, Germany, version 2.02) and 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, Germany). Visual field result on RE was preserved loss of the upper half of the visual field (Figure 6). The pachymetry results were 590 μm in RE and 554 μm in LE. During hospitalization filtration surgery performed on RE. The BCVA postoperatively was 0.8 in RE and 1.0 in LE and IOP was 12 mmHg and 14 mmHg.

DISCUSSION

PACG is preventable, yet is leading cause of blindness globally (8, 9). It is responsible for nearly half of patients who have a bilateral blindness caused by glaucoma (10). Because PACG appears to cause blindness more frequently than POAG, it is an important public health issue. In the study undertaken by Quigley et Broman (6), they predict that there will be 1.5 million people with PACG in Europe in 2020. Although POAG is seen more frequently than PACG in our population, PACG is more common than previously thought and we have common experience of it in our clinical practice. Outcome of PACG depends of stage of glaucoma. That is the reason why is necessary to recognize PACG on time, correct prophylaxis, treatment and follow-up. In our 3 cases, all of the patients presented with dramatic but characteristic symptoms of acute angle-glaucoma (AAG). There is, however, often significant overlap in the clinical presentation, as patients with underlying chronic disease may also present acutely during the course of the disease, and patients with acute angle closure can be subsequently go on to develop chronic angle–closure glaucoma.

It is important to know more about the pathophysiology and risk factors of PACG to improve prevention. Several risk factors have been identified for PACG, including female gender, older age, race, family history and ocular risk factors as shallow anterior chamber depth (ACD), hyperopia, short axial length, thick crystalline lens, steep corneal curvature (11, 12). New findings suggest iris volume and choroidal thickness to have a key role in the mechanisms of angle closure (13). In our 3 cases, the patients were female with hyperopic refractive errors. Women are known to be more susceptible to angle closure. They tend to have shallower anterior chamber depth and narrower angle than men, which is believed to predispose them to angle closure (14). It has been reported that PACG happens more often in hyperopic eyes (15), like in our patients. In our study, two of them were over 60 years old and were with positive family history of glaucoma. It is known that increasing age is also major risk factor for developing PACG, with the relative risk of acute angle-closure glaucoma in patients above the age of 60 being 9 times higher compared to younger patients (8). Family screening is vital in families with PACG as there is robust evidence for significant increased risk of angle closure in family members of an affected patient: first degree relatives may have a 1 in 4 risk of a primary angle-closure (PAC) disease requiring treatment (16).

No diagnosis of PACG without gonioscopy; gonioscopic examination remains the most important method of identifying signs of angle closure and should be performed on all patients in whom angle closure is suspected to evaluate angle anatomy, appositional closure, and presence of peripheral anterior synechiae (PAS).

The guidelines of the European Glaucoma Society (3) state that if gonioscopic measurements indicate the anterior chamber angle (ACA) is in appositional contact between the iris and the posterior trabecular meshwork over at least 180°, the eye should be designated primary angle closure suspect (PACS). If PAS are present, PAC is diagnosed. Further, if glaucomatous optic neuropathy (GON) and a corresponding visual field defect are evident in eyes with PAC, the condition is termed PACG. Acute PACG, if left untreated, can cause devastating blindness in a very short time.

Ultrasound biomicroscopy and anterior segment optical coherence tomography (AS-OCT) contribute to a better understanding of the mechanisms of angle closure, helping the ophthalmologists in the diagnosis and treatment (13). With AC-OCT we can better evaluate anterior segment structural features - the angle, iris, and lens by obtaining an in vivo cross section of the entire anterior segment in a single image (17, 18).

The purpose of treatment is to preserve visual function and maintain quality life by preventing PACG or AAC from developing (12). Laser iridotomy is a definitive treatment to relieve pupillary block in PAC and PACG (19, 20). Iridotomy alone is not adequate as long-term therapy in eyes with PAC or PACG, and patients almost always require additional medical or surgical treatments (19). When laser iridotomy fails to open the ACA, laser iridoplasty may be recommended as one of the options in treatment for angle-closure. Laser peripheral iridoplasty works by shrinking and pulling the peripheral iris tissue away from the trabecular meshwork. But laser peripheral iridoplasty is usually as an adjunct to laser peripheral iridotomy (9, 20). Filtering glaucoma surgery is treatment when laser procedures and topical medications fail and trabeculectomy is the usual procedure in Clinic for eye diseases. Some studies document that lens extraction significantly widens the ACA in eyes with narrow, occludable angles and in angle-closure glaucoma (21, 22, 23) but it is not commonly used interventions in Clinic for eye diseases. In the study undertaken by Tham et al. (21), they compared phacoemulsification versus fs20 trabeculectomy in medically uncontrolled chronic angle-closure glaucoma without cataract and concluded that both, phacoemulsification and trabeculectomy are effective in reducing IOP, as trabeculectomy is more effective than phacoemulsification in reducing dependence on glaucoma drugs, but is associated with more complications.

It is important to highlight that the other eyes of patients presenting with acute angle-closure glaucoma are at risk of developing a similar attack because of the

similar anatomical structure in both eyes. Previous studies documented that without treatment, the high proportion of contralateral eyes of patients with acute angle-closure glaucoma go on to sustain acute attacks or develop some form of angle-closure glaucoma (24), since approximately half of fellow eyes of acute angle-closure patients can develop acute attacks within 5 years (25). Medical regime as pilocarpine has been shown to be entirely protective against AAC (26). As such, peripheral iridotomy/or iridectomy to the fellow eye has been advocated as prophylaxis against the development of AAC in the long-term.

CONCLUSION

PACG is an important cause of visual morbidity in our country and many parts of the world. Ophthalmologists should be alert to the potential risk of PACG and to identify those patients who are at risk of developing PACG and AAG or in whom it is present. Furthermore, in view of its insidious nature, greater efforts will need to be targeted at screening and early detection of this condition. PACG cases should be managed promptly according to an established protocol that should include medications, laser or surgical treatment. It is important to reverse or prevent angle closure by considering the application of laser iridotomy on the fellow eye as well because it is at high risk for a similar event. With careful follow-up and timely measured IOP and the performance of certain diagnostic procedures (visual field testing, imaging technologies as HRT, OCT, GDx), disease progression can be halted.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

Abbreviations

PACG — Primary angle-closure glaucoma
POAG — Primary open-angle glaucoma
VA — visual activity
BE — both eyes
IOP — intraocular pressure
BCVA — the best corrected visual activity
RE — right eye
LE — left eye
GAT — Goldmann aplanation tonometry
HRT — Heidelberg retinal tomography
CCT — central corneal thickness
LPI — laser peripheral iridotomy
AAG — acute angle-glaucoma
ACD — anterior chamber depth
PAC — primary angle-closure
PAS — peripheral anterior synechiae
ACA — anterior chamber angle
PACS — primary angle closure suspect
GON — glaucomatous optic neuropathy
AS-OCT — anterior segment-optical coherence tomography

Sažetak

GREŠKE U DIJAGNOZI I LEČENJU PRIMARNOG GLAUKOMA SA ZATVORENIM UGLOM: PRIKAZ SLUČAJA

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Sažetak: Primarni glaukom sa zatvorenim uglom je vodeći uzrok slepila u svetu. Odgovoran je za gotovo polovinu pacijenata sa obostranim slepilom koji imaju glaukom. Primarni glaukom sa zatvorenim uglom je visoko prevalentan u Azijskim zemljama u odnosu na primarni glaukom otvorenog ugla koje je zastupljeniji među belom rasom; međutim prevalencija primarnog glaukoma sa zatvorenim uglom u Evropi je potcenjena. Rano otkrivanje sa odgovarajućom profilaksom i lečenjem mogu sprečiti pojavu slepila kao posledice angularnog glaukoma. Cilj ovog rada je da kroz prikaz slučaja 3 pacijentkinje sa primarnim glaukomom sa zatvorenim uglom naglasi značaj svake faze glaukoma: dijagnoze, lečenja i praćenja.

Ključne reči: Primarni glaukom sa zatvorenim uglom, slepilo, Yag laser iridotomija, profilaksa, faktori rizika.

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Case report

GIANT HAND LIPOMA — CASE REPORT OF A RARE LOCALIZATION OF A COMMON TYPE OF TUMOR

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Abstract: **Introduction:** A lipoma is a benign tumor of the adipose tissue and the most common tumor of the subcutaneous tissue which is most commonly found on the trunk. It appears as a round or oval subcutaneous mass of soft consistency, which is not attached to the skin or to the deeper tissues. Its growth can cause compressive symptoms, the most common being pain and paresthesia.

Case report: Considering the fact that lipomas very rarely occur in the hand and foot, in this paper we present a case of a large lipoma in the hand of a 70-year-old female patient, with a subcutaneous tumor, in the area of the ulnar side of the left palm, and the pain and tingling in the fourth and fifth finger.

Longitudinal incision on the medial side of the palm and transversal incision up to the proximal palmar crease were performed under general endotracheal anesthesia. The extirpated tumor was, due to its dimensions (5.6 x 3.4 x 2.5 cm), categorized as a giant hand lipoma. A histopathological analysis confirmed the diagnosis of lipoma.

Conclusion: A hand lipoma requires surgical treatment exclusively, involving a qualified hand surgeon, which is important because of the high functional and aesthetic importance of the hand.

Keywords: lipoma, hand tumors, hand lipoma.

INTRODUCTION

The most common tumor of the subcutaneous tissue is a lipoma, which is a benign tumor of the adipose tissue. Different morphological variations of this tumor have been described such as fibrolipoma, myxolipoma, myolipoma, chondroid lipoma, pleomorphic lipoma, angiolipoma and other (1). It is not attached to the skin or to the deeper tissues, usually appears as a round or oval bulge beneath the skin of soft consistency. It is noted that lipomas found in the superficial soft tissues usually have a well developed capsule, while those found in the deeper structures are not clearly separated from the surrounding tissue. Histologically, lipomas are composed of mature adipocytes and very rarely they undergo malignant alteration (1, 2).

Compressive symptoms may occur and the most common are pain and paresthesia. Lipomas can occur anywhere on the body where adipose tissue is present, but they most often appear on the trunk, shoulders and neck. Considering the fact that lipomas in the hand are very rare (3), the aim of this paper is to present a rare localization of a giant lipoma.

CASE REPORT

A 70-year-old female patient was admitted to the clinic with subcutaneus nodule on the ulnar side of the left palm. There were no pathological changes in the skin, the tumor had a soft consistency and irregular shape, and the mostly it was movable towards the deeper structures. The patient complained of pain and tingling in the fourth and fifth finger, as well as of the aesthetic appearance of the left palm. Additional examinations were conducted: ultrasonography and CT (Figure 1) by which a presence of a homogenous tumor was identified, of relatively clear demarcation and without visible internal vascularization.

