YU ISSN 0042-8450

ВОЈНОСАНИТЕТСКИ ПРЕГЛЕД

Часопис лекара и фармацеута Војске Србије

Military Medical and Pharmaceutical Journal of Serbia

Vojnosanitetski pregled

Vojnosanit Pregl 2016; August Vol. 73 (No. 8): p. 699–794.

Frederick Chapman Robbins

YU ISSN 0042-8450 vol. 73, br. 8, 2016.

VOJNOSANITETSKI PREGLED

Prvi broj *Vojnosanitetskog pregleda* izašao je septembra meseca 1944. godine

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

IZDAVAČ
Uprava za vojno zdravstvo MO Srbije

Adresa redakcije: Vojnomedicinska akademija, Institut za naučne informacije, Crnotravska 17, poštanski fah 33–55, 11 040 Beograd, Srbija. Informacije o pretplati: Tel.: +381 11 3608 997. E-mail (redakcija): **vsp@vma.mod.gov.rs**

Radove objavljene u „Vojnosanitetskom pregledu“ indeksiraju: Science Citation Index Expanded (SCIE), Journal Citation Reports/Science Edition, Index Medicus (Medline), Excerpta Medica (EMBASE), EBSCO, Biomedicina Serbica. Sadržaje objavljuju Giornale di Medicine Militare i Revista de Medicina Militara. Prikaze originalnih radova i izvoda iz sadržaja objavljuje International Review of the Armed Forces Medical Services.

Časopis izlazi dvanaest puta godišnje. Pretplate: Žiro račun br. 840-314849-70 MO – Sredstva objedinjene naplate – VMA (za Vojnosanitetski pregled), poziv na broj 1227423129552141 5. Za pretplatu iz inostranstva obratiti se službi pretplate na tel. 3608 997. Godišnja pretplata: 5 000 dinara za građane Srbije, 10 000 dinara za ustanove iz Srbije i 150 € (u dinarskoj protivvrednosti na dan uplate) za pretplatnike iz inostranstva. Kopiju uplatnice dostaviti na gornju adresu.

Štampa Vojna štamparija, Beograd, Resavska 40 b.

YU ISSN 0042-8450 vol. 73, No. 8, 2016

VOJNOSANITETSKI PREGLED

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

PUBLISHER
Military Health Department, Ministry of Defence, Belgrade, Serbia

Editorial Office: Military Medical Academy, Institute for Scientific Information, Crnotravska 17, PO Box 33–55, 11 040 Belgrade, Serbia. E-mail: **vsp@vma.mod.gov.rs**

Papers published in the Vojnosanitetski pregled are indexed in: Science Citation Index Expanded (SCIE), Journal Citation Reports/Science Edition, Index Medicus (Medline), Excerpta Medica (EMBASE), EBSCO, Biomedicina Serbica. Contents are published in Giornale di Medicine Militare and Revista de Medicina Militara. Reviews of original papers and abstracts of contents are published in International Review of the Armed Forces Medical Services.

The Journal is published monthly. Subscription: Giro Account No. 840-314849-70 Ministry of Defence – Total means of payment – VMA (for the Vojnosanitetski pregled), refer to number 12274231295521415. To subscribe from abroad phone to +381 11 3608 997. Subscription prices per year: individuals 5,000.00 RSD, institutions 10,000.00 RSD, and foreign subscribers 150 €.

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

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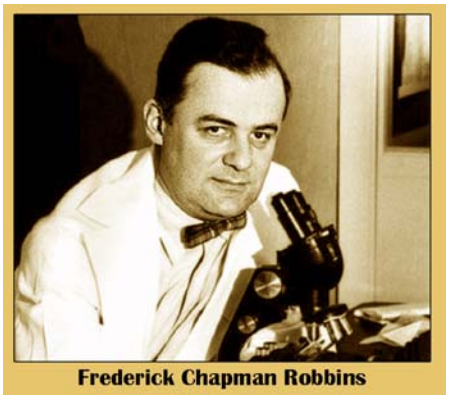
Frederick Chapman Robbins

Frederick C. Robbins (August 25, 1916 – August 4, 2003) was an American paediatrician and virologist who, along with John F. Enders and Thomas H. Weller, won the 1954 Nobel Prize in Physiology or Medicine. They were awarded for discovery of the ability of poliomyelitis viruses to grow in cultures of various types of tissue. This was a revolutionary discovery of that time as it helped to grow the virus *in vitro* and in turn develop a vaccine that eventually eliminated the crippling disease from most of the countries across the globe. The tissue culture technique helped isolate increasing number of viruses and also had important implications for cancer research.
This August marks the 100th anniversary of Roobbins' birth and the 13th anniversary of his death.

Frederik Robins (25. avgust 1916 – 4. avgust, 2003) američki pedijatar i virolog, zajedno sa Džonom Endersom i Tomasom Velerom, dobitnik je Nobelove nagrade za medicinu 1954. godine. Oni su nagrađeni za otkriće sposobnosti virusa polimijelitisa da raste u kulturama različitih tkiva. To je bilo revolucionarno otkriće u to doba jer je omogućilo razmnožavanje i rast virusa *in vitro* i, posledično, razvoj vakcine koja je dovela do eliminacije bolesti širom sveta. Tehnika tkivnih kultura u razmnožavanju poliovirusa pomogla je u izolaciji i drugih virusa a, takođe, imala je važnu ulogu i u proučavanju kancerskih ćelija.
U avgustu ove godine obeležava se 100 godina od rođenja i 13 godina od smrti Frederika Robinsa.

ORIGINAL ARTICLES

UDC: 37:61-057.875]::616-056.7-039.33
DOI: 10.2298/VSP150326094M

The attitudes of medical students towards rare diseases: A cross-sectional study

Stavovi studenata medicine o retkim bolestima: studija preseka

Branislava Medić*, Nevena Divac*, Bojan Stopić†, Katarina Savić Vujović*, Andreja Glišić‡, Nataša Cerovac§, Radan Stojanović*, Dragana Srebro*, Milica Prostran*

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Abstract

Background/Aim. Rare diseases are chronic, degenerative and may lead to permanent disability. We aimed to assess knowledge and attitudes of the 3rd and 6th year medical students towards the treatment of rare diseases in Serbia. **Methods.** In this cross-sectional study, two samples of students were questioned for a survey: 350/446 (78.48%) students of the 3rd year, and 242/517 (46.81%) students of the 6th year. **Results.** Sixth year students estimated that they were more informed on the issue analyzed than the 3rd year students (median value of 4 and 3, interquartile range of 3–5, and 1–4, respectively; $p < 0.05$). However, a significant percentage of participants estimated incorrectly the prevalence of rare diseases according to the European Union standards (3rd year – 42.68%, 6th year - 49.55%). Core curriculum subjects were the main source of information on rare diseases (3rd year – 63.14%; 6th year – 92.14%). Our participants agreed that the most important problems are the following: high drug prices, difficult access to drugs and lack of public information. Students found, without any differences, that community access to effective drugs for rare disease should be improved (median value – 10, interquartile range 8–10 in both groups, $p < 0.05$). In order to improve pharmacotherapy of rare diseases in Serbia, the participants suggested establishment of a National Plan for Rare Diseases, approval of more appropriate drugs, simplified access to appropriate medicines, and more rapid diagnostics. **Conclusion.** It is necessary to improve the knowledge and attitudes of medical students towards pharmacotherapy of rare diseases.

Key words:
rare diseases; students, medical; education; serbia.

Apstrakt

Uvod/Cilj. Retke bolesti predstavljaju hronična degenerativna stanja koja mogu dovesti do trajne onesposobljenosti. Cilj ovog rada bio je procena znanja i stavova studenata treće i šeste godine medicine o lečenju retkih bolesti u Srbiji. **Metode.** U studiji preseka, dve grupe studenata ispunile su upitnik napravljen za potrebe ovog istraživanja: 350/446 (78,48%) studenata treće godine i 242/517 (46,81%) studenata šeste godine. **Rezultati.** Studenti šeste godine procenili su stepen svoje informisanosti o retkim bolestima kao bolji u odnosu na studente treće godine (medijana 4 i 3, interkvartilni opseg 3–5 i 1–4; $p < 0,05$). Međutim, značajan procenat učesnika netačno je procenio prevalenciju retkih bolesti definisanu prema standardima Evropske unije (treća godina – 42,68%, šesta – 49,55%). Obavezni predmeti bili su glavni izvor informacija o retkim bolestima (treća godina – 63,14%, šesta – 92,14%). Svi učesnici istraživanja bili su jedinstveni u stavu da su najvažniji problemi obolelih: visoke cene lekova, nedostupnost terapije i nedovoljna informisanost javnosti. Svi studenti bili su saglasni u stavu da društvo treba da poboljša dostupnost terapije za retke bolesti (medijana 10, interkvartilni opseg 8–10, $p < 0,05$). U cilju unapređenja farmakoterapije retkih bolesti u našoj zemlji, učesnici su predložili formiranje nacionalne strategije za retke bolesti, registrovanje većeg broja lekova, pojednostavljivanje procesa nabavke lekova i ubrzavanje dijagnostičkih procedura. **Zaključak.** Neophodno je unaprediti znanje i stavove studenata medicine o farmakoterapiji retkih bolesti.

Ključne reči:
retke bolesti; studenti medicine; obrazovanje; srbija.

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Introduction

It is widely accepted that rare diseases (RDs) affect less than 1 in 2,000, or 5 in 10,000 people [1, 2]. Most of those diseases are due to genetic abnormalities (around 80% of cases). First symptoms appear at birth or in early childhood (around 50% of cases). Diseases are chronic, degenerative and may lead to permanent disability. There are between 6,000 and 8,000 rare diseases and pharmacotherapy is not available for many of them. According to the European Organization for Rare Diseases (EURORDIS), these diseases affect thirty million European Union citizens. It is estimated that there are approximately half a million cases in Serbia [3].

Patients affected with rare diseases, in general, face many problems. Some of these diseases have a devastating impact on all aspects of patients' and carers' lives. Also, healthcare professionals usually lack awareness of the possibility of coming across rare diseases in their professional careers [4]. The consequence is often misdiagnosis and/or delayed diagnosis. It is estimated that it takes approximately seven years to be diagnosed with a rare disease [5]. A patient-oriented coding and classification system ("p-classification") has been recently developed in Germany in order to strengthen patients' efforts and improve exchange of information. However, there is a breakdown in the exchange of information between experts and public on RDs. In addition, the majority of the health workforce is not sufficiently informed on RDs [6].

In Serbia, the problem of the diagnosis and treatment of RDs is currently under public scrutiny. Patients are often misdiagnosed or the diagnosis is delayed due to several problems: lack of awareness among physicians, lack of expertise, unavailability and/or high costs of diagnostic tests. According to the National Organization of Patients with Rare Diseases in Serbia (NORBS), many diagnostic procedures have to be conducted abroad and the process comprises many difficulties: high costs, travel expenses or transportation of biological material [3]. Although national legislation ensures the availability of drugs for those diseases, pharmacotherapy is faced with many problems. Licensed drugs are not always or not readily available and provision of unlicensed medicines is very difficult not just due to legislative obstacles. Also, people affected with rare diseases may require other medicinal devices such as diapers, special nutritional preparations, wheelchairs etc. and these expenses are not reimbursed by the national health insurance. All these obstacles in the treatment and care of patients with rare diseases has led to many charitable actions aimed at collecting donations for the treatment of patients and the involvement of media in raising public awareness of rare diseases. The still no national registry of rare diseases in Serbia, as well as national strategy regarding these diseases [7, 8].

Knowledge about rare diseases among medical doctors is crucial for the improvement of perspectives for those patients. Education on rare diseases contributes not only to more accurate and timely diagnosis and treatment of particular patients, but also improves general aspects of this problem such as planning of national strategy, funding, foundation of expert centres etc. Therefore, the role of undergraduate medical education is essential in providing good foundation for future doctors involved in this issue.

In particular, rare diseases are extensively discussed through various undergraduate courses, but there is not a specific course dedicated to such a problem. We aimed to assess and compare knowledge, awareness and attitudes of the 3rd and 6th year medical students from the Faculty of Medicine, University of Belgrade, towards the issue of rare diseases in Serbia. These two groups of students were selected for particular reasons: 3rd year students complete preclinical, while 6th year students finish clinical curriculum. We tried to establish whether clinical curriculum improved knowledge and attitudes of students regarding this issue.