Under general endotracheal anesthesia, using a tourniquet and surgical loops, a longitudinal incision was performed on the medial side of the palm while the transversal incision was performed up to the proximal palmar crease. After that, the tumor was separated from the surrounding tissues and it was seen that one part of it spreaded below the flexor tendons and above the hypothenar muscles, while the other part of it extended into the region of the fourth commissure. Macroscopically, the tumor resembled a lipoma (Figure 2) of a maximum length 56 mm, maximum width 34 mm and maximum

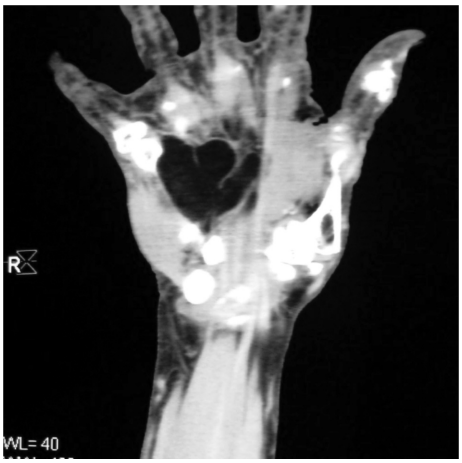

Figure 1. *Computed tomography showing the tumor with relatively clear demarcation and spreading tendency, therefore condensing the surrounding structures in the palm*

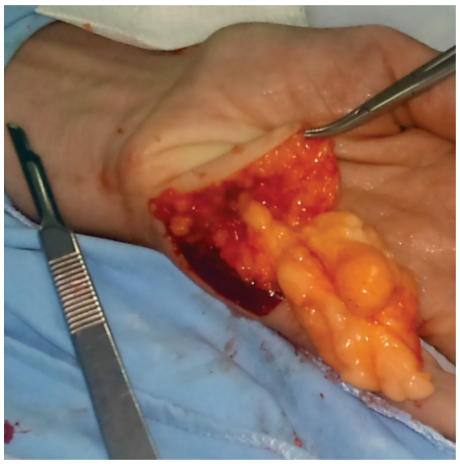

Figure 2. *Intraoperative appearance of the tumor, of irregular shape, recalls as lipoma*

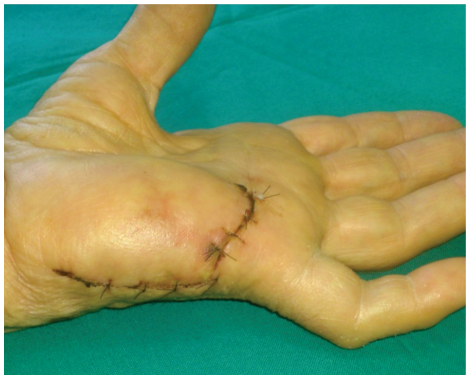

Figure 3. *The patent's hand on the fifth postoperative day*

thickness 25 mm. It was completely removed and sent for histopathological analysis. The wound was closed with individual stiches (polyamide, 5-0) while vacuum drains were placed through a separate incision. There were no complications in the postoperative period. On the second postoperative day, the drain was removed

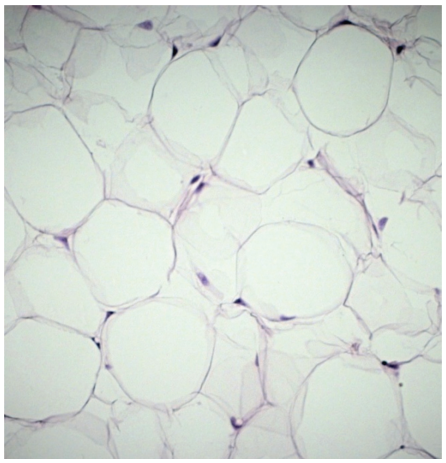

Figure 4. *Histological appearance of the lipoma: uniform cells with cytoplasmic vacuoles suppressing the nucleus towards the cell membrane (H&E x200)*

and the patient was discharged on the third day after surgery with a reduced pain and tingling and without signs of fluid accumulation in the wound (Figure 3). The wound healed per primam and the stiches were removed on the tenth postoperative day. The pathohistological report (Figure 4) confirmed that it was a lipoma.

The patient was referred to physical therapy. On the follow-up examination, one month after surgery, there was no subjective discomfort, the scar healed properly and was in the maturation phase, while the function of the hand was normal, with good neurocirculatory function of the IV and V finger.

DISCUSSION

Benign subcutaneous tumors of the hand are relatively rare and the most common among them are ganglion cyst, giant cell tumor and hemangioma. Although lipomas are the most common subcutaneous tumors, their occurrence in the hand is very rarely reported. The first documented case of a lipoma in the hand dates from 1959 when McEnery at al. described this tumor in the palm (4). Later, other cases of different localizations of hand lipoma were described (5, 6), such as thenar (7) or fingers (8, 9).

Hand lipoma is usually found on the palm and palmar side of the fingers, while it is rarely formed on the dorsal side of the hand, due to poorly developed fat tissue. Considering a subtle hand morphology, comprised of a of various tissues seated in a relatively narrow space, the symptomatology in these cases is diverse and it is most often manifested with paresthesia and pain. These symptoms are the most noticeable when the lipoma is localized in the carpal canal (10, 11, 12). Limited and difficult movement of the fingers occur when the tumor compresses the muscles and tendons of the hand, which has a high functional significance for daily activities.

Moreover, depending on the size of tumor, there are also varying degrees of aesthetic impairment due to the fact that the hand is an exposed part of the body (13).

Moreover, lipomas can grow large in size; however, it should be pointed out that the concept referring to a large tumor in surgery does not depend mainly on its size, but also on its anatomical localization, as well as functional and aesthetic importance of that area. With the consensus in the literature that any hand lipoma that has a maximal diameter greater than 5 cm belongs to the group of giant lipomas (13, 14, 15), we classified this lipoma into the group of rare giant hand lipomas.

A diagnosis of the lipoma is primarily based on clinical examination and intraoperatively, while it is finally made on the basis of a pathohistological analysis. However, due to the occasional presence of differential diagnostic dilemmas and possible occurence of liposarcoma in the hand (16), in order to diagnose a hand lipoma there is sometimes a need for additional procedures, such as ultrasonography, computed tomography and MRI (17). This is important in cases when the tumor is large, firmer in consistency and to a certain degree attached to the deeper tissues. Using the above mentioned diagnostic procedures, a lipoma can be differentiated from other tumors, and it is of particular importance to exclude the existence of a deep hemangioma or sarcoma (18).

The only definitive method for successful lipoma treatment is surgery that must be performed under general or regional anesthesia and in a bloodless operative field, which is achieved by placing a pneumatic tourniquet. Besides, in most cases, it is necessary to perform surgery with the use of magnification with binocular surgical loupes and appropriate surgical instruments for hand surgery. Planning incisions in the hand has to be in accordance with the general principles of plastic surgery. The incisions are planned in order to avoid occurence of desmogenous finger contractures. Sometimes, it is necessary to make a vertical incision, due to the easier extirpation of a tumor in the hand and that kind of incision requires a Z-plasty. During surgery, it is very important, not only to remove the tumor completely, but also to avoid the damage of healthy tissues, particularly neurovascular elements. Considering the fact that a cavum remains after extripation of large tumors, wound drainage is very important and it is recommended to be performed through a separate incision, using a firm and fixed multi-perforated silicone catheter attached with a vacuum system (19, 20).

Postoperative complications are possible, such as hematoma, seroma, dehiscence, infection, lesions in the deeper structures during surgery, desmogenous contracture in improperly placed incisions and recurrence, if the tumor is not completely removed. The most common specific complication is digital nerve lesion. During the whole treatment, a postoperative intensive and qualified physical therapy is of a great importance (3, 20, 21).

CONCLUSION

Diagnosis of subcutaneous tumors of the hand should be exact and, for this reason, additional diagnostic procedures are necessary such as ultrasonography, CT, MRI and angiography. This is particularly important for large tumors, such as the giant lipoma in the hand which is presented in this paper.

A lipoma in the hand is exclusively treated surgically and includes the participation of a qualified hand surgeon, which is important because of a great functional and aesthetic character of the hand. The tumor presented in this paper had a rare localization for its kind and larger dimensions in relation to the area it was encountered in.

Conflict of interest

The autors declare that there are no conflicts of interest.

Abbreviations

CT — computed tomography
MRI — Magnetic resonance imaging

Sažetak

GIGANTSKI LIPOM ŠAKE — PRIKAZ SLUČAJA RETKE LOKALIZACIJE ČESTOG TUMORA

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Uvod: Lipom je dobroćudni tumor masnog tkiva i najčešći tumor potkožnog tkiva koji se najčešće javlja na trupu. Prezentuje se kao okrugao ili ovalni potkožni čvor, mekše konzistencije, koji nije fiksiran za kožu, a

najčešće ni za dublja tkiva. Svojim rastom može da uzrokuje kompresivne simptome, od kojih su najčešći bol i parestezija.

Prikaz slučaja: Obzirom da se lipomi veoma retko javljaju na šaci i stopalu, u ovom radu prikazujemo veliki lipom šake kod pacijentkinje stare 70 god. sa potkožnim izraštajem u predelu ulnarne strane levog dlana i bolom i trnjenjem u četvrtom i petom prstu. U opštoj endotrahealnoj anesteziji je urađena longitudinalna incizija na medijalnoj strani dlana i poprečna incizija do proksimalne dlanske brazde. Ekstirpiran tumor je zbog svojih dimenzija (5,6 x 3,4 x 2,5 cm) kategorisan kao gigantski lipom šake. U postoperativnom toku nije bilo komplikacija, a rana je zarasla per primam. Histopatološkom analizom je potvrđena dijagnoza lipoma.

Zaključak: Lečenje lipoma šake je isključivo operativno i podrazumeva učešće hirurga koji je edukovan za hirurgiju šake, što je od važnosti zbog velikog funkcionalnog i estetskog značaja šake.

Ključne reči: lipom, tumori šake, lipom šake.

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Case report

DE ANQUIN SYNDROME-RARE CAUSE OF LOW BACK PAIN: A CASE REPORT WITH REVIEW OF LITERATURE

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Abstract: **Introduction:** Low back pain is common medical disorder that can be caused by different etiologies, some of them being very rare. During the past decades, much of the etiology and pato-mechanics of low back pain has been clarified. However, defining precise cause of low back pain in a small subset of patients is still challenging.

Case presentation: We are presenting a case of long lasting low back pain caused by impingement of the enlarged spinous process of the fifth lumbar spine into the spina bifida of the first sacral segment, so called De Anquin syndrome. We delineated the precise morphology of the anomaly using CT scans, and since the patient was symptomatic, the resection of the enlarged spinous process was undertaken. During the follow up period, the patient remained completely symptom free.

Discussion and Literature review: We undertook literature review and small number of studies describing De Anquin syndrome were found. The most remarkable finding of the case presented is the immediate and complete release of pain.

Conclusion: We do recommend seeking for the exact etiology in the patients with long lasting low back pain.

Keywords: De Anquin syndrome, low back pain, clasp knife deformity, sciatica.

INTRODUCTION

Low back pain is common medical complaint. The condition itself is associated with significant disabilityand considerable cost (1). It isestimated that up to 84.1% of the general populationhave experienced low back pain during their lifetime (2). It is the most common reason for visits to the orthopedic surgeons and neurosurgeons (3). The annual prevalence of chronic low back painranges from 15% to 45%, with a point prevalenceof 30% (2, 4-7). Contrary to the common belief that low back painprevalence remains the same, (8) studies have shown alarming increase in the past two decades (9-13). The percentage of the workforce affected varies from 2% to 8% with days of absence ranging from 9 days inthe United States, to 40 days in-Sweden, per pt. per year (13, 14).

Low back pain is a disorder with manypossible etiologies, occurring in different groups of the population.Despite high prevalence and research, there is still professional uncertainty about optimal therapeutic approach (15). During the past decade, huge scientific work and widespread use of imaging studies have clarified much of the etiology and pato-mechanics of low back pain (6). Seeking for the exact etiology is mandatory in patients with long lasting low back pain and failure of conservative therapy (9). In such instances, high level of suspicion for rare etiology as a possible cause for low back pain should be present.

We are reporting a patient who suffered long lasting low back pain caused by very rare congenital osseous anomaly of the lumbosacral junction known as clasp-knife deformity or de Anquin syndrome.

CASE PRESENTATION

A 43-year-old man presented to the outpatient clinic for evaluation of the low back pain. The current episode of low-back pain started 2 months ago. At the beginning, the pain was localized at his lower back, but subsequently it became radiating along his both legs. He also noticed that his sexual function started to deteriorate and bowel habits become irregular.

His past medical history is remarkable. He had suffered cerebral palsy in his childhood, having gait impairment as a consequence. He also hasprognathiathat was surgically treated and lumbar spondylolisthesis for which he underwent surgical treatment eight years

ago. After the last surgery, he remained symptom free for two years when he started to experience some pain in the central part of his lower back. This time, the pain developed during his regular air-pistol shooting practice. Subsequently, the patient noticed that the pain is occurring at the time when the back is hyperextended, while performing his daily routines and during sleeping on his back. Furthermore, he realized that the pain is relieving by flexion of the back. Since then, the episodes become more regular and disabling, requiring increasing doses of analgesics and frequent courses of physical therapy. The symptom free periods become shorter, lasting no more than month or two.

During the days before the actual examination, the pain while standing and walking caused considerable suffering and forced the patient to come to the clinic on a wheelchair. The patient was well developed individual and his back was straight. Vital signs, regular lab findings were within the normal range.Both flexion and extension of low back were quite limited and very painful. The clinical exam revealed healed surgical scar in the midline of his back from a previous operative fixation of the spondylolisthesis at the level of the second and third lumbar vertebrae. Palpation at that level did not reveal any pain. As the palpation of the spinous processes was going downwards, he reported intense pain at the level over the lumbo-sacral junction and upper part of the sacrum. We did not note any atrophy of the gluteal, thigh and calf muscles. Spasm of the lumbar musculature was present on both sides.

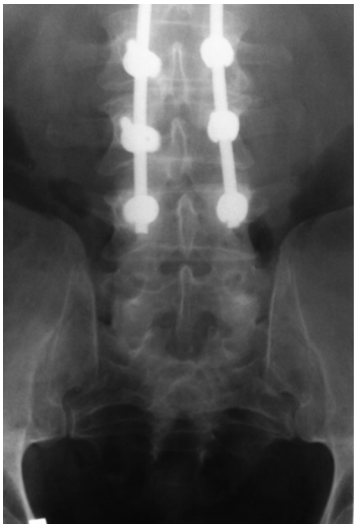

Figure 1. *Preoperative radiography demonstrating spina bifida occulta on the first sacral segment*

Neurological examination demonstrated signs of nerve root compression. Namely, the pain was radiating along his both legs and deep tendon reflexes were diminished. The rectal tone was also decreased. Motor power was difficult to test accurately because of the intense pain caused by manipulation and positional changes. The findings of the sensory examination were also remarkable. Pain and numbness were present in multiple dermatomas, most affected being L5 and S1 dermatome. Pain on straight leg rising was not present.

The point of maximum tenderness was marked with a ruler and radiographies of the lumbo-sacral spine were ordered. Roentgenograms of the lumbosacral spine (Figure 1) showed slight reduction in the normal lumbar lordosis, possibly associated with the muscle spasm.

The point of maximum tenderness precisely corresponded with the lumbosacral junction. Focused anteroposterior view of the lumbosacral junction revealed spina bifida at the level of fifth lumbar vertebra which was overlooked in the previous radiology exams. On a profile view, the spinous process looked enlarged and elongated. In order to delineate the precise morphology of the lumbosacral junction, CT scan was ordered (Figure 2).

The findings revealed excessively large, elongated and hooked spinous process of the fifth lumbar vertebra intruding into the osseous defect over the first sacral segment. Additionally, electromyography findings demonstrated reduced sensomotor conductivity originating from the fourth and fifth lumbar nerve roots as well as first two sacral roots.

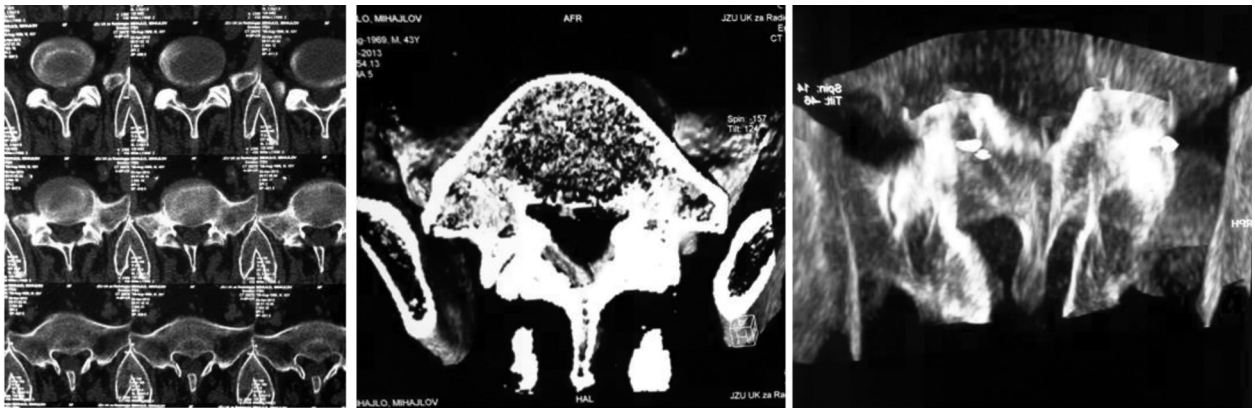

Figure 2. *Transverse CT scans demonstrating laminar defect and adjacent spinous process protruding into the defect (left) and 3-D reconstructions at the same level (middle and right)*

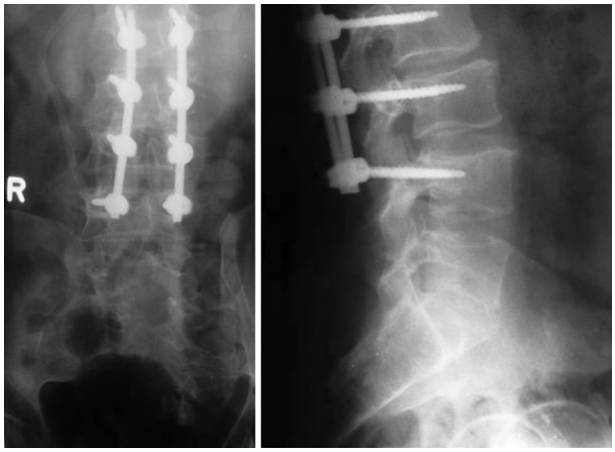

Figure 3. *Postoperative radiographies*

It was clear that the pain and neurologic deficit could be attributed to the impingement of the fifth spinous process on a sacral spina bifida.

Since the conservative treatment was unsuccessful, the pain was increasing and the neurologic deficit occurred, we decided to operate on the patient.

The lumbosacral junction was exposed through the midline incision. We exposed the spina bifida and defined its limits. The fifth lumbar spinous process was excised by cutting it off at its base and by separating adhesions between it and the fibrous membrane across the posterior osseous defect of the first sacral segment. Postoperative radiographies are shown on Figure 3.

Postoperative period went uneventful. Operative wound healed with no complications. During the immediate postoperative check up the patient reported that the pain while lying on his back as well as the pain along his both legs has diminished. In the next few days of his hospital stay we undertook regular neurologic examinations. The complete neurologic recovery was evident, including tendon reflexes and sphincter function.

Outpatient clinic checkups were undertaken at four weeks, three months and six months and a year post surgery. During the follow up period the patient was completely symptom free and satisfied with the surgery. Neurologic examinations revealed complete recovery.

DISCUSSION AND LITERATURE REVIEW

Low back pain is a common medical complaint with prevalence as high as 73% (2). In most cases, it subsides with no medical treatment or short courses of physical therapy. However, in less than 1% of cases low back pain is caused by congenital deformity of the spine (8). Since its first description in 1875 by Virchow, spina bifida occulta alone has usually been addressed as a cause of low back pain (16, 17). The association between spina bifida occulta and enlarged spinous process of the fifth lumbar spine was first described by Ferguson in 1934 (18). He indicated the possibility of existence of a free remnant of the first sacral spinous process or a single enlarged and hooked spinous process of the fifth lumbar spine that intrudes into the posterior defect of the first sacral segment thus compressing the dural sac and producing pain.

To our knowledge, there are only few papers focusing on spinous engagement syndrome.The literature search was conducted in order to identify papers focusing on de Anquin syndrome. “Pubmed Medline” and “Google Scholar”, without language and publication date limitation, were searched. The following search terms and Boolean operators were used: de Anquin syndrome or de Anquin disease or Morbus de Anquinor Spinous impingement syndrome or Spinous engagement syndrome. In order to complete the list of published studies, we also searched the reference lists of already detected studies. The search results are presented in Table 1.

Table 1. *Overview of the studies*

Study	Year	Patients	Treatment	Outcome	Comment
Ferguson AB	1934	single case	no treatment described	no outcome described	radilogic study presenting x-rays of a single case with this anomaly
Bellerose MN	1935	single case	no treatment described	no outcome described	morphological study
De Anquin CE	1959	15 cases	conservative in 4, operative in 11 patients	excellent results in operatively treated patients	the first study to describe the anomaly and treatment options in detail
Stark WA	1971	single case	operative	described as good	the anomaly was diagnosed intraoperatively
Goobar JE et al	1988	2 cases	conservative	some success with conservative treatment	the authors do not discuss the possibility of operative treatment
Bruns J et al	1994	6 cases	operative in all patients	immediate release from or decrease in pain in all patients	most detailed description of the syndrome
Dieckmann C et al	1995	6 cases	operative in all patients	excellent in 3 patients	revision of the nerve roots and division of adhesions performed

Bellerose reported one case of a patient with enlarged and curved spinous process of the fifth lumbar vertebra protruding into the adjacent spina bifida occulta (19). De Anquin was the first to describe this peculiar anomaly in detail (17). He published a study of 15 patients suffering low back pain caused by spinous engagement at the lumbosacral junction. Eleven out of 15 patients in his study were treated operatively, with excision of the fifth lumbar spinous process and a good clinical outcome. He also described two different types of the syndrome. Type I is characterized with pain at the lumbosacral junction caused by protrusion of the enlarged fifth lumbar spine into the posterior defect of the first sacral segment with no signs of nerve root compression, while type II is associated with nerve root compression. In 1971, Stark reported on a case of de Anquin syndrome with signs of nerve root compression (20). The patient was operated with excision of the fifth lumbar spinous process and posterior lumbosacral fusion. Goobar et aldescribed two cases of de Anquin syndrome that were treated conservatively that led to decrease in the severity of the symptoms (21). They used the term "dynamic type of stenosis" to explain the pain producing mechanism in these two patients. In 1994, Bruns et al published a study of 6 patients with long lasting low back pain caused by de Anquin syndrome (22). All of them were treated operatively after numerous courses of physiotherapy. According to their results, the most impressive finding was the immediate decrease in pain reported by all patients included in the study. However, remaining complaints of two of the patients were attributed to the osteoarthritic changes of lumbosacral facets.In 1995, Dieckmann published study of six operatively treated patients, with result very similar to those of Bruns (23).

We are reporting on a case of a young individual who practices active lifestyle despite serious comorbidities. Our decision to operate on the patient was based on the findings of abovementioned studies and case reports, ineffective attempts of conservative treatment for few years and the progressivenessof the neurologicdeficit. The most remarkable finding was immediate and complete postoperative release of pain. Subsequently, he also regained bowel and urinary sphincter function, as well as sexual function. Our postoperative result is similar to those described in the literature.

CONCLUSION

Despite being very common, low back pain can be caused by rare and curable etiologies. Presence of low back pain associated with spina bifida occulta should always raise the suspicion of coexistence of spinous impingement caused by enlarged adjacent spinous process. Awareness of the existence of this peculiar anomaly is the cornerstone in the treatment of these patients. The treatment itself is straightforward and consists of simple surgical excision of enlarged spinous process. Published studies and case reports have shown excellent clinical outcomes following surgical treatment.

Conflict of interest

The authors have no conflict of interests to declare.

Sažetak

DE ANQUIN SINDROM — REDAK UZROK BOLA U DONJEM DELU LEĐA: PRIKAZ SLUČAJA I PREGLED LITERATURE

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Uvod: Bol u donjem delu leđa je čest zdravstveni problem koji može biti uzrokovan različitim etiološkim faktorima, a neki od njih su vrlo retki. Tokom proteklih decenija, većina etioloških faktora i patoloških mehanizama bola u donjem delu kičme je razjašnjena. Međutim, definisanje tačnog uzroka ovog bola kod malog broja pacijenata i dalje je izazov.

Prikaz slučaja: Predstavljamo slučaj dugotrajnog bola u donjem delu kičme, uzrokovanog udaranjem uvećanog spinoznog nastavka petog lumbalnog pršljena u spinu bifidu prvog sakralnog segmenta, što karakteriše takozvani De Anquin-ov sindrom. Identifikovali smo tačnu morfologiju anomalije pomoću CT-a, a budući da je pacijent imao simptome, izvršena je resekcija uvećanog spinoznog nastavka. Tokom perioda praćenja, pacijent je bio potpuno bez tegoba.