Methods

Participants

The cross-sectional study was conducted over five days at the Faculty of Medicine, University of Belgrade[*]. Two randomly chosen samples of the 3rd and 6th year undergraduate students were chosen for the survey. The questionnaire was completed by a total of 350 out of 446 (78.48%) students of the 3rd year, and 242 out of 517 (46.81%) students of the 6th year. The participants were recruited during regular classes.

Questionnaire

All the students completed an anonymous questionnaire entitled "Knowledge and attitudes of medical students about rare diseases in Serbia" (Addendum 1). The questionnaire was developed at the Department of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade and reviewed by experts on rare diseases from several clinical fields (neurology, paediatric neurology, gynaecology and internal medicine). It was a pilot questionnaire tested with 50 third year medical students. Pilot test included the same questions as the study questionnaire and revealed appropriate understanding of questions and very low rate of skipped answers. The verbal feedback from the pilot tested students was overall positive. The questionnaire was approved by the Ethics Committee of the Faculty of Medicine in Belgrade (Number 29/XI-14). Both closed and open questions were used when appropriate. The questionnaire consisted of general data (such as gender, age and the average study score), questions about awareness of rare diseases and their treatment, attitudes about problems of these patients, as well as the possibilities of overcoming them. Students' attitudes towards RDs were assessed by the 10-point Likert scale.

Statistics

The results were presented as descriptive statistics (nominal scale) and median value and interquartile range (results scores). A statistical analysis was performed using χ^2-test and Mann-Whitney U test, with a statistical significance level of 0.05.

[*]Most prestigious, biggest and the oldest Faculty in Serbia, on the Shanghai List of Universities.

Results

General characteristics of the participants

General characteristics of the 3rd and 6th year medical students who responded to a questionnaire survey on attitudes towards rare diseases treatment were shown in Table 1. There was a total of 350 3rd and 242 6th year students, with similar gender distribution and similar average grades in both groups.

Samples did not differ in any of the characteristics presented.

Students' self-assessment of rare diseases knowledge (general knowledge and treatment possibilities)

The students were asked to rate their knowledge about rare diseases in general, based on the 10-point Likert scale. As expected, the 6th year students rated their knowledge as significantly better than the 3rd year students (median score 3.0 *vs* 4.0, $p < 0.001$) (Figure 1, Panel A).

The overall quality of healthcare of patients affected with rare diseases in general was rated as low by both groups of students. Based also on the 10-point Likert scale, the 3rd year students' score for this question was 2.2, and the 6th year students' 2.4 ($p < 0.05$) (Figure 1, Panel B).

The complications associated with obtaining drugs for rare diseases in Serbia were graded as significant by both groups of students, but year 6th students opinion was more favorable. Based on 10-point Likert scale, the points ranged from 1 (extremely complicated) to 10 (not complicated at all). The score provided by 3rd year students was 2.2 *vs* 2.7 provided by the 6th year students ($p < 0.001$) (Figure 1, Panel C).

Both groups of students graded lowly the possibilities

Table 1

General characteristics of the study population (3rd and 6th year medical students)

Medical students	3rd year	6th year
Number of respondents	350	242
Sex (male/female), n (%)	109/241 (31/69)	74/168 (30/70)
The year of enrolment to Faculty of Medicine, median values (interquartile ranges 25–75%)	2009 (2008–2009)	2006 (2005–2006)
Average score during the studies, median values*	8–9	8–9

***Score rank 6–10.**

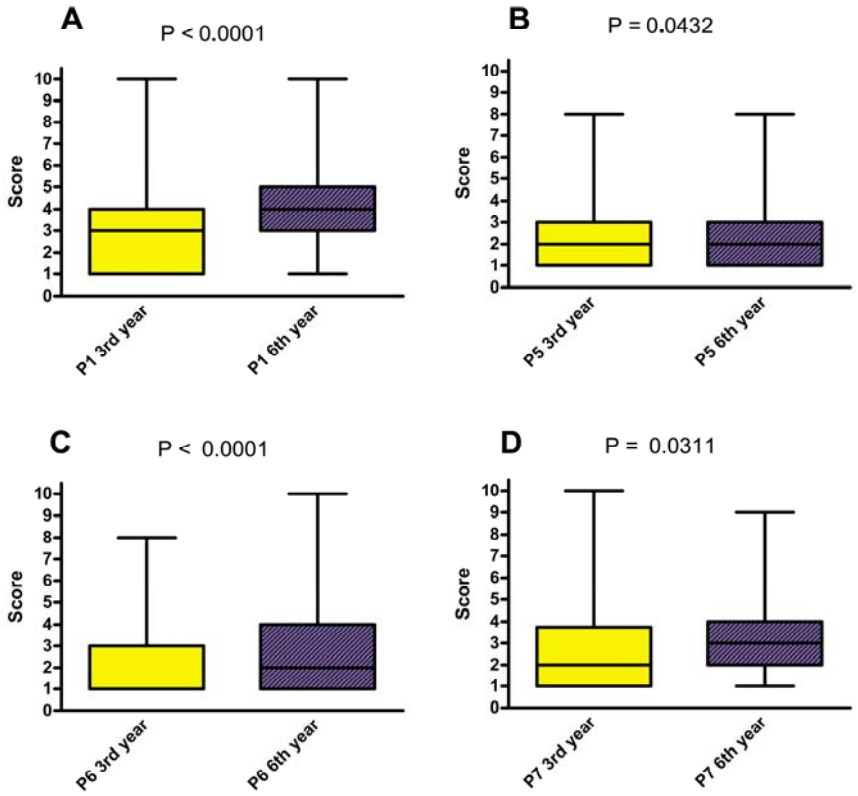

Fig. 1 – The average values of the selected scores (median value, interquartile range 25–75%) of the 3rd and 6th year medical students, concerning their attitudes and awareness towards the issue of treatment of rare diseases in our community. Panel A: Awareness towards the issue of treatment of rare diseases (scale 1–10); Panel B: Attitudes towards the possibilities of obtaining drugs for rare diseases in Serbia (scale 1–10); Panel C: Awareness towards the possibilities of obtaining drugs for rare diseases in Serbia (scale 1–10); Panel D: Attitudes towards the availability of drugs for rare diseases in our country (scale 1-10). The results are shown in a graph box ("Box plot") with a median value and interquartile range (25–-75%). Ordinate: arbitrary score. The significance of the difference between the 3rd and 6th year students was determined by Mann-Whitney U-test.

of obtaining drugs for rare diseases in Serbia. However, the estimate made by the 6th year students (2.8) was significantly more favorable compared to 3rd year students (2.6) ($p < 0.05$) (Figure 1, Panel D).

Objective assessment of students' basic knowledge on rare diseases

The knowledge on the prevalence of rare diseases in Europe was tested with a multiple choice question. The prevalence of rare diseases according to EU standards was correctly estimated by a slightly more than half of participants in both groups of students (3rd year – 57.32%, 6th year – 50.45%, $p > 0.05$).

The participants recognized rare diseases from the list comprising both common and rare diseases, in the following percentages: acromegaly (3rd year – 36.57%, 6th year – 21.07%), haemophilia (3rd year – 35.14%, 6th year – 30.99%), Gaucher disease (3rd year – 48%, 6th year – 83.05%) and Non-Hodgkin's lymphoma (3rd year – 34%, 6th year – 8.2%) (3rd year *vs* 6th year, $p > 0.05$, each). However, the overall distribution of answers differed significantly between the 3rd and the 6th year students, surprisingly in favor of the 3rd year students ($p < 0.0001$).

We also tried to establish which sources of information on rare diseases students mostly used, with the question that allowed more than one answer. The 3rd and 6th students used different sources of information on rare diseases. The former group indicated core curriculum subjects as the main source of information on the rare diseases (for example, Pathology, Pathological Physiology, Immunology, Internal medicine and Neurology) – 63.14%, followed by some other extracurricular sources (television, internet) – 39.42%, and a large number of elective courses – 11.4%, while the latter group cited the same sources in the following percentages: 92.14%, 6.67% and 27.68%, respectively.

Students' attitudes regarding rare diseases as a societal and bioethical issue

The next set of questions aimed to assess students' attitudes regarding rare diseases as a broader societal problem.

Using the 10-point Likert scale, both groups of participants rated the importance of rare diseases in our society as a problem of secondary importance (3rd year 5.9 and 6th year 5.8; $p > 0.05$). Also, using a multiple choice question which allowed more than one answer, they identified particular problems of Serbian patients affected with rare diseases (Table 2).

The students were asked to identify the most competent factors (e.g. medical professional associations, drug manufacturers and distributors, patients associations or state regulatory bodies) which could improve availability of drugs for rare diseases. As the most responsible, both groups of students unanimously identified state regulatory bodies (Table 3)

Regarding measures for improving pharmacotherapy of rare diseases in Serbia, the collaboration between physicians and pharmacists in order to advance the availability of drugs for rare diseases was highly ranked, with no difference between the groups ($p > 0.05$).

When asked to evaluate whether to provide costly medical care for patients with rare diseases or to spend on treatments for more common conditions affecting larger numbers of people, participants mainly supported the former opinion (10-point Likert scale, 3rd year 7.9; 6th year 7.9; $p > 0.05$).

Table 2

The 3rd and 6th year medical students' opinion on the most important problems of patients with rare diseases

The most important problems of patients	Students (%)		
	3rd year	6th year	*p* value
Lack of information among general public	67.71	56.61	< 0.01
Lack of scientific knowledge	31.42	37.19	> 0.05
Lack of access to correct diagnosis	46.28	42.56	> 0.05
Lack of appropriate quality healthcare	49.71	40.08	< 0.05
Lack of registered drugs for rare diseases	41.43	70.24	< 0.0001
Complicated procedures of drug provison	60.00	63. 22	> 0.05
High prices of drugs	86.29	80.58	> 0.05
Other causes	2.00	1.65	> 0.05

Table 3

The 3rd and 6th year medical students' opinion on ways for improving availability of the drugs for rare diseases

Availability of drugs for rare diseases can be improved by greater iinvolvement of ...	3rd year (mean)*	6th year (mean)*	*p* value
The State	8.9	8.8	> 0.05
Drug manufacturers and distributors	7.9	7.8	> 0.05
Associations of patients with rare diseases	6.8	6.7	> 0.05
Medical profession associations	6.0	5.8	> 0.05

***Mean of the 10-point Likert scale (1 – minimal; 10 – maximal).**

However, the majority of participants would refrain from taking responsibility regarding funding treatment for rare diseases, especially at the expense of more common treatments (3rd year - 58.19%, 6th year – 61.99%, $p > 0.05$).

In order to improve the pharmacotherapy of rare diseases in Serbia, the participants suggested the following: raise the general awareness about this topic, well-timed diagnostics, simplified drug approval processes, full implementation of national and international legislation on that matter, tight regulation of drug provision through the private pharmaceutical sector, approval of new drugs for rare diseases, establishment of a National Strategy for Rare Diseases and specific rare disease patient registries (Table 4).

Table 4

The 3rd and 6th year medical students' opinion on ways of improving pharmacotherapy of rare diseases in Serbia

How to improve pharmacotherapy of rare diseases	Students (%)		
	3rd year	6th year	*p* value
Raise general awareness and expertise	30.57	60.00	< 0.0001
Well-timed diagnostics	44.86	63.22	< 0.0001
Simplified procedures for drug provision	50.00	70.66	< 0.0001
Compliance with legislation in its entirety	8.29	17.77	< 0.01
Registration of novel drugs	55.43	69.01	< 0.01
The establishment of the National Plan for Rare Diseases	64.57	74.38	< 0.05
Creating the registry of rare diseases	54.58	53.72	> 0.05

Discussion

This survey shows that the 3rd and 6th year medical students have similar views towards the issue of rare diseases in our community. The latter group was more confident in their knowledge of issues regarding rare diseases, but unexpectedly, the 3rd year students were able to more accurately recognize rare diseases than the 6th year students. This might be due to recent completion of the Pathology and Pathophysiology course by the 3rd year students, in which great attention is paid to some rare diseases. It is slightly disappointing that this knowledge is not retained throughout the complete duration of their medical studies, and not improved during clinical courses. However, the identification of rare diseases is not sufficient to fully evaluate students' knowledge and in this study was used just for rough estimate. The prevalence of rare diseases was correctly estimated by more than 50% of both groups of participant, which indicates the correct understanding of the subject of "rareness". As preferable sources of information, greater percentage of 6th year students chose curriculum subjects and elective courses provided by the Faculty than the 3rd year students. However, the 3rd year students chose television and internet as trustworthy sources of information on rare diseases in significantly greater percentage than the 6th year students. It is possible that the 6th year students are more aware of questionable quality of many internet sources and sometimes sensationalistic media presentations and therefore find university courses more reliable. It is important to note that both groups of students recognized the treatment of patients with rare diseases in our community as a serious problem and expressed significant level of awareness regarding problems of drug provision and low quality of health care.