Diskusija i pregled literature: Pregledom literature pronađen je mali broj studija koje opisuju De Anquin sindrom. Najznačajniji nalaz kod prezentovanog slučaja je to što je došlo do neposrednog i potpunog oslobađanja od bola.

Zaključak: Preporučujemo precizno ispitivanje etiologije kod pacijenata sa dugotrajnim bolovima u donjem delu leđa.

Ključne reči: De Anquin syndrome, bol u donjem delu leđa, clasp knife fenomen, išijas.

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Review article

GLUT-1 DEFICIENCY: FROM PATHOPHYSILOGY AND GENETICS TO ABROAD CLINICAL SPECTRUM

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Abstract: The classical GLUT-1 deficiency syndrome (GLUT-1 DS, De Vivo disease) was described over 2 decades ago as a metabolic encephalopathy characterized by developmental delay, secondary microcephaly paroxysmal neurological symptoms (epilepsy) and movement disorders. The biochemical parameters of this disease, used in diagnosis, are low levels of glucose in the cerebrospinal fluid, normal level of glucose in the blood and consequent low ratio of cerebrospinal fluid vs. blood glucose levels (< 40–45%). So far, more than 200 cases of the classical GLUT-1 DS have been described in the literature. Genetic research demonstrated that this disease is caused by mutations in SLC2A1 gene coding for GLUT-1, a transporter of glucose across the blood brain barrier. Over the last few years the clinical spectrum of GLUT-1 deficiency was expanded to include other rare diseases such as paroxysmal exertional dyskinesia and early-onset absence epilepsy, but also some more common diseases such as idiopathic generalised epilepsy (1-2%). GLUT-1 deficiency is an important pathophysiological basis of these diseases as early diagnosis (aided by DNA mutation testing) and treatment (ketogenic diet) could lead to improved disease outcomes.

Key words: GLUT-1 deficiency, De Vivo disease, SLC2A1, epilepsy, idiopathic generalised epilepsy, paroxysmal exertional dyskinesia, hypoglycorrachia.

INTRODUCTION

Human brain uses glucose as a principle fuel for its function. It is estimated that on average an adult human brain uses at least 20-25% (up to 80% in infants) of the total body glucose supply (1-7). Glucose molecule does not diffuse freely across the blood-brain barrier and GLUT-1, an uniporter glucose transporter, allows facilitated glucose transport across the blood-brain (and other blood-tissue) barriers (1, 2).

GLUT-1 is encoded by SLC2A1 gene (solute carrier family 2, facilitated glucose transporter member 1, OMIM 138140) located on the short arm of chromosome 1p34.2, 35kb long comprising 10 exons (1). It is highly conserved, with a 98% homology between human and mouse GLUT-1 sequence and also 40% homology to other GLUT transporters (1-6). GLUT-1 is constitutively expressed in most tissues and cells, with particularly high level of expression in brain microvessels and astroglia as well as the erythrocyte membrane (1-4). It consists of intracellular C- and N- terminal domain and 12 hydrophobic domains, each of which is forming a transmembrane helix (1-4). GLUT-1 transporter is hypothesised to oscillate between two conformations: "open" conformation when glucose level in the target tissue/cell is low allowing glucose to be transported across the cell membrane and "closed" conformation acquired by GLUT-1 once the level of glucose have increased to meet the metabolic need.

THE CLASSICAL DE VIVO GLUT-1 DEFICIENCY SYNDROME (GLUT-1 DS)

Human pathology associated with GLUT-1 was first described by Darryl De Vivo, who more than 3 decades ago reported two cases of GLUT-1 deficiency syndrome (GLUT-1 DS) (3-7). This syndrome was characterized clinically by infantile seizures, developmental delay and acquired microcephaly, accompanied by laboratory findings of low cerebrospinal fluid (CSF) glucose – hypoglycorrhachia, normal plasma glucose levels, low CSF-to-plasma glucose ratio and low-to-normal cerebrospinal lactate levels (3-7).

Within the following decade the same group demonstrated that the observed GLUT-1 DS phenotype is due to mutations in the gene encoding GLUT1 –SLC2A1 (5). The mutations identified in this first report of the molecular genetic basis of GLUT-1 DS aro-

se "de novo" and were either larger deletions (GLUT-1 hemizygosity) or point mutations that generate truncated non-functional GLUT-1 likely to be degraded before reaching the erythrocyte membrane. The pathogenicity of these SLC2A1 mutations was confirmed by showing approximately 50% reduction GLUT-1 protein expression and 30-50% reduction in glucose uptake by patient's erythrocytes (5). Following this initial report, a number of studies around the world reported findings of SLC2A1 mutations in GLUT-1 DS.

The animal model of GLUT-1 DS provided further evidence that mutations reducing GLUT-1 transport function are responsible for GLUT-1 DS: heterozygous GLUT-1 knock-out mice recapitulated the human GLUT-1 DS phenotype (microcephaly, epileptiform discharges on EEG, impaired motor activity and incoordination) and the homozygous GLUT-1 loss was lethal in the early embryonic development of the GLUT-1 null mice (3, 8).

Since the first reports of GLUT-1 DS and its molecular genetic basis, more than 200 cases of GLUT-1 DS have been published, providing further insight in both the clinical and molecular genetic features of this rare syndrome (1-7). As the number of reported GLUT-1 DS patients increased, the clinical phenotype of the syndrome became more variable (for example varying degree of developmental delay and intellectual deficit, various severity and type of seizures), but was generally consistent with a major metabolic encephalopathy characterized by developmental delay, microcephaly, seizures and often included complex movement disorders, ataxia and/or spasticity (5, 6, 7).

Thus, GLUT-1 deficiency syndrome was established as a rare, monogenic, autosomal dominant disease, most frequently caused by sporadic and "de novo" mutations in SLC2A1. These mutations inactivate one SLC2A1 allele (deletions and truncating mutation, or point mutations affecting amino acid residues critical for normal structure and function of GLUT-1, affecting various regions and amino acid residues within the GLUT-1 molecule), and this leads to severe functional impairment of GLUT-1 glucose transport capacity and reduced glucose transport across the blood-brain barrier (3-7). The established diagnostic criteria for GLUT-1 DS included clinical findings consistent with metabolic encephalopathy (microcephaly, developmental delay often accompanies by paroxysmal symptoms such as seizures and movement disorders) and confirmed by low CSF glucose levels (hypoglycorrhachia, SCF glucose < 2.2 mmol/L) with normal plasma glucose levels and low ratio of blood-to-cerebrospinal fluid glucose (usually< 40-45%) (1-7). Ketogenic diet provided therapeutic benefits of varying degree for the diagnosed GLUT-1 DS patients, being more successful in controlling the paroxysmal symptoms then the cognitive function (20, 21).

EXPANDING THE GLUT-1 DS SPECTRUM, PAROXYSMAL EXERTIONAL DYSKINESIA (PED)

More recently, the clinical spectrum of GLUT-1 DS was expanded to include paroxysmal exertional dyskinesia. PED is an extremely rare type of paroxysmal dyskinesia characterized by involuntary, sudden, dystonic movements, including repetitive twisting motions and painful posturing. The attacks are usually triggered by exercise (or other physical exertion), usually affect the part of the body being exercised and last from a few minutes to an hour (9-12). PED can exist as an isolated condition or it can be accompanied by additional neurological features, such as epilepsy (10). A few recent studies implicated GLUT-1 deficiency as pathophysiological basis for PED and broadened the clinical spectrum of GLUT-1 deficiency (10-12).

A genetic linkage analysis of a five generation Belgian family segregating PED and epilepsy pointed to SLC2A1 as a candidate gene for the observed complex phenotype (10). Indeed, SLC2A1 mutations were found in this and three additional nuclear families segregating similar clinical phenotypes including PED. The identified SLC2A1 mutations were heterozygous missense mutations and frameshift mutations that were not found in normal healthy controls. Affected individuals had reduced CSF-to-plasma glucose ratios and the mutated GLUT-1 molecules were found to have reduced capacity to transport glucose in vitro, both findings establishing the pathogenicity of the identified SLC2A1 mutations in these PED patients (10). Interestingly, while most of the affected individuals in this study displayed both PED and epilepsy, there were also cases with PED or epilepsy phenotypes only. The seizure types were absences, generalized tonic-clinic seizures, complex and simple partial seizures and/or myoclonic seizures. In one family the mutation arose "de novo" and in the other 3 the mutations were inherited (10).

Another family with a complex clinical phenotype, including PED, epilepsy, intellectual deficit and haemolytic anemia, was shown to segregate a 4 amino acids deletion (Q282_S285del) affecting the 7th transmembrane helix of GLUT-1 (11). Interestingly, the complex phenotype in this family included hemolytic anemia, characterized by increased Na+ and decreased K+ levels in patients' erythrocytes, suggesting a "cation leak" through the mutant GLUT-1 as a likely pathophysiological mechanism underlying the hemolytic anemia phenotype. This study reported SLC2A1 mutations in 2 out of 4 additional families with PED (11).

Following these two initial reports linking PED to GLUT-1 deficiency, a number of research groups published similar findings of SLC2A1 mutations in familial, but also sporadic cases of PED with one study reporting SLC2A1 mutations in 2/10 sporadic cases of PED (12).

A recent literature review identified 41 patients with PED due to GLUT-1 deficiency and found that most cases had onset in early childhood (mean age at onset 8.6 years) with varying frequency of attacks (from sever per day to 1 per month). Attacks were mostly choreo-dystonic and lasted between 15 and 40 min. Concomitant disturbances included epilepsy, learning difficulties, ataxia, pyramidal signs and hemolytic anemia (13).

EXPANDING THE GLUT-1 DS CLINICAL SPECTRUM: EPILEPSY SYNDROMES, EARLY-ONSET ABSENCE EPILEPSY (EOAE), IDIOPATHIC GENERALISED EPILEPSY (IGE)

With the exception of rare families segregating monogenic Mendelian epilepsy syndromes (mostly due to mutations in genes coding for ion channels, such as SCN1A), epilepsy is considered to be a common complex disease whose ethology includes both, a complex interaction between certain environmental factors and the genetic make-up as well as a complex interaction of a few to many genes with minor genetic contribution (14). In familial forms of epilepsy, the pedigree analyses usually confirm complex patterns of inheritance.

Given the presence of various epilepsy syndromes (including absence epilepsy) in the reported cases of GLUT-1 DS (both the classical De Vivo syndrome and/or milder PED variants), we and others looked for SLC2A1 mutations in various forms of epilepsy. An initial study looked for mutations in SLC2A1 in 34 patients with early-onset absence epilepsy (age of onset under 4 years of age) and found mutations in 12% of patients (4/34, 2 “de novo”, 2 familial), indicating GLUT1 deficiency may be the cause of a significant proportion of early-onset absence epilepsy (15).

A confirmatory cohort included 55 cases of early-onset absence epilepsy (and 500 controls) found that 7 patients (13%) had mutations in SLC2A1 (5 missense, 2 deletions) and confirmed that about 1 in 10 cases of early-onset absence epilepsy are due to mutations in SLC2A1 (16). Importantly, this study also showed that while the diagnostic criteria of the classical De Vivo GLUT-1 DS includes CSF glucose levels < 2.2 mmol/L and CSF-to-blood glucose ratio of < 50%, the milder GLUT-1 deficiency cases, presenting clinically as EOAE or other “midler” phenotype, may have both higher (and even normal) levels of CSF glucose and also CSF-to-blood glucose ratio of above 50% (16). The high frequency of SLC2A1 mutations in early-onset absence epilepsy also raises the question for routine use of genetic testing in cases with early onset epilepsy (especially onset under the age of 4 years and absence type epilepsy).

We also tested the hypothesis that GLUT-1 deficiency clinical spectrum may include not just rare conditions (PED, early-onset absence epilepsy), but also a more common condition such as idiopathic generalised epilepsy, traditionally considered to be a complex genetic disease (the lifetime incidence of epilepsy is 3%, with IGE accounting for 25% of all epilepsy cases) (12-19). To assess the contribution of GLUT-1 deficiency and SLC2A1 mutations in idiopathic generalised epilepsy, we screened for SLC2A1 mutations in 504 patients with IGE and found that 7 patients (1.4%) had mutations, functionally validated to reduce the transport function of mutant GLUT-1 in vitro (17). All of the affected probands fulfilled the diagnostic criteria for idiopathic generalised epilepsy and had normal development and intellect, some of the families co-segregated PED (17).

Another Swiss study found SLC2A1 mutations in 2.1% (2/93) of IGE cases (18). This study also reported combined results on the frequency of SLC2A1 mutations in various forms of epilepsy form the published literature: overall SLC2A1 frequency in epilepsy was 29/1110 or 2.9% (combined 7 studies), the highest rate being in EOAE - 5.6% (4 studies including 303 patients) (18).

The finding that around 1-2% of IGE is actually monogenic disease (GLUT-1 IGE) is quite intriguing as it directly challenges the standing concept of the complex genetic architecture of epilepsies in general and IGE in particular. The autosomal dominant Mendelian inheritance pattern of GLUT-1 IGE may be obscured in many cases due to the incomplete penetrance and “de novo”nature of SLC2A1 mutations in many cases (17). The findings establishing SLC2A1 mutations in the genetic architecture of IGE and GLUT-1 deficiency as an underlying pathophysiology of IGE are important as they may have implications both for diagnosis and treatment of these patients.

CONCLUSIONS: EARLY DIAGNOSIS AND TREATMENT CONSIDERATIONS

While glucose is the primary (and perhaps preferred) source of energy for the brain (either as glucose or in the form of lactate), the brain can also switch to alternative sources of energy such as ketone bodies, produced in the course of a ketogenic diet (1, 3, 20, 21). This therapeutic approach has been used in the treatment of medication-refractory seizures for many years

with varying success. The theoretical concept that by-passes the defective glucose transport across the blood-brain barrier by offering the brain an alternative source of energy (ketone bodies) was proven therapeutically beneficial in GLUT-1 DS and over the decades the ketogenic diet become the "golden standard" in the treatment of this condition (6, 20, 21).

In patients with GLUT-1 DS ketogenic diet has been shown to be particularly beneficial in controlling seizures (reported cased of refractory seizures responding very well to ketogenic diet) and abnormal motions, including PED (refractory PED severely limiting walking responding to this treatment within days), without the need for anticonvulsants (20, 21). Although the cognitive function is least responsive to ketogenic diet, reports suggest that patients that started earlier with ketogenic diet have overall better outcomes (6, 20, 21).

Historically, the diagnostic approach included glucose testing in blood and CSF (low levels < 2.2 mmol/L and/or CSF-to-blood ratio < 40-45% was considered consistent with the diagnosis) when there was a clinical suspicion of this extremely rare and under-recognised condition (the classical De Vivo GLUT-1 DS) – and this led to delays in diagnosis or in many cases perhaps non-diagnosis. Recent developments in understanding GLUT-1 deficiency and the associated clinical spectrum as well as the accessibility and affordability of the genetic testing (which may yield positive results in 25-50% of selected cohorts) makes the early diagnosis and early treatment a realistic prospect. Early seizures (often within the first 6 months), abnormal eye/other movements and paroxysmal neurological phenomena, acquired microcephaly, accompanied by normal blood glucose levels and low CSF level, including low CSF-to-blood ratio (< 50% in cases with high clinical suspicion, < 60% in cases with low clinical suspicion, caution: milder GLUT-1 DS phenotypes may have low-normal to normal CSF) should raise the suspicion of GLUT-1 DS and prompt genetic testing (22).

The expanding clinical spectrum of GLUT-1 deficiency is in the spotlight for a few reasons. Firstly, while GLUT-1 deficiency was initially considered to be a rare genetic condition (GLUT-1 DS) it is now clear that this pathophysiological mechanism underlies a few more common clinical entities, such as PED, early-onset absence epilepsy, idiopathic generalised epilepsy and perhaps others (1-16). The classical and rare De Vivo GLUT-1 DS comprises the severe end of the GLUT-1 deficiency spectrum that includes patients with a significant reduction in GLUT-1 glucose transport function (40-75%), whereas the non-classical milder forms (intermittent neurologic phenomena, such as PED, epilepsy) arise when mutations lead to milder reduction in glucose transport function (20-35%) (1). Secondly, ketogenic diet seems to be effective in treating all clinical conditions with GLUT-1 deficiency as an underlying pathophysiological mechanism (6, 20, 21). The increased awareness of these conditions among pediatricians and neurologists and relaxed and improved diagnostic criteria including genetics testing may lead to earlier diagnosis, earlier treatment and better outcomes. Lastly, genetic research in rare disorders may shine light on the genetic architecture of more common and traditionally considered complex genetic disorders (16, 17).

Abbreviations

IGE — idiopathic generalised epilepsy
EOAE — early-onset absence epilepsy
PED — paroxysmal exertional dyskinesia
GLUT-1 (SLC2A1) — glucose transporter 1, solute carrier family 2, facilitated glucose transporter member 1
GLUT-1 DS — GLUT-1 deficiency syndrome
CSF — cerebrospinal fluid

CONFLICT OF INTEREST

The author has no conflict of interest to disclose.

Sažetak

GLUT-1 DEFICIT: OD PATOFIZIOLOGIJE I GENETIKE DO ŠIROKOG KLINIČKOG SPEKTRUMA

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Klasični GLUT-1 deficit je opisan pre više od 20 godina kao metabolička encefalopatija koja se karakteriše usporenim psihomotornim razvojem, sekundarnom mikrocefalijom, paroksizmalnim neurološkim simptomima (epilepsija) i poremećajima pokreta.

Tokom zadnjih nekoliko decenija opisano je preko 200 slučajeva ovog klasičnog GLUT-1 deficita poznatog kao bolest De Vivo. Biohemijski parametri ove bolesti su nizak nivo glukoze u cerebrospinalnom likvoru, normalni nivo glukoze u krvi i posledično nizak

odnos glukoze u cerebrospinalnom likvoru prema krvi (< 40-45%).

Genetska istraživanja su pokazala da su uzrok ove bolesti mutacije u genu SLC2A1 koji kodira transporter za glukozu 1 (GLUT-1) koji pomaže transport glikoze preko hematoencefalne barijere.

Tokom zadnjih nekoliko godina spektar GLUT-1 deficita je proširen na druge retke bolesti (paroksizmalna diskinezija pri naporu i absans epilepsije sa ranim početkom), ali i neke češće bolesti, kao što je idiopatska generalizovana epilepsija (1-2%).

GLUT-1 deficit je važna patofiziološka osnova ovih bolesti koja treba da se zna i prepozna zato što rana dijagnoza (potpomognuta DNA testiranjem) i terapija (ketogena dijeta) daju bolje rezultate.

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Review article

PORTAL VEIN THROMBOSIS — ULTRASOUND IMAGING

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Abstract: Portal venous system, apart from the main portal vein, includes its tributaries: superior and inferior mesenteric vein, as well as splenic vein, so the term portal venous thrombosis encompasses a broad spectrum of pathological conditions. Usually, one or more causative factors can be recognized, either local endothelial/flow disturbances, or systemic inherited/acquired conditions. Portal vein thrombosis can be associated with benign or malignant disorders. Weather we are speaking about acute or chronic thrombosis, the clinical presentation is different. Acute thrombosis can be presented in a wide range, from mild abdominal discomfort to a state of intestinal ischemia and life-threatening infarction. Chronic thrombosis is usually recognized when variceal bleeding or other symptoms of portal hypertension express. Fast and accurate diagnosis sometimes is a life-saving procedure, especially in acute vascular alterations. Recently, due to the improvement of imaging procedures the number of patients with diagnosed portal vein thrombosis is increasingly growing. With a negative predictive value of 98% color Doppler ultrasound is considered as imaging modality of choice in detecting portal vein thrombosis. Based on large studies it is presumed that overall risk of getting portal vein thrombosis during lifetime is 1% in general population, but much bigger 5%-15% in cirrhotic patients. Existence of specific ultrasound criteria, if fulfilled, has ensured that diagnosis of portal vein thrombosis is fast and non-invasive. Procedure is convenient for the patient and healthcare providers, and above all, allows prompt treatment preventing further deterioration.

Key words: portal vein, portal vein thrombosis, portal hypertension, ultrasound, color-Doppler ultrasound.

INTRODUCTION

Main portal vein (PV) arises behind the head of pancreas where the superior mesenteric vein (SMV) bringing blood from small intestine and part of pancreas, and splenic vein (SV) bringing blood from the spleen, join together. Blood running from large intestine through inferior mesenteric vein (IMV) usually drains into SV, while the blood from the stomach and part of pancreas drains directly into the main PV. In the liver hilum, PV divides in two main branches, one for each liver lobe. Consequently, regarding anatomy of the portal venous system, the term portal venous thrombosis (PVT) includes clot formation in the main portal vein, its branches or its tributaries.

Due to common risk factors, thrombosis may appear in one, or in several parts of portal venous system. Accordingly, clinical signs may be confusing, and symptoms may overlap. Splenic vein thrombosis can be present as isolated condition, while thrombosis of superior and inferior mesenteric vein is usually accompanied with thrombus in the main portal trunk.

Occlusion may be complete, involving the whole vessel lumen, or partial, with adherent clot and flow present on the periphery of the vein. Several classifications of PVT nowadays are used.

The anatomical classification into four categories refers to extra hepatic PVT: thrombosis in the main PV behind the confluence of the SMV and SV (grade1), thrombus extended in the SMV but not in the mesenteric vessels (grade 2), complete thrombosis of splanchnic veins with presence of huge collaterals (grade 3) and diffuse splahchnic thrombosis with only small collateral vessels (grade 4).

Another frequently used classification, especially in planning liver transplantation, proposed by Yerdel identifies 4 different grades of PVT as shown in Table 1 (1, 2).

Both classifications besides anatomical, have important etiological and prognostic relevance, since patients with extensive thrombosis have a greater risk of bowel infarction then those with isolated PVT who are prone to variceal bleeding.

ETIOLOGY

According to recent knowledge, occurrence of venous thrombosis including PVT results from more than

Table 1. *Classification of PVT according to Yerdel*

Grade 1: Minimal or partial thrombosis of portal vein, the clot is defined on less than 50% of vessel lumen, with/without minimal extension in the SMV
Grade 2: more than 50% occlusion of the portal vein lumen, including total occlusion, with/without occlusion of SMV
Grade 3: complete thrombosis of portal vein and proximal part of SMV (distal part of SMV is clot-free)
Grade 4: complete thrombosis of portal vein and proximal as well as distal part of SMV

one causative factor. Risk factors, local or systemic, may contribute to development of PVT. Changes in any part of Virchow's triad (coagulation disturbances, reduced flow or endothelial lesion) can be responsible for clot formation.

Most frequent risk factors are hypercoagulable disorders, inherited or acquired prothrombotic conditions. Decreased flow velocity in portal hypertension is most common cause among cirrhotic patients, while local precipitating risk factors, such an inflammation or infection, results in endothelial disturbances and thrombus formation.

In one big retrospective study involving 225 patients with PVT, based on patients medical history, risk factors were divided in a low grade risk factors (hypertension, diabetes mellitus, tobacco or alcohol use, SLE or sarcoidosis and illicit drug use) and high grade risk factors (preexisting liver disease in 69%, and regional cancer present in 47% of PVT patients, pancreatitis, hereditary thrombophillia, family history of thrombosis) (3). Another study clearly supports the hypothesis that concurrence of several prothrombotic factors favors development of PVT. Studying influence of several disorders : protein C, protein S and antithrombin deficiency, antiphospholipid syndrome; factor V-Leiden, factor II and methylene-tetrahidrofolate–reductase (MTHFR) gene mutations, French group concluded that PVT "should be regarded as an index for one or several prothrombotic disorders, whether or not local precipitating factors or oral use of contraceptives is found"(4). Risk factors for portal vein thrombosis are shown in Table 2.