Although there was a difference in the distribution of responses between the 3rd and 6th year medical students, most of our respondents agreed that the most important problems of these patients were the following: lack of information among the general public, but also among healthcare professionals, complicated procedures for drug provision and the high prices of drugs. Similar observations were noted among healthcare professionals (physicians and clinical pharmacists) in a pilot study performed at the University Hospital "Bežanijska kosa" in Belgrade (unpublished data from our group). A survey entitled "Attitudes of physicians and pharmacists towards the pharmacotherapy of rare diseases in Serbia" was designed and conducted by employees at the Department of Pharmacology, Clinical Pharmacology and Toxicology.

The students find, without any differences, that greater involvement of the state is needed. However, the activities of the state are actually dependent on professionals' (policy makers, members of the regulatory bodies, creators of healthcare strategies) knowledge and attitudes.

The prospective of patients affected with rare diseases in most cases relies heavily on pharmacological treatment, but the lack of interest in pharmaceutical industry in their development is evident [9]. Drugs for many rare diseases have the status of orphan drugs. In the EU, a drug will receive orphan status designation if it is intended for the diagnosis, prevention, or treatment of a life threatening or chronically debilitating condition which affects not more than five people per 100,000 in the Community (Regulation (EC) No 141/2000). Therefore, the development or acquisition of orphan drugs, regarding their costs, is a serious ethical dilemma [10]. Our respondents considered it quite reasonable to invest large amounts of money to treat a small number of patients, but they did not know or refused to answer what was more justifiable for them – to invest in medications for common diseases or to invest in the purchase of drugs for rare diseases. This neutral students' position on prioritizing funds was actually expected and reflects the complexity and

controversial nature of the issue of pharmacotherapy of rare diseases in general [11, 12]. The justification for paying the premium prices of orphan drugs diseases must rest on the question: should we value the health gain to two individuals differently because one individual has a common disorder and the other has a rare disease disorder? The National Institute for Health and Clinical Excellence (NICE) recently recommended that the National Health Service (NHS) should consider paying premium prices for drugs for rare diseases based on three criteria: the severity of the disease, evidence of health gain, and whether the disease is life threatening [13]. But, it should be pointed out that is virtually impossible to assess cost-effectivness of treatments for rare diseases using conventional criteria. Current curriculum provides basic knowledge on symptoms, diagnostic procedures and possible treatment options of rare diseases. However, it would be useful to offer deeper insight into the ethical dilemmas regarding expensive treatment of low prevalence diseases. Medical students should be aware that even the most expensive treatment for rare diseases could actually be cost-effective if it reduces life-time standard health-care costs and improves patients' ability to work or live without assistance.

It is evident that students in Serbia showed interest and willingness to respond to a very sensitive issue of rare diseases. There is a high level of awareness among students that rare diseases are a big medical, socio-economic and bioethical concern. However, certain lack of knowledge was noted among participants in this study, as well as in other countries [4, 14, 15]. Therefore, it is crucial to improve education on rare diseases, but especially on bioethical issues both at undergraduate and postgraduate level [16].

As a non-EU member, Serbia has a chance to be an observer monitor of the EUROPLAN II project (2012–2015) which is designed to support the efforts of national authorities to develop public health strategies on rare diseases throughout Europe following common guidelines. The Integrated EU-national strategy focuses on a few essential building blocks such as information, centers of expertise, registries, and access to medicines [17, 18]. Concerning this, we believe that this is the critical moment for the improvement of education on rare diseases among medical students in Serbia.

Conclusion

Rare diseases are an important bioethical concern. Medical students are aware of that and familiar with the most important problems regarding the diagnostics of rare diseases and enormous costs of research of treatment and available treatment prices. Students are also informed about difficulties with orphan drugs registration and acquisition. However, further efforts should be made in educating medical students, as future participants in health-care policy making, on complex matter of cost-effectiveness of orphan diseases treatment.

Acknowledgement

This work was supported by the Ministry of Education, Science and Technological Development of Serbia (Grant No. 175023).

The authors wish to express their gratitudes to Prof. Zoran Todorović for his help in preparing some of the questions in the survey.

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Received on March 26, 2015.
Revised on April 29, 2015.
Accepted on May 4, 2015.
Online First September, 2015

Addendum 1

THE KNOWLEDGE AND ATTITUDES OF MEDICAL STUDENTS IN SERBIA CONCERNING RARE DISEASES

THE SURVEY IS ANONYMOUS

Thank you for participating in our survey. We assure you that you will not have any negative consequences for participation and that we will respect your privacy.

The aim of this study is to investigate the knowledge and attitudes of medical students concerning the treatment of rare diseases in our community. The results will be used in the development of scientific research, exclusively. The authors of this survey are pharmacologists employed at The Departmennt of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade.

We ask you to write legibly and to honestly answer all questions that is the only way your answers will have value.

GENERAL CHARACTERISTICS:

SEX (please circle) M F

YEAR OF BIRTH ----------

YEAR WHEN THE STUDY STARTED (enroll) ----------

CURRENT YEAR OF STUDY (enroll) ----------

AVERAGE SCORE DURING THE STUDIES (round off)

< 7 7–8 8–9 9–10

SCORE IN PHARMACOLOGY AND TOXICOLOGY (if you passed this course) ----------

THE ATTITUDES REGARDING THE TREATMENT OF RARE DISEASES IN SERBIA:

HOW DO YOU RATE YOUR CURRENT KNOWLEDGE ABOUT RARE DISEASES IN GENERAL?

(Mark with X)

(poor) (excellent)

HAVE YOU HAD THE OPPORTUNITY TO MEET SOMEONE WHO IS SUFFERING FROM A RARE DISEASE?

1. YES 2. NO 3. I DON'T KNOW

THE PREVALENCE OF RARE DISEASE IN EU COUNTRIES IS SMALLER THAN:

1. 1/100 2. 1/500 3.1/2000 4. Something else ----------

COULD YOU RECOGNIZE RARE DISEASES FROM THE FOLLOWING LIST? (round off)

1. Acromegaly 2. Osteoporosis 3. Hemophilia

4. Multiple Sclerosis 5. Gaucher disease 6. Schizophrenia

6. Familiar breast cancer 7. Non Hodgkin's lymphoma

THE MAIN SOURCE OF INFORMATION ON RARE DISEASES, ACCORDING TO YOU, ARE?... (enroll)

1. core curriculum subjects (specify them) ----------

2. elective courses (specify them) ----------

3. some other, extracurriculum souces (specify them) ----------

HOW DO YOU RATE THE IMPORTANCE OF SUCH AN ISSUE IN OUR COUNTRY? (enroll X)

(I don't consider it important) (very important)

HOW DO YOU RATE THE POSSIBILITIES OF OBTAINING DRUGS FOR RARE DISEASES IN SERBIA? (enroll X)

(very bad) (excellent)

ACCORDING TO YOU, THE MOST IMPORTANT PROBLEMS OF PATIENTS SUFFERING FROM RARE DISEASES ARE?

(you may select more than one answer)

1. Lack of information among the general public

2 Lack of scientific knowledge

3. Lack of access to correct diagnosis

4. Lack of appropriate quality healthcare

5. Lack of a sufficient number of registered drugs

6. Complicated procedures of drug provison

7. High prices of drugs

8. Lack of observance of legislation

9. Unavailability of these drugs in private pharmacies

10. Other ----------

ARE YOU AWARE OF THE POSSIBILITIES OF OBTAINING DRUGS FOR RARE DISEASES IN SERBIA? (enroll X)

(not at all) (fully aware)

THE AVAILABILITY OF DRUGS FOR RARE DISEASES CAN BE IMPROVED BY GREATER INVOLMENT OF...

MEDICAL DOCTORS

(have no impact) (crucial role)

CLINICAL PHARMACISTS

(have no impact) (crucial role)

PHARMACEUTICAL COMPANIES AND PHARMACIES

(have no impact) (crucial role)

THE STATE

(has no impact) (crucial role)

ASSOCIATIONS OF PATIENTS SUFFERING FROM RARE DISEASES

(have no impact) (crucial role)

HOW DO YOU RATE THE IMPORTANCE OF COLLABORATION BETWEEN PHYSICIANS AND PHARMACISTS IN ORDER TO ADVANCE THE AVAILABILITY OF DRUGS FOR RARE DISEASES?

(no impact) (crucial role)

RARE DISEASES ARE DISEASES WHICH, WITHOUT APPROPRIATE THERAPY, MOST OFTEN, LEAD TO A PERMANENT DISABILITY. HOWEVER, THE TREATMENT OF PATIENTS SUFFERING FROM RARE DISEASES IS EXTREMELY EXPENSIVE. DO YOU FEEL THAT IT IS ETHICALLY JUSTIFIED TO SPEND A LOT OF MONEY FOR A SMALL NUMBER OF PATIENTS?

(not at all) (fully justified)

WOULD YOU (IN A POSITION TO MAKE SUCH DECISIONS) PROVIDE COSTLY MEDICAL CARE FOR PATIENTS SUFFERING FROM RARE DISEASES RATHER THAN SPEND MONEY ON TREATMENTS FOR MORE COMMON CONDITIONS AFFECTING A LARGE NUMBER OF PEOPLE?

1. YES 2. NO 3. I DON'T KNOW/NEUTRAL POSITION

ACCORDING TO YOU, HOW CAN PHARMACOTHERAPY OF THESE PATIENTS BE IMPROVED IN OUR COMMUNITY?
(you may select more than one answer)

1. Raise general awareness and expertise

2. Well-timed diagnostics

3. Simplified procedures for drug provision

4. Compliance with legislation in its entirety

5. Adequate control of drugs available in private pharmacies

6. Registration of more appropriate drugs

7. The establishment of the National Plan for Rare Diseases

8. Creating the registry of rare diseases

9. Other ----------

THANKS FOR YOUR COOPERATION!

ORIGINAL ARTICLE

UDC: 614.8::616-07/-08
DOI: 10.2298/VSP141231137B

Adverse event reporting in Slovenia – the influence of safety culture, supervisors and communication

Prijavljivanje neželjenih događaja u Sloveniji – uticaj svesti o njihovom značaju, rukovodećih struktura i međusobne saradnje zaposlenih

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Abstract

Background/Aim. The provision of safe healthcare is considered a priority in European Union (EU) member states. Along with other preventative measures in healthcare, the EU also strives to eliminate the "causes of harm to human health". The aim of this survey was to determine whether safety culture, supervisors and communication between co-workers influence the number of adverse event reports submitted to the heads of clinical departments and to the management of an institution. **Methods.** This survey is based on cross-sectional analysis. It was carried out in the largest Slovenian university hospital. We received 235 completed questionnaires. Respondents included professionals in the fields of nursing care, physiotherapy, occupational therapy and radiological technology. **Results.** Safety culture influences the number of adverse event reports submitted to the head of a clinical department from the organizational point of view. Supervisors and communication between co-workers do not influence the number of adverse event reports. **Conclusion.** It can be concluded that neither supervisors nor the level of communication between co-workers influence the frequency of adverse event reporting, while safety culture does influence it from an organizational point of view. The presumed factors only partly influence the number of submitted adverse event reports, thus other causes of under-reporting must be sought elsewhere.

Key words:
patient safety; medical staff; communication; culture; slovenia.