Table 2. *Risk factors for portal vein thrombosis*

Hypercoagulable states:	
Inherited:	antithrombin deficiency
	Protein C deficiency
	Protein S deficiency
	Heterozygous factor V Leiden
	Prothrombin mutation
	MTHFR mutation
Acquired:	Malignancy
	Myeloproliferative disorders
	Use of oral contraceptive pills
	Paroxysmal nocturnal hemoglobinuria
	Inflammatory bowel disease
	Antiphospholipid syndrome
Reduced flow/portal hypertension:	Cirrhosis
	Hepatobiliary malignancies
Endothelial disturbance:	Local inflammation/infection
	- pancreatitis
	- cholangitis
	- diverticulitis
	- appendicitis
	- neonatal omphalitis
	Abdominal surgery
	TIPS
	Fine needle aspiration biopsy
	Glue treatment of gastric varices

PATHOPHYSIOLOGY

PVT has several consequences on systemic and splanchnic hemodynamic and their relevance depend on the extension of the clot. If clot is limited on the main portal vein, upstream of the thrombus there are no consequences on the intestines. As a result of portal vein obstruction, liver is left without two thirds of its blood supply; circumstances in which two "buffer" mechanisms intervene to compensate the loss.

The first one is almost immediate increase in arterial blood flow through dilation of hepatic artery. The second is so called "venous rescue"; development of collateral vessels with aim of bypassing the obstructed part of the vein. The appearance of "collaterals" is very rapid; it starts after occlusion, becoming visible almost in several days.

Imaging methods are revealing portal vein as a tiny cord, surrounded by irregular dilated vessels, mimicking vascular tumor. First time when this phenomenon was noticed, it was named "cavernoma" since it was considered as development anomaly in children. Collaterals are present in porta hepatis and in adjacent organs like gallbladder wall, duodenal wall, surrounding pancreatic head (5, 6).

Liver is rarely suffering from decreased portal flow, although transient signs of decompensated liver disease may be present. In experimental models, after portal vein ligation in mice, histology revealed marked apoptosis of hepatocytes, with increased mitotic acti-

vity and compensatory hypertrophy in other, well- perfused lobe.

Same model of compensatory hypertrophy is seen after surgical resection of liver segments in patients with liver tumors. At this stage portal hypertension develops, in order to support enough flow through collateral vessels into the liver. Simultaneously, systemic vascular resistance decreases with an increase in cardiac output leading to hyperdinamic circulation. In case where thrombosis is extended to the mesenteric vessels, mesenteries arches cannot drain the blood, functioning as collaterals. Meanwhile, arterial vasoconstriction as a reflex mechanism if prolonged can lead to intestinal wall infarction, one of the most detrimental events following PVT (7, 8, 9).

EPIDEMIOLOGY

In a big epidemiological study based on autopsies, population prevalence of PVT is 1%. 28% of PVT cases had underlying cirrhosis, 23% primary and 44% secondary hepatobiliary malignancies, while 10% had major abdominal infections or inflammatory disease, and the rest 3% had myeloproliferative disease (10, 11).

Although low in general population, prevalence among cirrhotic patients ranges between 4, 4% and 15%. According to some investigators PVT is responsible for 5%-10% of overall cases of portal hypertension, up to 40% in developing countries (12, 13). The prevalence among the patients candidates for orthotopic liver transplantation ranges between 0.6%-16%, and around 6,5% among the patients with hepatocellular carcinoma (14, 15, 16).

CLINICAL PRESENTATION

PVT presentation depends on severity of onset, therefore it is divided in two rather huge categories: acute and chronic. Sometimes it can be difficult to make a difference between the two types on the basis of symptoms. Likewise, both acute and chronic PVT may be covered by symptoms of underlying disease/condition.

Acute PVT can be presented from mild abdominal discomfort, through classical image of intestinal ischemia with colicky pain, nausea, diarrhea and fever. Depending on the extent of PVT and involved mesenteric vessels, bowel ischemia will give rise to occult stool bleeding in 50% of cases, and hematemesis, hematochesia or melena in 15% of cases. Signs of peritonitis and sepsis develop in approximately one to two thirds of patients. Sometimes ascites may appear due to venous congestion, while splenomegaly is almost always present. If the condition is not recognized and treated on time, very fast signs of intestinal perforation and shock will emerge. Physical examination will reveal abdominal distension, tenderness or guarding in case of intestinal perforation or peritonitis caused by inflammation. Prognosis of acute PVT depends on the grade of thrombosis and underlying disease. Consequently, mortality varies from 0-76%, among patients with mesenteric vein thrombosis from 20-50% of cases (17, 18, 19).

Chronic PVT can stay unrecognized in absence of liver disease, until the onset of variceal bleeding (hematemesis, melena) which is the first sign of PVT in 20-50% of cases. Patients with PVT without cirrhosis will present with signs of portal hypertension (bleeding, splenomegaly), but without ascites and encephalopathy, due to preserved liver function. Portal hypertensive billiopathy is present in almost 80% of patients with extrahepatic portal vein obstruction. Due to the compression of "cavernoma" or periportal varices on common bile duct, peridochal fibrosis or ischemical strictures with proximal dilation of billiary tree are frequently recognized. However, billiary stasis and choledochal stone formation will cause jaundice, cholangitis and abdominal pain in less than 30% of cases. Physical signs in chronic PVT are those of portal hypertension, liver cirrhosis and hypertensive billiopathy.

Prognosis of chronic PVT depends more on underlying disease then on PVT itself. Patients with cirrhosis and PVT according some studies have approximately hundred times greater risk of bleeding episode. Mortality is rather small and varies from less than 10% to 26% in patients with cirrhosis or malignancy (20-25).

Regarding PVT and survival in patients with cirrhosis, in one single center big retrospective cohort study (a total of 3295 patients; 4, 5% had PVT) "the presence of PVT at the time of transplantation was associated with an increased risk of liver death at 30 days" (26).

DIAGNOSIS

Establishing diagnosis of PVT is based mainly on imaging and laboratory findings. Ultrasound (US), magnetic resonance angiography (MRA), computed tomography (CT) and catheter angiography (only in case when invasive-shunt is planned) are imaging procedures used in patients with suspected PVT.

Ultrasound is the first imaging modality which is reliable with high degree of accuracy in detecting and follow-up of PVT. During the years, refinement of the method and development of duplex and color Doppler US, the sensitivity and specificity is improved, ranging from 60-100%. Contrast-enhanced US added an extra quality in distinguishing benign from malignant PVT (27, 28, 29).

Real–time or gray-scale US demonstrates portal vein, its caliber and presence of thrombus within the lumen. Apart from portal vein and liver parenchyma, appearance

of concomitant changes during the onset of PVT, such as splenomegaly and ascites, can be revealed by gray-scale.

In acute PVT ultrasound will demonstrate dilation of portal vein diameter (> 13 mm) and thrombus apparition which is virtually anechoic. Also, dynamic scan will confirm absence of respiratory variations of the vessel lumen. In chronic PVT thrombus is mainly hyperechoic, sometimes even accompanied by calcifications on the periphery (30).

Color-Doppler US must be performed in patients with suspected PVT, where gray-scale has not succeeded to visualize the thrombus inside the vessel. Sometimes in fresh thrombosis the echogenicity of the thrombus is rather the same as one of the flowing blood, in such cases (10-33%) during Doppler-imaging there will be a lack of signal in part of PV filled with thrombotic material (31). According to Yerdel Doppler US has a sensitivity of 73%, specificity of 99%, positive predictive value of 86% and negative predictive value of 98% (2). Similar results were published by Tessler et al. with sensitivity, specificity, positive predictive value and negative predictive value of 89%, 92%, 62% and 92% respectively (32). When Doppler-US has failed to discover thrombus and there is a clinical suspicion of PVT, or vice-versa: there is lack of Doppler-US in part of vessel due to sluggish flow but no clinical signs of PVT, it is necessary to use other imaging modality (Figure 1).

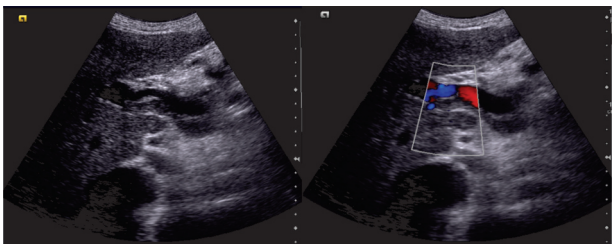

Figure 1. *Ultrasound and color Doppler findings in patient with liver cirrhosis and portal vein thrombosis. Portal thrombosis represented by the presence of echogenic material inside the portal vein on gray-scale; flow revealed on the periphery of the vessel*

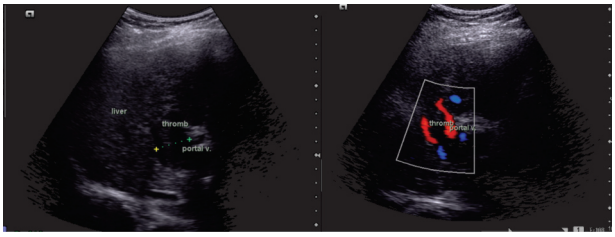

Figure 2. *Ultrasound and color Doppler findings in patient with portal vein thrombosis. Enlarged portal vein fulfilled with echogenic material on gray-scale; Color Doppler demonstrated the presence of flow in periportal collaterals*

Likewise in both, acute or chronic PVT, Doppler-US will reveal collaterals, disturbances in flow-pattern and hepatic artery changes. Collaterals, portoportal and portosystemic are detectable even by gray-scale, but when tortuous vessels are so big mimicking abdominal masses, color-Doppler US has decisive role. Perisplenic and retroperitoneal varices are most frequently found. Not so rare finding, especially in cirrhotic patients are enlarged paraumbillical vein and superficial collaterals extending distally. In acute PVT development of collaterals can be detected several days (from 7 days to 3 weeks) after thrombus appearance, while in chronic PVT collaterals are present during the first US examination (Figure 2).

PVT can be incidental finding, when "network of small tortuous vessels" with duplex/color-Doppler features of portal flow, is discovered instead of normal portal vein. This "cavernous transformation" is often accompanied with collaterals around common bile duct, gallbladder wall, hepatoduodenal ligament and pancreas.

Disturbances in flow pattern discovered on duplex/color-Doppler are slow flow (below 15 cm/sec), reversed (hepatofugal) and sometimes bi-directional (hepatoportal and hepatofugal) flow. Flow reversal is result of portal hypertension and development of collaterals, and is usually present in certain vessels like intrahepatic portal branches, splenic vein or coronary vein.

Hepatic artery changes as enlarged vessel diameter, flow increase and increased velocity, are concomitant finding due to "arterialization" of liver blood supply.

Whether we are speaking about benign or malignant thrombosis, Doppler US is reliable in defining the thrombus nature. Finding of "pulsatile flow" (inside the thrombus) on power Doppler, is accepted criterion of malignancy, with overall sensitivity of 82,5 % and specificity of 100%. Apart from power Doppler, contrast- enhanced ultrasound has been increasingly used in differentiating benign from malignant thrombosis. Positive enhancement of portal vein thrombus, when contrast agent is applied during US examination, yielded overall sensitivity and specificity of 100% in determining malignancy (31, 32).

When different ultrasound modalities are not able to determine the nature of the thrombus, biopsy can be helpful. Although there are studies where trans-abdominal fine needle aspiration (FNA) of portal thrombus was safely performed (81, 3% sensitivity), this procedure has not been accepted widely. Recently, endoscopic-ultrasound FNA of PVT was proposed with few advantages over classic trans-abdominal approach. Better visibility of the thrombus, avoiding the collateral vessels and above all shorter needle path and lower potential of seeding malignant cells, are promising features of this technique (33, 34, 35).

CONCLUSION

Portal vein thrombosis has small prevalence among general population (1%), but it is responsible for 5-15% of overall cases of portal hypertension. Clinical picture can vary in a broad spectrum, from mild abdominal discomfort through fulminant hepatic faiulure, variceal bleeding or bowel infarction with high mortality rate. Regarding possibility of fatal consequences, fast and accurate diagnosis of PVT is an implication. Recent development of imaging techniques, especially non-invasive, have allowed increasing detection of PVT. Among them, color-Doppler US (including contrast enhanced and endoscopic US), with negative predictive value of 98% is imaging procedure of choice. Of course, this technique has certain limitations; in such cases other modalities like MRA and CT- angiography are used.