Apstrakt

Uvod/Cilj. Bezbedno pružanje zdravstvene nege smatra se prioritetom u zemljama članicama Evropske unije (EU). Osim drugih mera preventive u zdravstvenoj zaštiti, EU čini napore da izbaci sve uzroke koji oštećuju ljudsko zdravlje. Cilj istraživanja bio je da se utvrdi da li bezbednosna kultura, nadređeni i komuniciranje među saradnicima utiču na broj predatih izveštaja o bezbednosnim komplikacijama rukovodstvu kliničkog odeljenja i rukovodstvu ustanove. **Metode.** Istraživanje je sprovedeno kao studija preseka. Anketiranje je izvedeno u najvećoj slovenačkoj univerzitetskoj bolnici. Vraćeno je 235 anketa. Anketirani su saradnici zdravstvene nege, fizioterapije, radne terapije i radiološke tehnologije. **Rezultati.** Bezbednosna kultura utiče na broj izveštavanja o bezbednosnim komplikacijama rukovodstvu kliničkog odeljenja i to u pogledu organizacije. Komunikacija između saradnika i nadređenih ne utiče na broj izveštavanja o bezbednosnim komplikacijama. **Zaključak.** Može se zaključiti da ni rukovodeća struktura, ni nivo komunikacije i međusobne saradnje ne utiču na broj izveštavanja o bezbednosnim komplikacijama. Međutim, bezbednosna kultura utiče na prijavljivanje neželjenih događaja u pogledu organizacije. Pretpostavljeni faktori delimično utiču na broj predatih izveštaja o bezbednosnim komplikacijama zbog čega uzroke za izveštavanje treba tražiti i na drugim mestima.

Ključne reči:
bolesnik, bezbednost; kadar, medicinski; komunikacija; kultura; slovenija.

Introduction

The provision of safe healthcare is considered a priority in European Union (EU) member states [1]. Along with other preventative measures in healthcare, the EU also strives to eliminate the "causes of harm to human health" [2]. In EU member states, 8–12% of hospital patients experience an adverse event [3]. As noted by Robida [4], a 2000 study by the Institute of Medicine found that 35,000 patients were harmed in the course of their treatment in public hospitals in Slove-

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nia. More people – between 410 and 890 – die in hospitals than they do in traffic accidents. The Slovenian Patient Rights Act grants patients the right to proper, high-quality and safe healthcare [5]. The Ministry of Health confers the responsibility to provide systematic patient care and continuously improve its quality upon healthcare institutions [6].

Robida [7] defines safety as the minimisation of adverse events in patients during diagnostic procedures, treatment and rehabilitation; safety involves the prevention of harm to patients' health caused by the provision of healthcare, which should be to their benefit. According to UK Advisory Committee on the Safety of Nuclear Installations safety culture in an organization is defined as "the product of individual and group values, attitudes, perceptions, competencies, and patterns of behaviour that determine the commitment to, and the style and proficiency of, an organization's health and safety management" [8].

"An organization with a positive safety culture is characterized by communications founded on mutual trust, by shared perceptions of the importance of safety and by confidence in the efficacy of preventive measures" [8]. As noted by Dobnik [9], every organisation comprises individuals who communicate and attempt to solve problems and resolve interpersonal conflicts. Frequently, communication may fail. This is due to interference, which may be of emotional or social origin, rather than it being the result of lacking verbal skills. Conversation partners will often ignore each other due to being preoccupied with their own thoughts or because they are waiting their turn to share their opinions [9]. One of the responsibilities of the hospital management is ensuring employee satisfaction since, according to Golmajer [10], the level of employee satisfaction affects the quality and efficiency of their performance. As noted by Robida [4], healthcare professionals consider the safe treatment of patients their top priority. Every member of the staff should feel that they can participate in and contribute to safer performance and a higher quality of work. According to Donik [11], the most important factor in creating a good workplace atmosphere are senior professionals who are usually responsible for introducing innovations into the work environment, who know how to influence the behaviour and performance of individual members on a healthcare team, and can guide the actions of their staff to reach desired goals and fulfil a desired purpose with the aid of communication, motivation and their personality traits [11].

There are several definitions of adverse events (AE). Common to all definitions is that they define that AE occur during medical treatment, that they are accidental and that they are not caused by the patient's disease [8, 12, 13]. Safety incidents can be categorized into two groups, namely: "adverse events" and "sentinel events". Adverse events are classified as unexpected event or circumstance which would have resulted, or may result in unnecessary damage to the patient such as: fall, pressure ulcer, burn, or missing patient…., while sentinel events, can be described as an unexpected event involving death or serious physical or psychological injury, or the risk of such an event [14].

Data from 2011 show that in the largest Slovenian hospital 2,346 safety incidents were reported of which 49 reports were classified as sentinel events. Among those sentinel events 19 cases of falls, which resulted in severe deterioration of health were included. Furthermore, a case of suicide (n = 1), complication relating to medications (n = 4), complications of invasive procedures (n = 5) and other complications (n = 20) which were the consequence of inappropriate referral of the patient or improper medical treatment such as an inadequate response times for cardio-pulmonary resuscitation, were included. As it can be noted, a higher rate of adverse events cases were reported (n = 2297). Most prevalent were falls and pressure ulcers. Also, other adverse events were included into statistics, such as the injury of health professionals with a sharp object, patient violence directed toward clinicians and others [15]. Breathnach et al. [16] in their study find that the most common adverse events are fall or slip of the patient.

Studies suggest that a larger proportion of AE are being reported by nurses. Furthermore, Rowin et al. [17] note that physicians reported incidents in only 1.1% of cases, of which dominant were sentinel events. Similarly Breathnach et al. [16] in their study find that the physicians report about 4% of adverse events.

The system for management of safety incidents in an environment where the study was carried out aims at detecting and identifying adverse and sentinels events. It is not targeted at those involved, but into the events and its elimination. Safety incidents can be reported through information system; furthermore it is also possible to a report the event by written forms and/or oral by phone. Choosing the way of reporting event is left to a reporter (health professional). Also, reporting in full anonymity can be provided, it is possible to report event without identifying the participants and locations [15, 18].

It was this that led us to study the situation in a specific clinical setting in Slovenia, since no studies which would look into the causes of reporting of adverse events (unexpected event or circumstance which would have resulted, or may result in unnecessary damage to the patient such as: fall, pressure ulcer, burn, or missing patient) in healthcare institution in Slovenia could be found upon reviewing the literature on the subject.

Based on the definition of the problem and theoretical issues, we formed the following hypotheses: H1 – The level of safety culture influences the frequency of adverse event reporting; H2 – The attitude of supervisors influences the frequency of adverse event; H3 – The level of communication between co-workers influences the frequency of adverse event reporting.

Taking into account these hypotheses, the aim of this study was to determine whether safety culture, supervisors and communication between co-workers influence the frequency of AE reporting.

Methods

Population and sample

A total of 235 health care professionals employed in different organizational units of the chosen medical institution in Slovenia participated in the survey. The following staff positions were included: health care assistants, registered nurses, occupational therapists, physiotherapists, radiological engineers

as those deal directly with the reporting and recording of the occurrence of adverse events and therefore we assume that they have the most useful information about studied phenomenon.

The survey was conducted between 4 June and 16 July 2012. Questionnaires were distributed in proportion to the number of employees and the number of individual staff positions at a particular clinic or department included in the survey. The respondents submitted completed questionnaires in sealed, enclosed envelopes to the researchers.

Data collection

Data and information were obtained through a standardized questionnaire The Hospital Survey on Patient Safety Culture published by the American Association for Healthcare Research and Quality (AHRQ) in November 2004.

It was designed to assess opinions of hospital staff about patient safety, adverse events and adverse event reporting. The questionnaire focuses on 12 key dimensions of patient safety culture, namely: communication openness, feedback and communication about error, frequency of error reporting, handoffs and transitions, management support for patient safety, non-punitive response to error, organizational learning–continuous improvement, overall perceptions of safety, staffing, supervisor/manager expectations and actions promoting safety, teamwork across units, and teamwork within the unit. The questionnaire also includes questions on patient safety grade and the number of adverse events reported in the past 12 months [19].

The questionnaire was partially adapted to suit our empirical survey and is now divided into nine components (prevalent workplace, supervisors, communication, frequency of event reporting, patient safety grade, medical institution, the number of events reported, basic information or demographic information, comments) and contains 51 closed-ended items and one open-ended item. Respondents had to rate the closed-ended items or statements on a five-point Likert scale. The parts of the questionnaire concerning work areas, employees' roles (changes relates to the roles and names of roles) and adverse event reporting frequency (change from categorical variable to numerical variable) suit to our survey.

We preformed systematic approach for questionnare translation [20]. Firstly, two authors (both native speakers of Slovene and professionally familiar with the topic) independantly translated English version into Slovene version. Authors compared English and Slovene version of questionnaire and consensus was achieved. In the next step, a blind professional translators, translated questionnaire from Slovene to English. All the authors compared both versions of questionnare and agreement on translation was achieved. Two healthcare professionals were asked to assess the understanding of the translated questionnaire. They found that questionnaire was clear.

The reliability of the measurement instrument was further tested using the Cronbach's coefficient which showed the instrument reliable (0.893; 52 items).

The survey received ethical approval from the Medical Ethics Committee of the Republic of Slovenia (No.: 34/02/12). The authors had no conflicts of interest to declare.

In presenting the model, we used the frequency distribution and presented data using cross tables. For question sets relating to safety culture, communication level and the overall situation in the hospital, we carried out a factor analysis using the Principal Axis Factoring (PAF) method, which served as the basis for determining dimensions. Factor analysis is used to uncover the latent structure of manifest variables. It reduces attribute space to a smaller number of factors [21]. Furthermore, we used the Bartlett's test (χ^2 = 812,88: sig.: < 0.001) and the Kaiser-Meyer-Olkin (0.832) to measure the sampling adequacy to determine the suitability for factor analysis [21]. Both tests showed the sample suitable for factor analysis.

Dimensions were calculated as the average of the variables with higher weights on individual factors. Further, analysis of variance was used to assess the differences in average dimension values with respect to characteristics of respondents. When checking for multicollinearity between independent variables, Variance Inflation Factors (VIF) were also taken into account. The "R" has been used to determine the percent of the variance in the dependent variable, explained by the independent variables [21]. For regression analysis Student's *t*-test was used to test hypothesis in case beta coefficient was different from 0.

Results

Most respondents worked in one of the following three areas where the most serious adverse events could occur: surgery (24.3%), intensive care and therapy in any department (20.4%) and emergency (9.8%). Surveyed staff from the internal medicine department and the department of obstetrics and gynaecology accounted for 8.9% each. Respondents working in the department of paediatrics accounted for 7.7%, while other departments accounted for 4.3% each. The latter include rehabilitation departments, postoperative care units and employees working in several different hospital units. The remaining 6.8% of respondents work in other organizational units (Figure 1). Figure 2 shows that almost half (47.2%) of the surveyed professionals were health care assistants (secondary nursing school). Registered nurses accounted for a slightly smaller proportion (42.9%), and the remaining respondents include occupational therapists (0.9%), physiotherapists (6.1%), radiological engineers (1.3%) and others (1.7%).

Furthermore, the surveyed staff members were asked how long they had been employed in the department and in the institution, and how long they had worked in their profession. Thus, just under a third (31.9%) of the respondents had worked in their profession for more than 20 years, and a slightly smaller proportion (30.2%) in this institution for more than 20 years. Furthermore, in the surveyed medical institution there were no significant fluctuations among employees at the departmental level. Only few of those who worked in the institution for five years or less had changed departments, while 12.3% of the respondents who had worked in the institution for 6–10 years had changed departments. Among those who had worked in the institution for more than ten years, the proportions of those who had worked in the same department for the same number of years ranged from two thirds to just

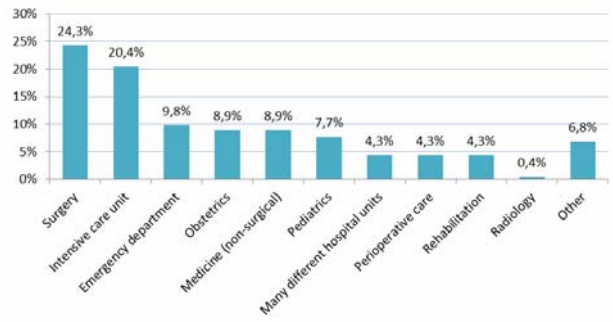

Fig. 1 – Work areas of the respondents in the hospital.

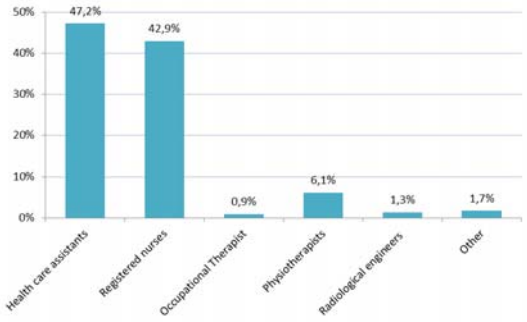

Fig. 2 – Staff position in the hospital.

over three quarters. If we generalize our findings from the sample of surveyed health professionals to the whole population, we can conclude that the studied population had significant experience in their work area, which was relevant in the context of the studied subject. It should also be noted that 96.1% of respondents had regular contact with patients.