Conflict of interest

The autors declare that there are no conflicts of interest.

Abbreviations

CT — computed tomography
EUS — endoscopic ultrasound
FNA — fine needle aspiration
IMV — inferior mesenteric vein
MRA — magnetic resonance angiography
PV — portal vein,
PVT — portal vein thrombosis
SV — splenic vein,
SMV — superior mesenteric vein
US — ultrasound

Sažetak

PORTNA VENSKA TROMBOZA – ULTRAZVUČNI IMIDŽING

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Portni venski sistem, pored glavne portne vene, uključuje i njene pritoke: gornju i donju mezenteričnu venu kao i spleničnu venu, zbog čega termin portna venska tromboza obuhvata širok spektar patoloških stanja. Obično se može prepoznati jedan ili više uzročnika, kao što su: lokalni poremećaji endotela krvnih sudova/protoka krvi ili sistemske nasledne/stečene bolesti. Portna venska tromboza može biti povezana sa benignim i malignim bolestima. Klinička prezentacija je drugačija kod akutne i hronične tromboze. Akutna tromboza može biti predstavljena u širokom opsegu, od blage abdominalne nelagodnosti do stanja crevne ishemije i tromboze koja ugrožava život. Hronična tromboza se obično prepoznaje kada nastane krvarenje zbog varikoziteta ili drugih simptoma portne hipertenzije. Brza i tačna dijagnoza ponekad znači spašavanje života, naročito kod akutnih vaskularnih stanja. Zbog poboljšanja radioloških-vizuelnih procedura, broj pacienata sa dijagnozom portne venske tromboze je u porastu. Kolor dopler se smatra dijagnostičkom metodom izbora u otkrivanju portne venske tromboze, sa negativnom prediktivnom vrednošću od 98%. Na osnovu velikih studija pretpostavlja se da je ukupni rizik od dobijanja portalne venske tromboze tokom života 1% u opštoj populaciji, ali je mnogo veći, od 5-15% kod pacijenata sa cirozom jetre. Ako su ispunjeni posebni ultrazvučni kriterijumi, dijagnoza portne venske tromboze je brza i neinvazivna. Metoda je pogodna za pacijenta i lekara, i što je najvažnije omogućava brz tretman i sprečava dalje pogoršanje bolesti.

Ključne reči: portna vena, portna venska tromboza, portna hipertenzija, ultrazvuk, kolor Dopler ultrazvuk.

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Review article

GENERAL ANESTHESIA: IS IT SAFE FOR NEWBORNS, INFANTS AND YOUNG CHILDREN?

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Abstract: The exposure of neonates, infants and small children to general anesthesia is becoming a common occurrence.Accumulating preclinical data indicate that exposure to commonly used general anesthetic agents during key periods of brain developmentin this population (between late gestation and 3 to 4 years of age), can lead to apoptotic neurodegeneration, synapse loss, and cognitive and neurobehavioral deficits that persist as the organism matures. New work suggests that infants and small children undergoing some types of surgery could have better recovery if they receive regional anesthesia rather than general anesthesia. In response to this concerns, the Food and drug administration (FDA) and the International Research Society in anesthesia (IARS) started an initiative called Smart Tots (Strategies for Mitigating Anesthesia- related neuro Toxicity in Tots)which examine the effects of anesthesia on brain development.Also another two major prospective studies are ongoing in children: PANDA (Pediatric Anesthesia Neurodevelopment assessment Study) project is a large, multi-center study based at the Morgan Stanley Children's Hospital of New York at Columbia University, and another one is GAS study which is a multisite randomized controlled trial comparing neurodevelopment outcomes in infant receiving general anesthesia compared to spinal and other regional anesthetics to the stress response to surgery.

The findings from these studies will help researches to design the safest anesthetic regimens and to develop the new and safer anesthetic drugs for use in pediatric medicine.

Keywords: pediatric anesthesia, newborn, infant, small children, neurotoxity risk, neurocognitive outcome.

INTRODUCTION AND CONTEXT

The exposure of newborns, infants and very young children to general anesthesia is becoming a common occurrence. The frequency of operating suite visits has increased, as have the lengths of stay in intensive care units, resulting in the annual administration of many millions general anesthetics to the pediatric patient population (1).

In newborns and infants morbidity and mortality from general anesthesia is higher than in adults,in infants is higher than in premature and those with body weight < 2 kg compared with newborns at term. Newborns are at greater risk to infants while they are at higher risk to children and of course smaller children compared to older children and adults. These correlations resulting among other things, and from the differences in anatomical and physiological features between newborn, infants and small children. Consistently cited as one of the greatest discoveries of modern medicine, general anesthesia has garnered widespread respect and acceptance for its remarkable ability to safely render a person unconscious with nothing to show for it afterward but a short-lived hangover. However, begining approximately a decade ago, studies began to challenge the premise that the brain is restored to its erstwhile pristine state after general anesthesia. Nowhere is the possibility of long-term alteration in brain function of greater concern than when an infant needs a procedure that requires general anesthesia. Accumulating preclinical data indicate that exposure to commonly used general anesthetic agents during key periods of brain development can lead to apoptotic neurodegeneration, synapse loss, and cognitive and behavioral deficits that

persist as the organism matures (2, 3). In addition, neonatal anesthetic exposure alters neurogenesis and synaptogenesis in animals (4, 5), indicating that anesthetic medications influence neuroplasticity (6). The brain is most vulnerable to this neurotoxicity and neuroplasticity during the brain growth spurt, which corresponds to a critical period of synaptogenesis and activity-dependent pruning and sculpting of synaptic architecture (2, 3). Because synaptogenesis in humans is believed to occur between late gestation and 3 to 4 years of age, than newborns, infants and small children who require general anesthesia during these years are possibly at risk for cognitive or neurobehavioral sequelae, if the animal data can be extrapolated to humans.

Anesthetic agents used for premedication, general anesthesia and pain treatment in new born, infant and small children

Premedication

Recommendations forpremedicationofpediatric patientsvary widely. Basicallyapremedication with sedativesis not practicedfor newbornsand infantswith severeclinical picture.Atanxiety children are indicated giving Midazolam 0,1-0,15 mg/kg^{-1} i.m or per os in the form of syrup. Preoperative intramuscular atropine as anticholinergic is justified by the following: reducing bradycardia and hypotension in induction and during anesthesia in newborns and infants up to 3 months, also acts antisialogenic by reducing the secretion, thereby facilitating intubation. Also atropine is recommended to be given in neonates and infants operated under neuroaxialblocks. It is given in doses of 0.15-0.2 mg/kg^{-1} i.m, some anesthesists practice to give intravenously immediately before induction of anesthesia, and some only if bradycardia appear (7, 8).

General anesthesia

General anesthesia in these population are applied with intravenous or inhaled technique. Intravenous induction is indicated if the newborn or infant is delivered by intravenous cannula. Barbiturate is given with a rapid onset of action (for newborn thiopental 3 mg/kg^{-1} infant 5 mg/kg^{-1}) or propofol (2-3 mg/kg^{-1}). Propofol as hypnotic is allowed to be given in infants older than 1 month, but there are studies of newborn and premature where it is used as a hypnotic for induction and maintenanceof anesthesia (1.0 mg/kg^{-1}). In infants the doses of propofol are higher, because of the large volume of distribution and faster decomposition. The appearance of hypotension and cardio-circulatory instability is a negative side effectof this hypnotic (9, 10). In newborn and infant analgesia during intravenous anesthesia can be established by using remifentanyl or fentanyl. As a opioids especially fentanyl in these patients may produce respiratory depression (residual effect) and usually practiced applying it, if premature or infant goes on a ventilator after surgery. Because propofol known to give cardio-circulatory instability it may be combined with ketamine (ketofol), in order to reduce the possibility of hypotension. Often in newborns with certain malformations are indicated intubation in live, but this is only possible if the infant has inserted intravenous cannula for possible complications (laryngospasm, bronchospasm). If the newborn has no intravenous cannula we tried to insert it by using few breaths of 7-8% sevoflurane -potent volatile anesthetic gas. The intubation are performed by using sevoflurane and intravenously by using depolarizing (succinylcholine) or non-depolarizing (rocuronium bromid, vecuronium bromid) muscle relaxant. In newborns and infants isoflurane and desfluranot do not find their place, because they are stronger, more iritable at induction in anesthesia (can be given cough, apnea, laryngospasm). Gas anesthesia alone does not make for itself a remarkable intraoperative analgesia and therefore need to be supplement with analgesic anesthetic (remifentanyl or fentanyl). Routinelyfor postoperative painacetaminophen is analgesic of choice, which should not be given more than 3 days because of its hepatotoxicity.

Waking from anesthesia requires reversing the block, breathing, grimacing, crying, attempted to selfextubation.

Postoperative apnea is serious problem in the newborn, especially if there is a history of prematurity, apnoic previous episodes, bradycardia, congenital defect, anemia, chronic lung disease (respiratory distress syndrome). Infants have a lower rate of Type 1 fibers and are at risk for fatigue. Residual anesthetic agents from operative intervention can also give apnea. Treatment consists of using tactile stimulation, oxygen support, use of caffeine, methylxanthines, and if it more frequent, endotracheal intubation and mechanical ventilation are required (8, 9, 10). In these newborns if the operative procedure is on lower extremities or lower part of abdomen, neuroaxial blocks(spinal, caudal, epidural) are regional technique of choice.

In recent years, the question is whether anesthesia for newborns, infants and young children is harmful?

Concerns about the potential impact of general anesthesia on brain development appeared about 10 years ago, when in certain studies of young animals exposed to anesthesia has been shown that there are changes in the brain that are associated with behavior prob-

lems. In these studies it has been shown that anesthetics which are usually used in anesthesia performed inhibition of neural activity through the disruption of synaptic transmission (depression of the nervous activity and decay of apoptotic cells) including GABA (↑ receptor activity) and NMDA receptors (blockade) (6). In May 2015 American Society of Anesthesiologists has published the first on line edition of the official medical journal of Anaesthesiology which were publicized two studies from Royal Children Hospital, Melbourne, Australia,involving infants with hernia repair operated under the general and regional- spinal anesthesia. Experts examined the effects of general anesthesia in infants and young children and believe that these patients undergoing general anesthesia several times in the first three years of life, may beathigher risk in the development and learning difficulties. When it showed that the possibility of complications postoperative apnea and breathing complications are much lower in the group of infants operated under spinal anesthesia (11, 12, 13, 14, 15).

American Society of Anesthesiologists (ASA) in May 2015 made recommendations:

"Experts have long examined the effects of anesthesia on infants and toddlers, and many believe infants who undergo general anesthesia in their first year of life may be at higher risk of developmental and learning issues. New work suggests that infants undergoing some types of surgery could have better recovery if they receive regional anesthesia rather than general anesthesia" (11, 12, 14, 15).

The most referent studies for possible impact of anesthesia on childhood cognitive function in children, learning disabilities, the occurrence of ADHD (Attention deficit hyperactivity disorder) came out from Mayo Clinic, published in Anesthesiology/march/ 2009. The first study included 5,000 children born between 1976 and 1982 in Olmstead County, Minnesota. The study monitored male children, because the number of operative procedures in infants and children with hernioplasty are most to them. This study followed children with one, two or more surgery to 4 years of age, and their results in reading, writing, mathemathics tests cognitive problems up to 19 years of age (11, 12). Children who received two or more anesthesia twofold increased risk in terms of thinking, speaking, reading, spelling, performing calculations. Dr. Robert Wilder and co-authors of this study noted thatžthe data are preliminary and do not necessarily suggest a direct or definitive causal link between anesthesia and learning disabilities, only an association. "We clearly have not demonstrated that anesthetics are the cause of learning disability," says Wilder. "We don't want this to alarm the public to the point they aren't giving children appropriate medical care." It could be dangerous to deny children surgery to spare them the anesthesia, Wilder says, since in most cases of pediatric surgery, the procedure is a necessary and potentially lifesaving one that cannot be avoided or postponed (13). Scientists from this department allude to a dose-dependent effect, i.e. how long the baby was anesthetized more likely to develop later problems with reading, writing and mathematics.