In determining if and how the level of safety culture influenced the frequency of AE reporting we observed the following variables: independent variables as the dimensions of safety culture in a department (reciprocity and support, organization, systematic and efficient management of AE, and emphasizing personal responsibility). Table 1 shows that only 2.1% of variance in the frequency of AE reporting in the department could be explained by the influence of safety culture; this was a very small proportion, but this influence can nevertheless be confirmed statistically. If the degree of organization of a department is low, the frequency of AE reporting in the department is high and *vice versa* (t = -2.784, p = 0.006). Safety culture, especially regarding department organization, affects the frequency of AE reporting. Thus, the hypothesis was confirmed in this part. It should also be mentioned that VIF factors, which indicated the extent to which multicollinearity is present between independent variables, were close to 1, which means that there was no multicollinearity and thus the requirements for regression analysis were met. None of the dimensions of safety culture affected the frequency of AE reporting to the hospital management. The hypothesis was rejected in this part. Finally, we wanted to determine the influence of safety culture dimensions on the relationship between the frequency of AE reporting within the department and the frequency of AE reporting to the hospital management. None of the dimensions of safety culture affected the relationship between the frequency of AE reporting within the department and the frequency of AE reporting to the hospital management. The hypothesis was rejected in this part.

A total of 54% of the respondents felt they suffered from staff shortages; 77% of the staff reported working as a team in situations with increase in workload and limited time; and 53% of employees believed interpersonal relationships between staff respectful.

In our study 79% of respondents believed they actively carried out measures to improve safety. Fewer than half of the respondents believed that adverse events had led to positive changes.

This study found that 55% of respondents felt that they were lucky that no major AE occured at their department; 40% agreed that there is a level of mutual assistance during work. A total of 29% of respondents felt that if an AE involving a patient was reported, the professional involved in the event, rather than the issue at hand, was singled out, while 50% disagreed with the statement and 21% had no opinion.

As a consequence, more than half of the staff members reviewed the efficiency of the improvement introduced after the AE had occurred. A total of 34% of the respondents felt that they sought to do too much over an insufficient period of time, while 57% claimed they never put a patient's safety at risk in order to be more efficient. Nearly 30% feared that their AE were being recorded in their personal files, while 31% had no opinion on the subject.

In determining if and how the attitude of supervisors influences the frequency of AE reporting we observed the following variables: the "supervisors' attitude towards employees" dimension is the independent variable (Table 2). It should be mentioned that VIF values was not taken into account in this analysis, because it was a simple regression analysis with a single independent variable. As it can be seen from Table 2, supervisors' attitude does not affect the frequency of AE reporting within a department. The hypothesis was rejected in this part (p = 0.638). Also, the analysis showed that supervisors' attitude did not affect the frequency of AE reporting to the hospital management (p = 0.944). The hypothesis was also rejected in this part. Also, the influence of supervisors' attitude towards employees on the relationship between the frequency of AE reporting within a department and the frequency of AE reporting to the hospital management could not be confirmed (p = 0.88). Therefore, the hypothesis was rejected.

In determining if and how the level of communication between co-workers influences the frequency of AE reporting we observed the following variables: the "level of communication at department" dimension as the independent variable. It should be mentioned that VIF values have not been taken into account in this analysis, because it is a simple regression analysis with a single independent variable. First, we want to determine the influence of communication on the number of AE reports in a department (Table 3). The results of this analysis presented in Table 3 show that the level of communication within a department does not affect the frequency of AE reporting to the head of a department (p = 0.251). We continued by determining if the level of communication in a department have influence on the number of AE reports submitted to the hospital management, and found no

Table 1

Influence of safety culture

Parameters	Dependent variable: frequency of AE reporting to the head of department (adjusted R square: 0.021)			Dependent variable: frequency of AE reporting to the hospital management (adjusted R square: 0.000)			Dependent variable: relationship between the frequency of AE reporting within a department and to the hospital management (adjusted R square: 0.000)		
	beta	*p*	VIF	beta	*p*	VIF	beta	*p*	VIF
Constant	5.431	0.053		2.564	0.051		0.098	0.835	
Reciprocity, Support	0.491	0.297	1.291	0.129	0.547	1.257	-0.003	0.975	1.272
Organization	-1.625	0.006	1.246	-0.318	0.242	1.200	0.11	0.266	1.110
Systematic and efficient AE management	0.58	0.315	1.448	-0.015	0.954	1.397	0.072	0.506	1.372
Emphasizing personal responsibility	-0.399	0.472	1.035	-0.17	0.522	1.200	-0.058	0.532	1.007

AE – adverse event; *p* – level of significance; beta coefficient – represents the difference in the predicted value of Y for each one-unit difference in X1; VIF – Variance Inflation Factor; R square: ratio of explained variance.

Table 2

Influence of supervisors' attitude

Parameters	Dependent variable: frequency of AE reporting in the department (R square: 0.00; F = 0.005; *p*: value of prob(F) = 0.944)		The frequency of AE reporting to the hospital management (R square: 0.000; F = 0.221; *p*: value of prob (F) = 0.638)		Relationship between the frequency of AE reporting within a department and to the hospital management (R square: 0.000; F=0.023; *p*: value of prob (F) = 0.880)	
	beta	*p*	beta	*p*	beta	*p*
Constant	3.954	0.003	1.515	0.014	0.453	0.061
Supervisors' attitude towards employees	-0.178	0.638	0.012	0.944	0.011	0.880

AE – adverse event; *p*: level of significance; beta coefficient – represents the difference in the predicted value of Y for each one-unit difference in X1; R Square – ratio of explained variance; F value – test of the overall significance of regression model, *p* = the value of prob(F) is the probability that all of the regression coefficients are zero.

Table 3

Influence of communication within a department

Parameters	Dependent variable: frequency of AE reporting in the department (R square:0.006; F = 1.326; *p*: value of prob(F) = 0.251)		Dependent variable: frequency of AE reporting to the hospital management (R square: 0.006; F = 1.393; p: value of prob(F) = 0.239)		Dependent variable: relationship between the frequency of AE reporting within a department and to the hospital management (R square: 0.008; F = 1.018; p: value of prob(F) = 0.315)	
	beta	*p*	beta	*p*	beta	*p*
Constant	1.687	0.254	0.766	0.263	0.209	0.459
Level of communication in a department	0.456	0.251	0.218	0.239	0.077	0.315

AE – adverse event; p – level of significance; beta coefficient – represents the difference in the predicted value of Y for each one-unit difference in X1; R square – ratio of explained variance; F value – test of the overall significance of regression model, *p* = the value of prob(F) is the probability that all of the regression coefficients are zero.

influence (p = 0.239). We also wanted to determine the influence of the level of communication on the relationship between the frequency of AE reporting within a department and the frequency of AE reporting to the hospital management and found the relationship could not be confirmed (p = 0.315).

Our study revealed that 11% of the department staff had never received feedback on changes and improvements made in the wake of an AE, while 27%, 34%, 19% and 9% received feedback rarely, occasionally, frequently or always, respectively.

We found that the staff members frequently speak out if they feel a patient might be at risk. In 66% of the time, the staff was notified of AE as they occured at the clinical department. In 34% of AE, however, were unaccounted for and frequently remained unknown to the staff responsible for the safety of patients. This share was alarmingly high and those AE were at risk of being repeated. More than half (58%) of the staff always felt comfortable with inquiring as to the reasoning behind specific safety-related decisions and measures by senior staff. Those staff members feel accepted by their team, while this was not necessarily true for the significant portion of those not comfortable with such questions. A total of 67% of respondents reported having discussions within the department on AE prevention as a response to partial disregard of patient safety. A total of 65% of the respondents felt comfortable reporting irregularities, while this was occasionally true for 22% of the respondents and never true for 13% of the respondents, which indicated those irregularities repeated and may evolve into a major AE.

The statement that the "staff members feel comfortable speaking out about the safety of a patient at risk" had an above-average score (AM = 4.0). However, the staff tended to disagree rather than agree with the statement that they received feedback about improvements made in the wake of an adverse event (AM = 2.9).

Discussion

The phrase "adverse event" in itself implies it is an issue stemming from the environment (system) rather than an individual, while the word error has the connotation of an individual behind it. Therefore the Slovenian Ministry of Health recommends that the phrases professional and medical error no longer be used due to their frequent misuse and the implication that the incident is necessarily the fault of a professional [22]. However in using this definition a caution is needed, especially from the legal point of view, since error might not lead to AE [23]. In 2014, Ristić Ignjatović et al. [24] focused on topic in proving medical errors and stresses out the importance in understanding the terminology and difficulties in proving errors. Furthermore, the authors reported a low rate of proven malpractice in Serbia. The authors pointed out several reasons for low rate; however, a possible underreporting, false accusation of individual and system irregularities must also be taken into account. Clemmer [25] explains the rule 85/15, which states that 85% of unwanted events occur due to irregularities in the work system while only 15% can be traced back to the individual. However, it must be stressed that an individual takes responsibilities for their acts but cannot take responsibility for the system at work.

All hypotheses postulate the effect of certain factors on the scope of AE reporting. Upon testing the Hypothesis 1, which postulates that the existence of a safety culture affects the number of AE reports, it could be confirmed that the degree of organisation at a hospital department has a negative effect on the scope of AE reporting to heads of department, but not to the hospital management. Operating under the presumption that the vast majority of AE is identified and reported within departments, it may be concluded that the degree of organisation decreases the scope of AE. The hypothesis could be confirmed.

The hypothesis 2 postulates, that the attitude of senior staff affects the scope of AE reporting. The hypothesis 3 postulates that the level of communication affects the scope of AE reporting. These two hypotheses could not be verified.

It has been noted that the fear of punishment and the lack of understanding that even the best make mistakes persists [26, 27]. Half of the respondents in our study felt that they worked longer hours than what would be advisable to ensure the safety of patients. Kociper and Robida [28] believe that safety and quality in healthcare cannot be the sole responsibility of a single professional group, as safety and quality include both the professional liability of the staff on the team as well as the responsibility of the education and healthcare system. According to Golmajer [10], workplace satisfaction of the staff affects the quality and efficiency of the work performed. A 2008 study on the situation in Slovenia by Andreja Strnad found that patients fell unprotected from medical errors. They saw the cause of this in the insufficient, inadequate communication, too limited medical staff and long wait times [29]. When dealing with AE "secondary victims" of adverse events must not be forgotten [30]. Studies find that those involved in an AE have to face it in silence, shame and frequently, isolation – despite an increased awareness of the stress they face among their colleagues [30–32]. Also the fear of their chances of promotion being affected was one of the leading factors in concealing medical errors in China [33]. The findings of our study show that the emphasis on personal responsibility in handling AE remains important. Numerous authors [2, 25, 28, 34] believe that laying the blame for AE on individuals is counter-productive, since event analyses almost always reveal a weakness in the work or management system rather than one of the individual. Moumtzoglou [35], in his study, which took place in 14 hospitals in Greece, finds that culture of reporting and personal discrediting are reasons whic had negative impact on AE reporting by nurses. This again confirms that blame free reporting must be standard in safety culture.

Safety culture, in particular regarding the organisation of work at a clinical department, affects the frequency of AE reporting. In other words, the frequency of AE reporting rise as the degree of organisation at a department decreases. According to Crigger [36], such events are the result of deficiencies in the organisation of the work process and system as well as individuals. In order to establish patient safety business and or-

ganisational system in a healthcare institution, the following factors must be controlled: strong leadership, practices based on scientific evidence, the maintenance of the just safety culture, staff training, patient cooperation, learning from errors, risk assessment and the evaluation of medical practice [4].

Researchers Parker [31], May and Plews-Ogan [32] talk about a type of communication in healthcare in which senior staff is initially unresponsive to and dismissive of risks. Our study, however, shows that senior staff do pay attention to repeating AE and do implement suggestions for improving patient safety. The study also finds that the senior staff commends the staff members for their contributions to greater patient safety as well as that lower-ranking staff has corroborated the existence of such commendations and encouragement to act positively, which is highly promising since, according to Robida [4], a healthcare professional who feels a sense of belonging to the team provides better care to patients and performs better. Employee satisfaction depends on whether employees have the chance of communicating orally and participating in decisions relating to their work [37].