However experts are not ready to say that babies should not be given anesthesia "We do not want to delay the operation of a child who has need of it," said Dr. Solpicio Soriano, an anesthesiologist at Harvard Medical School and Children's Hospital in Boston "but we need more research and clinical trials to find new drugs and new combinations of drugs that would affect less later cognitive function of the child" (12, 13).

The second study was conducted on 5357 children born between 1976 and 1982 at Mayo Clinic, Rochester, Minnesota. These children were followed up to 19 years. age regarding the occurrence of ADHD disorder. It was revealed that children who received an anesthesia up to 2 years. age in 10.7% appeared ADHD disorder and those who had received 2 or more anesthetics to 2 years old this disorder occurred in 17.9%. Children who did not receive anesthesia percentage of ADHD was 7.3%. This suggests a possible link between anesthesia and the emergence of ADHD disorder.Dr. Randall Flick, from the Mayo Clinic suggests of the neurotoxityof nitrous oxide which is widely used in dental offices in the United States (11, 12, 13).

Third major study from the Royal Children Hospital in Melbourne, Australia, was performed on 2900 children under 3 years of age who received more anesthesia. At 10 years of age they were assessed for learning ability, thinking, remembering, reasoning, use of language and the development of depression and aggression. It was found that these children have almost more than twice as likely to have a language disability .In particular, it increased the chance that a child would have trouble listening to and remembering spoken words.The researchers found no link between anesthesia and behavioral problems or attention, however (12).The major study from Taiwan performed on 3293 children which were exposed to general anesthesia before 3 yearsof age showed that there is no connection between anesthesia and attention deficit/hyperactivity disorder(ADHD) (16).

In addition to the relative lack of safety data, recent *in vitro* and *in vivo* studies have shown that the variety of anesthetic agents in children less than 3 years of age (neonates, infants, small children) cause neurotoxicity and possible long- adverse neurodevelopmental outcomes (17, 18, 19, 20). In response to this concerns, the Food and drug administration (FDA) and the

International Research Society in anesthesia (IARS) started an initiative called Smart Tots (Strategies for Mitigating Anesthesia- Related Neuro Toxicity in Tots) which examine the effects of anesthesia on brain development. Smart Tots seeks to ensure that children under age 4 will be as safe as possible when they need anesthesia during surgery. Studies have shown that this is a period of significant brain development in young children (21). Also another two major prospective studies are ongoing in children: PANDA (Pediatric Anesthesia Neurodevelopment assessment Study) project is a large, multi-center study based at the Morgan Stanley Children's Hospital of New York at Columbia University. The project aims to examine two groups of children - those who have been exposed to anesthesia and those who have not – and assess their neurodevelopment and cognitive functions. The goal of the PANDA project is to add to the body of knowledge surrounding the important topic of the long term neurodevelopmental effects of anesthesia and surgery in infants and young children (1).

The second study is GAS study which is a multisite randomized controlled trial comparing neurodevelopment outcomes in infant receiving general anesthesia compared to spinal and other regional anesthetics to the stress response to surgery (15).

The director of the Division of Anesthesia, Analgesia and Addiction Products at FDA,Bob Rappaport says "Our hope is that research funded through Smart Tots will help us design the safest anesthetic regimens possible" and "this research can potentially foster the development of new and safer anesthetic drugs for use in pediatric medicine" (21, 22).

Conclusion

The most of the mentioned studies found that a procedure of anesthesia/surgery in children before 4 years old is possibly associated with later neurodevelopmental deficits, especially multiple times of exposure to anesthesia. Due to the limitation of retrospective studies, prospective studies are needed to determine whether the association between anesthesia/surgery and neurodevelopmental deficits is causative.

Conflict of interest

The author declares no conflict of interest.

Abbreviations

GABA receptors — gamma-aminobutyric acid receptors

ASA — American Association of Anesthesiologists

NMDA receptors — N-methyl-D-aspartatereceptors

FDA — Food and Drug Administration

IARIS — International Research Society in anesthesia

PANDA — Pediatric Anesthesia Neurodevelopment assessment

GAS — Multi-site Randomized Controlled Trial Comparing Regional and General Anesthesia for Effects on Neurodevelopmental Outcome and Apnea in Infants

Sažetak

OPŠTA ANESTEZIJA: DA LI JE BEZBEDNA ZA NOVOROĐENČAD, ODOJČAD I MALU DECU?

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Izloženost neonatusa, odojčadi i male dece opštoj anesteziji postaje sve češća pojava. Sakupljanje preklinič kih podataka ukazuje da je izloženost, često primenjivanim opštim anesteticima, tokom ključnog perioda za razvoj mozga u populaciji (između kasnog gestacionog period do 3-4 godine života), može dovesti do apoptotskih neurodegenerativnih promena, gubitka sinapsi i kognitivnih i neurobihevioralnih deficita, koji ostaju prisutni i tokom sazrevanja organizma. Nova istrazivanja savetuju da odojčad i mala deca, koja su podvrgnuta operaciji, mogu da imaju bolji oporavak, ako dobijaju regionalnu anesteziju pre nego ako su uvedena u opštu anesteziju. Kao odgovor na ovaj problem, *FDA* (Food and drug administration) i *IARS* (International Research Society in anesthesia) su započeli kampanju nazvanu Smart Tots (Strategies for Mitigating Anesthesia- related neuro Toxicity in Tots), koja izučava efekte anestezije na razvoj mozga. Takođe dve

prospektivne studije su u toku: *PANDA* (Pediatric Anesthesia Neurodevelopment assessment Study) projekat je velika, multicentrična studija u Morgan Stanley dečjoj bolnici u Njujorku, na Kolumbija Univerzitetu i još jedna, *GAS* studija, koja upoređuje neurološke razvojne ishode kod odojčadi, koja su podvrgnuta opštoj anesteziji u poređenju sa odojčadima podvrgnutim spinalnoj ili drugim oblicima regionalne anestezije.

Otkrića ovih studija pomoći će istraživačima da dizajniraju najbezbedniji anesteziološki protokol i da razviju novi i bezbedniji anestetik za upotrebu u pedijatriji.

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UPUTSTVO AUTORIMA

SANAMED je medicinski časopis osnovan 2006. godine. Časopis objavljuje: originalne naučne i stručne članke, prikaze bolesnika, revijske radove, pisma uredniku, članke iz istorije medicine, prikaz objavljenih knjiga i druge medicinske informacije.

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Rukopis treba poslati u tri primerka, otkucan jednostrano na beloj hartiji formata A4. Tekst rada kucati u programu za obradu teksta *Word*, latinicom, sa dvostrukim proredom, isključivo fontom *Times New Roman* i veličinom slova 12 tačaka (12 pt). Sve margine podesiti na 25 mm, a tekst kucati sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm, bez deljenja reči (hifenacije).

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Svaki deo rukopisa (naslovna strana, itd.) mora početi na posebnoj strani. Sve strane moraju biti numerisane po redosledu, počev od naslovne strane. Prezime prvog autora se mora otkucati u gornjem desnom uglu svake stranice. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u zagradama, i to onim redosledom kojim se pojavljuju u tekstu.

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Naslovna strana. Naslovna strana sadrži naslov rada, kratak naslov rada (do 50 slovnih mesta), puna prezimena i imena svih autora, naziv i mesto institucije u kojoj je rad izvršen, zahvalnost za pomoć u izvršenju rada (ako je ima), objašnjenje skraćenica koje su korišćene u tekstu (ako ih je bilo) i u donjem desnom uglu ime i adresu autora sa kojim će se obavljati korespondencija.

Naslov rada treba da bude sažet, ali informativan.

Ako je potrebno, može se dodati i podnaslov.

Kratak naslov treba da sadrži najbitnije informacije iz punog naslova rada, ali ne sme biti duži od 50 slovnih mesta.

Ako je bilo materijalne ili neke druge pomoći u izradi rada, onda se može sažeto izreći zahvalnost osobama ili institucijama koje su tu pomoć pružile.

Treba otkucati listu svih skraćenica upotrebljenih u tekstu. Lista mora biti uređena po abecednom redu pri čemu svaku skraćenicu sledi objašnjenje. Uopšte, skraćenice treba izbegavati, ako nisu neophodne.

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Stranica sa sažetkom. Sažetak mora imati do 350 reči. Treba koncizno da iskaže cilj, rezultate i zaključak rada koji je opisan u rukopisu. Sažetak ne može sadržati skraćenice, fusnote i reference.

Ključne reči. Ispod sažetka treba navesti 3 do 8 ključnih reči koje su potrebne za indeksiranje rada. U izboru ključnih reči koristiti Medical Subject Headings — MeSH.

Stranica sa sažetkom na engleskom jeziku. Treba da sadrži pun naslov rada na engleskom jeziku, kratak naslov rada na engleskom jeziku, naziv institucije gde je rad urađen na engleskom jeziku, tekst sažetka na engleskom jeziku i ključne reči na engleskom jeziku.

Struktura rada. Svi podnaslovi se pišu velikim slovima i boldovano.

Originalni rad treba da ima sledeće podnaslove: uvod, cilj rada, metod rada, rezultati, diskusija, zaključak, literatura.

Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura.

Pregled iz literature čine: uvod, odgovarajući podnaslovi, zaključak, literatura.

Bolesnici i metode/materijal i metode. Treba opisati izbor bolesnika ili eksperimentalnih životinja, uključujući kontrolu. Imena bolesnika i brojeve istorija ne treba koristiti.

Metode rada treba opisati sa dovoljno detalja kako bi drugi istraživači mogli proceniti i ponoviti rad.

Kada se piše o eksperimentima na ljudima, treba priložiti pismenu izjavu u kojoj se tvrdi da su eksperimenti obavljeni u skladu sa moralnim standardima Komiteta za eksperimente na ljudima institucije u kojoj su autori radili, kao i prema uslovima Helsinške deklaracije. Rizične procedure ili hemikalije koje su upotrebljene se moraju opisati do detalja, uključujući sve mere predostrožnosti. Takođe, ako je rađeno na životinjama, treba priložiti izjavu da se sa njima postupalo u skladu sa prihvaćenim standardima.

Treba navesti statističke metode koje su korišćene u obradi rezultata.

Rezultati. Rezultati treba da budu jasni i sažeti, sa minimalnim brojem tabela i slika neophodnih za dobru prezentaciju.

Diskusija. Ne treba činiti obiman pregled literature. Treba diskutovati glavne rezultate u vezi sa rezultatima objavljenim u drugim radovima. Pokušati da se objasne razlike između dobijenih rezultata i rezultata drugih autora. Hipoteze i spekulativne zaključke treba jasno izdvojiti. Diskusija ne treba da bude ponovo iznošenje zaključaka.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, osim u pregledu literature, u kojem je dozvoljeno da ih bude do 50.

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1. **Članak:** (svi autori se navode ako ih je šest i manje, ako ih je više navode se samo prva tri i dodaje se *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg 2003; 29: 650–652.

2. **Knjiga:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Poglavlje ili članak u knjizi:**

Latković Z. Tumori očnih kapaka. U: Litričin O i sar. Tumori oka. 1. izd. Beograd: Zavod za udžbenike i nastavna sredstva, 1998: 18–23.

Tabele. Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu, sa nazivom tabele iznad. Svaku tabelu odštampati na posebnom listu papira i dostaviti po jedan primerak uz svaku kopiju rada.

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Treba poslati dva kompleta slika, u dva odvojena koverta, zaštićene tvrdim kartonom. Na pozadini slika treba napisati običnom olovkom prezime prvog autora, broj slike i strelicu koja pokazuje vrh slike.

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1. **Article:** (all authors are listed if there are six or fewer, otherwise only the first three are listed followed by *"et al."*)

Spates ST, Mellette JR, Fitzpatrick J. Metastatic basal cell carcinoma. J Dermatol Surg 2003; 29: 650–652.

2. **Book:**

Sherlock S. Disease of the liver and biliary system. 8th ed. Oxford: Blackwell Sc Publ, 1989.

3. **Chapter or article in a book:**

Trier JJ. Celiac sprue. In: Sleisenger MH, Fordtran J5, eds. Gastro-intestinal disease. 4 th ed. Philadelphia: WB Saunders Co, 1989: 1134–52.

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