Regarding the changes and improvements made in the field of an AE, our study reveals that more than half of respondents receive feedback never, rarely or occasionally despite the fact, that there as the existing evidence that shows learning from mistakes as the important and meaningful process for all included into event [32]. According to Seys et al. [30], it is of great importance that the professional involved in such an event, should be involved in studies, conferences and training in order to minimise the risk of repeating the event. Furthermore, recommendations have been made that the practice of reporting AE be bolstered by policy and support by healthcare professionals [38].

According to Weiss [39] the objective is to uncover, analyse and learn as much as possible from AE [39]. AHRQ studies up to this point have revealed concerning results, which speaks to the urgency of establishing open communication at clinical departments. According to the American Association for Healthcare Research and Quality, an estimated 44,000 of 98,000 deaths in 1999 were the result of medical error [40]. In 2000, every tenth patient in Europe suffered harm during treatment, according to The Hospitals for Europe's Working Party on Quality Care in Hospitals [41].

It might also be concluded from the results of this study that not all AE are treated or analysed equally and differing levels of attention are paid to individual AE. Certain AE may be less important in a given moment in time. However, it should be kept in mind that major AE evolve from minor events, meaning that none should be disregarded. According to Sorra et al. [19] previous recommendation was supported by the recommendation of the Institute for Health Care Improvement in 2006, which states that minor alterations with potential positive effects on the safety culture should be prioritised over major changes with little to no potential to succeed.

Regular AE reporting would indicate that the staff is aware of the issue and wants to work towards eliminating any unnecessary consequences of treatment. Reporting an AE should be seen as a noble, mature act of a forward-thinking professional.

We aimed to compare findings from our study with other from neighbouring countries; however, there are no studies available on reporting on the prevalence of AE from southern European countries. More studies covering AE in south European countries and presenting the whole context of reporting are urgently needed.

Limitations of the study

There is limited literature available and very little literature focuses on Slovenia, where this area is still widely unexplored and has received more attention only in recent years. The most important limitation is the sensitive nature of this matter, which could discourage respondents from giving honest answers or even to give an answer at all. Main methodological limitations of this research is that the survey covered only one Slovenian medical institution and the sample was relatively small (n = 400). In sampling employees there was a risk of selection bias; the majority of various health professionals were included into the study, however physicians were not included. Moreover questionnaires were distributed by head nurses in clinical departments. Questionnaires were not administered to respondents personally by researchers, but by respondents' supervisors. Again, because of this reason it is possible that employees who feel distrust and fear sanctions did not give honest answers or answer at all.

Conclusion

Based on the survey results, we can conclude that neither supervisors, nor the level of communication between coworkers influence the frequency of adverse event reporting, while the safety culture does influence it from an organizational point of view.

The results of this survey, which is first of its kind carried out in Slovenia, have given us new insights into adverse event reporting, since the results are unexpected and show that further causes of under-reporting should be sought elsewhere.

Acknowledgements

We thank all the anonymous reviewers and health care professionals who participated in the survey.

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Received on December 31, 2014.
Revised on April 30, 2015.
Accepted on May 12, 2015.
Online First December, 2015.

ORIGINAL ARTICLE

UDC: 617.52-089.844
DOI: 10.2298/VSP140829052J

Analysis of reconstructive methods in surgical treatment of nasal skin defects

Analiza rekonstruktivnih metoda za hirurško lečenje defekata kože nosa

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Abstract

Background/Aim. Surgeons often face with the problem when selecting a reconstructive method for nasal skin defects. The aim of this study was to determine functional and aesthetic characteristics of different reconstructive methods used for skin defects in different regions of the nose. **Methods.** The study involved 44 patients with basocellular carcinoma in nasal area. The nasal skin was divided into four subunits: the tip, the alar lobules, the sidewalls and the dorsum. The average skin defect size was 10 mm in diameter. Local flaps and full thickness skin grafts were used in the study. We analyzed the functional and esthetic results of different reconstructive methods used for nasal defects in different regions of the nose 12 months after the surgery. **Results**. The study shows that different reconstructive methods produce different functional and esthetic results in the same nasal subunits and that the same reconstructive method produces different results in different nasal subunits. **Conclusions.** Estimation the postoperative functional and esthetic characteristics of different reconstructive methods is one of the basic preconditions of successful reconstruction.

Key words:
nose; carcinoma, basal cell; reconstructive surgical procedures; surgical flaps; transplants; treatment outcome; esthetics.

Apstrakt

Uvod/Cilj. Hirurzi su često u nedoumici prilikom izbora metode za rekonstrukciju defekata kože nosa. Cilj rada bio je da se utvrde funkcionalne i estetske karakteristike različitih metoda za rekonstrukciju defekata kože nosa. **Metode.** Studijom su bila obuhvaćena 44 bolesnika sa bazocelularnim karcinomom kože nosa. Koža nosa je bila podeljena na četiri regije: vrh nosa, alarni predeli, lateralne strane nosa i dorzum. Prosečna veličina defekta kože nosa, nastalog nakon ekscizije bazocelularnog karcinoma, iznosila je 10 mm u prečniku. Za rekonstrukciju defekta kože nosa korišćeni su lokalni kožni režnjevi i transplantati kože pune debljine. Analizirane su funkcionalne i estetske karakteristike korišćenih rekonstruktivnih metoda, dvanaest meseci nakon operacije. **Rezultati.** Ova studija je pokazala da različite rekonstruktivne metode imaju različite funkcionalne i estetske rezultate u istim regijama nosa, kao i da ista rekonstruktivna metoda ima drugačije rezultate u različitim regijama nosa. **Zaključak.** Procena postoperativnih funkcionalnih i estetskih karakteristika različitih rekonstruktivnih metoda jedan je od osnovnih preduslova uspešne rekonstrukcije.

Ključne reči:
nos; karcinom, bazocelularni; hirurgija, rekonstruktivna, procedure; režnjevi, hirurški; graftovi; lečenje, ishod; estetika.

Introduction

Reconstruction of nasal defects often represents a significant challenge owing to several unique qualities of the nose, such as complex topography, mobile free margins, and multiple nasal subunits. Various methods have been described for the reconstruction of tumor-related defects of the nasal soft tissues such as local flaps, island flaps, and free skin grafts [1–4]. Local flaps are preferred for the reconstruction of the nasal skin as they offer a skin texture and color similar to the resected skin portion, thus providing good esthetic results [5, 6]. Grafting remains an excellent choice when other reconstruction options are not desirable [4]. However, the goal of nasal reconstruction is to create an esthetically inconspicuous nose while preserving the functional aspect, especially over the long term [7, 8].

Surgeons often face with the problem when selecting a reconstructive method for nasal skin defects. Generally, this dilemma is present because of the functional and esthetic po-

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stoperative differences, which occur in different reconstructive methods.

The aim of this study was to compare functional and esthetic results of different reconstructive methods used for nasal skin defects in different regions of the nose, in order to help surgeons in selecting an appropriate reconstructive method for nasal skin defects.

Methods

The study involved 44 patients, 29 men and 15 women, with basocellular carcinoma in the nasal area. The study was conducted from 2003 to 2013. The average age of the patients was 66 (range 46–84) years. The inclusion criteria were: basocellular carcinoma affecting only nasal skin, without infiltration of deeper structures; defect which appeared after tumor removal, localized in only one subunit; except for the defect, there are no other changes on the skin of the nose, e.g. tumors, scars and other; normal anatomy of the nose, without obvious deformities; patients had no complications such as dehiscence, flap and full thickness skin graft necrosis, partial or total, and recidivism until the examination.

The nasal skin was divided into four subunits: the tip, the alar lobules, the dorsum and the sidewalls [9]. Skin defect size ranged from 5 mm × 5 mm (alar lobule) to 18 mm × 18 mm (sidewall). The average defect size was 10 mm in diameter. The following reconstructive methods were used in the study: transposition flaps (n = 17), rotation flaps (n = 3), advancement flaps (n = 5), bilobed flaps (n = 4), glabellar flaps (n = 4), Rintala flaps (n = 3), and full thickness skin grafts (FTSG) (n = 8) from donor site, brachial area. Functional and aesthetic postoperative results of the used reconstructive methods were analyzed 12 months after the surgery. All the patients were tested by the same examiner. The recovery of sensation to pinprick, light touch and temperature of each flap and full thickness skin graft was tested. Two-point discrimination and functioning of sweat glands was also examined. Pain sensitivity was evaluated using pinprick, light touch was measured using von Frey hairs and hot and cold sensitivity was tested by thermal esthesiometer with water +10°C or water +40 °C [10, 11]. The lowest value at which the patient correctly identified 2 points at least 3 out of 5 times was recorded as the value for 2-point discrimination. The functioning of sweat glands was tested using ninhydrin test [11]. Sensory function and functioning of sweat glands was assessed on the central portion and 4 peripheral sectors of each flap and full thickness skin graft. The number of positive responses was registered. Comparison has begun with the surrounding recipient sites.

Esthetic parameters such as color, texture and contour, used in the nasal defect reconstruction, were visually assessed with regard to color, texture and contour of the surrounding recipient site. The color was visually assessed as lighter, darker or approximately the same, the texture was assessed as approximately the same or different, while the contour deformity was visually assessed as above, below and approximately at the level of the surrounding skin of the recipient site. Those esthetic parameters that were approximately the same with the surrounding recipient site were considered positive, while those which differed from the surrounding recipient site were considered negative. The patient's subjective assessment of the esthetic appearance of the reconstructed nose and of one independent examiner was graded as excellent, good, and fair.

Results

Recovery of sensation in all modalities in at least one-half of the local flap area was recorded in 32 of the patients with local flaps. Partial recovery was present in additional 4 of the patients. None of the local flaps remained insensitive. The recovery of pain and cold temperature was better than that of hot temperature or light touch. The mean 2-point static discrimination for local flaps was 10.4 mm. The functioning of sweat glands was detected in 35 patients with the local flaps. Reinnervation tended to be more pronounced at the periphery of the flap. The patients with full thickness skin grafts demonstrated sensory recovery that was of a partial nature. The mean 2-point static discrimination for full thickness skin grafts was 12 mm. The functioning of sweat glands was not detected in the patients with full thickness skin grafts. Reinnervation tended to be more pronounced at the periphery of full-thickness skin grafts. The average results of sensory and sweat gland function testing for local flaps and full thickness skin grafts were summarized in Table 1.

Table 1

Functional results of different reconstructive methods

Site	Number and type	Pin-prick (%)	Light touch (%)	Hot (%)	Cold (%)	Two-point discrimination (mm)	Ninhydrin test	
							yes (%)	no (%)
Tip	3 RF	86.7	53.3	53.3	86.7	10	100	/
Tip	5 TF	100	76	56	88	8.2	100	/
Tip	3 RiF	66.7	53.3	46.7	66.7	10.6	100	/
Tip	2 FTSG	60	40	20	40	/	/	100
Alar lobule	3 AF	93.3	86.7	60	86.7	9.3	100	/
Alar lobule	3 TF	73.3	53.3	53.3	66.7	11.3	100	/
Alar lobule	2 FTSG	40	40	20	40	/	/	100
Dorsum	4 TF	90	90	55	85	10.5	75	25
Dorsum	4 BF	88	76	60	76	9.25	100	/
Dorsum	2 FTSG	20	20	20	20	12	/	100
Sidewall	2 AF	100	86.7	60	86.7	13	100	/
Sidewall	5 TF	68	68	56	68	11.6	100	/
Sidewall	4 GF	60	55	45	55	11.25	100	/
Sidewall	2 FTSG	60	40	20	40	12	/	100

RF − rotation flap; TF − transposition flap; RiF − Rintala flap; FTSG − full thickness skin graft; AF − advancement flap; BF − bilobed flap; GF − glabellar flap.

All the three positive esthetic parameters were present in 11 of the patients with the local flaps. One or two positive esthetic parameters were present in additional 25 patients. Twenty-five patients have graded the aesthetic appearance of their nose as excellent, 11 patients as good, while none of the patients graded the aesthetic appearance of their nose as fair. Independent examiner graded 24 patients as excellent, 12 patients as good. Five of the patients with full thickness skin grafts had all of the negative esthetic parameters. Five of the patients graded the esthetic appearance of their noses as excellent, and 3 as good. An independent examiner graded 5 patients as excellent, 2 patients as good and 1 patient as fair. The results of color, texture, contour and patients' subjective assessment and the assessment of an independent examiner for the local flaps and full thickness skin grafts were summarized in Table 2.

For the reconstruction of nasal tip skin defects, the best functional postoperative results had rotation flaps (Figure 1), followed by transposition flaps, Rintala flaps and full thickness skin grafts. For reconstruction of alar lobule skin defects, the best functional postoperative results had advancement flaps, followed by transposition flaps, and full thickness skin grafts. Transposition flaps had the best functional result for the dorsum of the nose, followed by bilobed flaps and full thickness skin grafts. For reconstruction of sidewall skin defects, the best functional postoperative results had advancement flaps, followed by transposition flaps, glabellar flaps and full thickness skin grafts.

According to our study reconstruction of nasal tip skin defects, the best esthetic postoperative results, had transposition flaps, followed by rotation flaps, Rintala flaps and full-thickness skin grafts. For the alar lobule, the best esthetic results were obtained by full-thickness skin grafts, followed by transposition and advancement flaps. Transposition flaps were the best solution for the dorsum, followed by bilobed flaps and full-thickness skin grafts. For the sidewall, the best esthetic results were obtained by transposition flaps (Figure 2) followed by advancement flaps, glabelar flaps and full-thickness skin grafts.

Table 2

Esthetic results of different reconstructive methods

Site	Number and type	Color			Texture		Contour			Subjective assessment − patient			Subjective assessment − independent examiner		
		same	lighter	darker	same	different	same	below	above	excellent	good	fair	excellent	good	fair
Tip	5 TF	4	1	/	4	1	4	1	/	4	1	/	4	1	/
Tip	3 RF	2	1	/	2	1	2	1	/	2	1	/	2	1	/
Tip	3 RiF	2	1	/	1	2	1	2	/	2	1	/	2	1	/
Tip	2 FTSG	/	/	2	/	2	/	2	/	/	2	/	/	1	1
Alar lobule	2 FTSG	1	/	1	/	2	2	/	/	2	/	/	2	/	/
Alar lobule	3 TF	2	1	/	2	1	/	/	3	2	1	/	2	1	/
Alar lobule	3 AF	1	2	/	2	1	/	/	3	2	1	/	2	1	/
Dorsum	4 TF	3	1	/	3	1	3	/	1	3	1	/	3	1	/
Dorsum	4 BF	3	2	/	3	2	4	/	1	3	1	/	3	1	/
Dorsum	2 FTSG	/	/	2	/	2	/	1	1	1	1	/	1	1	/
Sidewall	5 TF	4	/	1	4	1	4	1	/	4	1	/	3	2	/
Sidewall	2 AF	2	/	1	2	1	/	/	3	1	1	/	1	1	/
Sidewall	4 GF	2	1	1	1	3	1	/	3	2	2	/	2	2	/
Sidewall	2 FTSG	/	/	2	/	2	1	1	/	2	/	/	2	/	/

TF − transposition flap; RF − rotation flap; RiF − Rintala flap; FTSG − full thickness skin graft; AF − advancement flap; BF − bilobed flap; GF − glabellar flap.

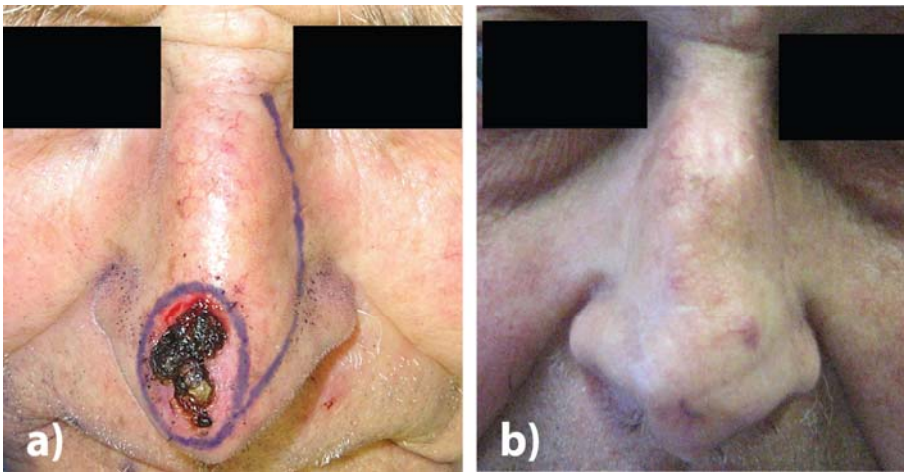

Fig. 1 − Rotation flap – nasal tip: a) before and b) a twelve months after the surgery.

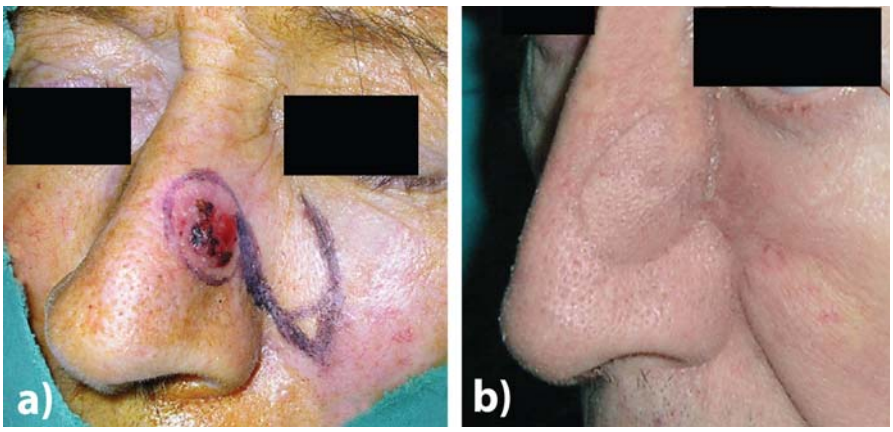

Fig. 2 − Transposition flap – sidewall: a) before and b) twelve months after the surgery.

Discussion

Functional characteristics

Recovery of sensation of local flaps and skin grafts was generally tested with qualitative psycho-physical methods, electrophysiological methods and quantitative methods [12]. Many authors indicate the time discrepancy of different types of sensation recovery, and the results of their examinations show that pain sensations are recovered first, followed by sensitiveness to thermal stimuli, and then light touch [12, 13]. Histochemical studies of the human skin grafts and flaps provide the basis for understanding of the mechanism of sensory recovery. Waris et al. [13] obtained biopsy samples from 9 patients who had undergone skin grafting and found histochemical evidence of regenerating nerves at the bed and margins of skin grafts 3 weeks after surgery. These nerves were orientated towards the denervated area, suggesting chemotactic factors in the orientation of neural regeneration. Similar findings in animal studies support the clinical observations of spontaneous sensory recovery in local flaps and skin grafts. Santoni-Rugiu [14] demonstrated neuroregeneration in recipient sites 25–30 days after skin grafting. This was followed by exuberant reinnervation within 8 weeks. Less complete degeneration was found in the skin flaps. Neuroregeneration was noted to begin at the base of recipient sites in all cases [15]. Ponten [16] proves that there is a sweat gland function recovery in the full-thickness skin grafts and local flaps. Local flaps and full-thickness skin grafts which lack the sensation, also lack the sweat gland function.

In our study we compared functional results of various reconstructive methods used in the nasal defects reconstruction. Spontaneous reinnervation did occur in local flaps and in full-thickness skin grafts used for the nasal defects reconstruction, although recovery was not always complete. The pattern of reinnervation was various with better recovery of pain and cold temperature sensation. It would appear that sensation to pain returns first, followed by cold temperature, then light touch. Sensation recovery is better with local flaps than with full-thickness skin grafts.

The present study demonstrates that functional recovery of local flaps and full thickness skin grafts depends on localization of defects in the nasal region. This is an important parameter that should be considered when selecting reconstructive method for nasal skin defects reconstruction.

Aesthetic characteristics

Millard [17] divided the face into facial aesthetic subunits and advocated the use of subunits in nasal reconstruction. Burget and Menick [9] further defined the nasal esthetic subunits. The reconstructive principle utilizing esthetic subunits promotes removal of an entire subunit if 50% or more is absent. Although the described approach to nasal reconstruction included an assessment of the skin color, texture and contour, the importance of these aspects has been neglected in the teachings and publications [18] subsequent to the introduction of Burget and Menick's [19] topographic nasal subunit principle. Singh and Bartlett [20] modify the nasal subunit principle taking into account local characteristics such as skin color, texture, contour, and actinic damage. Esthetic considerations, such as skin texture, color, and contour, used in the resurfacing of skin defects have been chronicled in the evolution of nasal reconstruction [21]. Skin color, texture and contour play a critical role in final determination of the reconstruction type [22]. Local flaps for the nasal skin coverage of defects evolved along the principle of "replacing like with like" in providing ideal skin color and texture match [23]. Local flaps typically offer better aesthetic results than full-thickness skin grafts [20, 22, 24].

The present study demonstrates that almost one-third of patients, who have local flaps inset into the nasal region, have all of the positive aesthetic parameters. Aesthetic parameters were better for local flaps than for full-thickness skin grafts, which is compatible with results of other authors [4, 20, 22, 25].

Conclusion

There are many reconstructive options for nasal skin defects. Our study demonstrates that different reconstructive methods produce different functional and esthetic results, in the same nasal subunits. In addition, the same reconstructive method produces different results in different nasal subunits. The results of our study could help surgeons in selecting the

appropriate reconstructive method for nasal skin defects. Estimation the postoperative functional and esthetic characteristics of different reconstructive methods is one of the fundamental prerequisites of successful reconstruction. Success of reconstruction lies in preoperative planning and strategy that will provide better functional and esthetic postoperative results.

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Received on August 29, 2014.
Revised on March 26, 2015.
Accepted on March 26, 2015.
Online First March, 2016.

ORIGINAL ARTICLE

UDC: 612.017:[616.314-002-08:616.31-74
DOI: 10.2298/VSP140227054S

Influence of dental filling material type on the concentration of interleukin 9 in the samples of gingival crevicular fluid

Uticaj tipa materijala za plombiranje zuba na koncentraciju interleukina 9 u uzorcima gingivalne sulkusne tečnosti

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Abstract

Background/Aim. Several cytokines and lymphokines (IL1β, ENA78, IL6, TNFα, IL8 and S100A8) are expressed during dental pulp inflammation. Analysis of gingival crevicular fluid (GCF) offers a non-invasive means of studying general host response in oral cavity. Although GCF levels of various mediators could reflect the state of inflammation both in dental pulp and gingiva adjacent to a tooth, GCF samples of those without significant gingivitis could be interpreted as reflection of pulpal process. The aim of this study was to investigate IL9 GCF values in patients with dental caries and to assess possible influence of various dental fillings materials on local IL9 production. **Methods.** The study group included 90 patients, aged 18–70, with inclusion and exclusion criteria in the prospective clinical study. Of the 6 types of material used for the restoration of prepared cavities, 3 were intended for temporary and 3 for definitive restoration. According to dental fillings weight, all the participants were divided into 3 groups: those with fillings lighter than 0.50 g, those with 0.50–1.00 g, and those with fillings heavier than 1.00 g. Samples were taken from gingival sulcus using the filter paper technique. Clinical parameters were determined by bleeding index, plaque index (Silness-Lou, 0–3), gingival index (0–3), and gingival sulcus depth. Cytokine concentrations were assessed using commercially available cytomix. **Results.** According to the weight of dental fillings, there was a clear decreament trend of IL9 values meaning that dental defects greater than 1.00 g of dental filling were associated with lower GCF IL9 concentration. The IL9 values correlated with the degree of gingival index and depth of gingival sulcus, being higher with more advanced gingivitis and more pronounced anatomical changes in the tooth edge. Different filling materials exerted various local IL9 responses. Zink polycarbonate cement and amalgam fillings induced a significant and long-lasting local IL9 decrement, while the use of Tetric EvoCeram and GMA-BISK significantly increased IL9 levels. **Conclusion.** The obtained results indicate that IL9 GCF could be regarded as a measure of odontoblasts' response to the extensity of dental caries. The type of material used for dental fillings could profoundly alter biological function of gingival and pulpal cells. Also, the results obtained in this study suggest that some materials could even enhance wound repair by modulating macrophage activation.

Key words:
dental caries; dental materials; gingival cervicular fluid; cytokines; interleukin-9.

Apstrakt

Uvod/Cilj. Jedan broj citokina i limfokina (IL1ß, ENA78, IL6, TNFα, IL8 I S100A8) izlučuje se tokom upale zubne pulpe. Analiza gingivalne sulkusne tečnosti (*gingival crevicular fluid* – GCF) omogućava neinvazivno proučavanje opšteg odgovora pacijenta na lokalne promene u usnoj duplji. Iako nivoi GCF mogu da odražavaju stanje upale kako u zubnoj pulpi, tako i u gingivi susednog zuba, uzorci GCF zuba bez značajnijeg gingivitisa mogli bi se tumačiti kao pokazatelji procesa u pulpi. Cilj ovog istraživanja bio je da se ispitaju nivoi IL9 u GCF kod pacijenata sa zubnim karijesom i da se

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utvrdi eventualni uticaj različitih materijala za zubne ispune na lokalnu proizvodnju IL9. **Metode.** U studiju je bilo uključeno 90 pacijenata, starih od 18 do 70 godina, uz primenu kriterijuma za uključivanje/isključivanje za prospektivne kliničke studije. Od ukupno šest materijala za punjenje pripremljenih kaviteta, tri je korišćeno za privremenu i tri za trajnu ispunu. Prema težini zubnog ispuna, pacijenti su bili podeljeni na tri grupe: oni sa ispunama lakšim od 0,50 g, sa ispunama od 0,50 do 1,00 g i sa ispunama težim od 1,00 g. Uzorci su uzimani iz gingivalnog sulkusa primenom tehnike filter papira. Korišćeni klinički parametri bili su indeks krvarenja, plak indeks (Silness-Lou, 0–3), gingivalni indeks (0–3) i dubina gingivalnog sulkusa. Koncentracije citokina određene su komercijalnim citomiksom. **Rezultati.** Težina zubne ispune ukazivala je na tendenciju opadanja vrednosti IL9, što je značilo da je veće oštećenje zuba, sa zubnom ispunom težom od 1,00 g, praćeno nižom koncentracijom IL9 u GCF. Vrednosti IL9 bile su u korelaciji sa stepenom gingivalnog indeksa i dubinom gingivalnog sulkusa, pogotovu u poodmaklom gingivitisu i izraženijim anatomskim promenama ivica zuba**.** Različite ispune izazivale su različite lokalne sekrecije IL9. Cink-polikarbonatni cement i amalgamska ispuna izazvale su značajan i dugotrajan pad nivoa lokalnog IL9, dok je primena tetrik-evocerama i GMA-BISK znatno povisila nivoe IL9. **Zaključak.** Rezultati dobijeni u ovoj studiji ukazuju da se IL9 u GCF može koristiti kao mera za reakciju odontoblasta na veličinu karijesa. Tip zubne ispune može da promeni biološku funkciju ćelija gingive i pulpe. Rezultati ove studije, takođe, ukazuju i na to da neke vrste ispuna mogu čak da ubrzaju zarastanje rane modulacijom aktivnosti makrofaga.

Ključne reči:
zub, karijes; zub, materijali za punjenje korenskog kanala; gingivalna sulkusna tečnost; citokini; interleukin-9.

Introduction

Intensive inflammatory and immune processes are mediated with numerous cytokines and lymphokines, which were detected in dental tissue and the pulp of the affected teeth, at gene and/or protein level. Dental tissue of carious teeth contains much more IL1b, ENA78, IL6, TNFa, IL8 and S100A8 than samples of healthy teeth [1]. Dental pulp of caries affected tooth is associated with high levels of IL-6, IL-8, IL-10, TNF-α and IFN-γ, CXCL10, VEGF, TNFa, and IL2 [2–6]. Finally, gingival crevicular fluid (GCF) around tooth with caries also shows elevated levels of IL8 [7]. Pulpal odontoblasts have several physiological roles. Their basic role of production extracellular dentin structure is supplemented in a carious tooth, because they are crucial in making the reparative dentin. Odontoblasts mediate local inflammatory response both directly and indirectly, with numerous cytokines, lymphokines and antimicrobial peptides [8, 9]. Studying the inflammatory gene expression profile of 96 different mediators in pulp and odontoblasts culture of carious and normal teeth, Horst et al. [8] reported that there were distinct profiles, and different dominant profiles of cytokines and lymphokines. Both micro-environments had rich expression of chemokines and IL1, but only odontoblasts expressed IL9, IL9R and IL13.

Interleukin 9 is one among mediators which exerts influence on numerous functions of different cell types. Produced by T cells, IL9 induces significant biological response on mast cells, hematopoietic progenitor cells, epithelial cells, smooth muscle cells, antigen presenting cells, B-lymphocytes and T-lymphocytes themselves [10–20]. IL9 was recognized as a growth factor of mast cells that enhances their survival, production of IL6 and proteases, and induce expression of IgE receptor [21]. Together with IL5, IL9 induces maturation and activation of eosinophils, making it crucial in allergic inflammation [22, 23]. It is assumed that IL9 together with IL5 and IL13 coordinately controls epithelial barrier functions [24].

The aim of this study was to investigate the concentration of IL9 in GCF of caries affected teeth and to correlate it with clinical parameters, as well as to follow IL9 dynamics after dental filling procedures and to evaluate IL9 response to different dental filling materials.

Methods

A total of 90 patients, aged 18–70, were included in this prospective clinical study. The inclusion criteria were the diagnosed approximal caries on frontal and side teeth, the existence of the same type of antagonists or natural teeth for the test or the control group, no fresh post-extraction or traumatic wounds in the restoration area or the area of restored surfaces, no signs of infection in the area of restored surfaces. Also, each patient had to meet the conditions for the duration of one restoration, and with satisfactory level of oral hygiene. The exclusion criteria were the presence of infection of endodontal or periodontal origin in the area of approximal or cervical filling, the presence of prominent periodontal pockets, the presence of fillings that were prominent outside the cavity, the patients who were on immunosuppressive therapy or those with heavy chronic bone metabolic or treated malignant diseases, the patients whose medical history included alcohol and drug abuse problems or mental diseases, those who smoked more than 20 cigarettes a day, those with bad oral hygiene, and unreliable for cooperation.

The monitored clinical parameters included bleeding index on probing (BOP), plaque index (PI, 0–3), gingival index (GI, 0–3), and depth of gingival sulcus (DGS). The second sample was taken from gingival sulcus fifteen days after setting the approximal filling .

All potential participants in the study filled out a form within a dental record in order to get information on their general health and oral condition. The patients were familiarized with the aim of the research, as well as with all of its procedures and duration, and gave written consent to participate in the research.

Before sampling GCF, the DGS was measured out against the approximal caries lesion graded with periodontal probe, and after that the procedure was repeated on the oppo-

site side with the gingival sulcus depth measured out against the surface of a healthy tooth.

Six types of material were used for the restoration of prepared cavities, 3 for temporary and 3 for definitive restoration. The materials used for temporary restoration of cavities were glass ionomer cement – filling group F (GC Fuji PLUS®, Green Circle, USA), zinc phosphate cement – filling group E (Cegal NV, Galenika), and zinc polycarboxylate cement – filling group A (Harvard). The materials used for definitive restoration were amalgam – filling group B (Extracap D caps, Galenika), Beautiful (Shofu, Japan), and Tetric EvoCeram – filling group C (Ivoclar Vivadent). Tetric EvoCeram and Beautifull – filling group D are nanohybrid composite materials that require UV light for binding in the cavity. The other materials in the cavity tend to bind, *ie* harden by themselves.

Upon the removal of caries lesions and rinsing the cavity, a matrix with the appropriate holder was placed into the interdental space, whose role was to prevent sub-gingival impression of the material and, on the other hand, enable construction of the contact point and bringing back the morphology to the restored tooth.

Results

Influence of dental fillings weight on IL9 GCF concentration

According to dental fillings weight, all the participants were divided into 3 groups (those with fillings lighter than 0.50 g, those with 0.50–1.00 g, and those with fillings hevier than 1.00 g). The highest average IL9 concentration was estimated in the samples of the group with the smallest dental defects, and consequently the smallest used dental filling weight (Table 1). The average IL9 concentration before the procedure was significantly decreased in GCF of teeth with biggest defects, that consequently needed more dental filling material. There was a clear decreament trend of IL9 values according to dental filling weight, meaning that larger dental defects were associated with the lower GCF IL9 concentration. The only significant difference in the average IL9 concentration was between the smallest weight filling group (< 0.50 g) and those that needed more than 1.00 g fillings (Mann Whitney $p = 0.0337$), with IL9 higher in those with smaler dental defects. Analysis of individual, serial samples

Table 1

Average interleukin 9 (IL9) gingival cervicular fluid (GCF) concentration according to the investigated parameters

Parameters	IL9 (pg), $\bar{x} \pm SD$		
	before (0)	control I	control II
Dental filling weight (g)			
< 0.50	50 ± 72	74 ± 84	47 ± 84
0.50–1.00	61 ± 74	43 ± 85	21 ± 33
> 1.00	12 ± 17	10 ± 14	17 ± 30
Filling material type			
A – zinc polycarboxilate cement	33 ± 23	13 ± 28	3 ± 5
B – amalgam	31 ± 40	14 ± 29	18 ± 30
C – tetric evoceram	53 ± 26	153 ± 102	117 ± 124
D – beautifill	44 ± 54	110 ± 103	78 ± 125
E – zinc phospate cement	37 ± 35	52 ± 44	30 ± 25
F – glass ionomer cement	42 ± 46	64 ± 52	40 ± 31
GI			
0	32 ± 47	31 ± 39	17 ± 27
1	51 ± 79	76 ± 102	50 ± 92
2	49 ± 69	64 ± 71	32 ± 55
3	29 ± 23	44 ± 32	135 ± 180
PI			
0	31 ± 36	43 ± 41	29 ± 35
1	50 ± 71	71 ± 90	43 ± 82
2	45 ± 71	59 ± 71	42 ± 74
3	42 ± 1	36 ± 40	5 ± 1
BI			
0	48 ± 75	69 ± 96	45 ± 85
1	45 ± 62	62 ± 70	34 ± 53
2	51 ± 75	57 ± 69	49 ± 92
3	21 ± 29	117 ± 75	11 ± 16
DGS			
0	27 ± 32	75 ± 99	74 ± 120
1	39 ± 62	52 ± 76	28 ± 57
2	73 ± 94	84 ± 88	55 ± 90
3	49 ± 51	66 ± 47	38 ± 25

GI – gingival index; PI – plague index; BI – bleeding index; DGS – depth of gingival values.

showed significant concentration changes in the smallest (Wilcoxon test, 0/I $p = 0.0073$, I/II $p = 0.0453$) and the intermediate (I/II $p = 0.0313$) dental fillings groups. There were no significant changes of IL9 in the group treated with dental filling heavier than 1.00 g.

IL9 GCF concentration and different dental filling materials

The highest average IL9 concentration was estimated in the C dental filling group, while the smallest detected was in the A dental filling group, at both check points. After the first 15 days, in the first control interval, the average IL9 values in samples treated with A and B fillings were significantly lower comparing to those estimated in the groups C and D (Table 2). Furthermore, the group with the highest average IL9 level showed a significantly higher concentration than the group with E and F type of dental fillings.

In the second control interval, the only significant difference was IL9 increament detected in the group C comparing with the group A. There were no significant differences between IL9 concentration in the first or the second control interval among the samples of the same group, neither between the average values, nor individual ones in serial samples.

Gingival index and IL9 GCF concentration

Before filling treatment, the smallest average IL9 concentrations were detected in the group with the smallest and the highest value of GI. At the first and the second control, the smallest IL9 concetrations were in the group with GI = 0. There were no significant differences in average IL9 levels between the groups with different GI. Analysis of individual serial samples showed a significant concentration change in the GI = 2 group (I/II $p = 0.0063$).

Plaque index and IL9 GCF concentration

The highest average IL9 level was detected in the samples of the group that had PI = 1, within the first control. There were no significant differences in the average IL9 levels between the groups with different PI. Analysis of individual, serial samples showed a significant concentration change in the PI = 1 group (I/II $p = 0.0256$).

BOP index and IL9 GCF concentration

The highest average IL9 level was detected in samples of the group that had BOP = 3 within the first control. There were no significant differences in the average IL9 levels among the groups with different BOP. Analysis of individual serial samples showed a significant concentration change in BOP = 1 group (I/0 $p = 0.0129$, I/II $p = 0.0124$).

Depth of gingival sulcus and IL9 GCF

The lowest IL9 concentration was detected before the filling treatment in the group without bleeding, contrary to other groups with different BOP values. On the other hand, the highest average IL9 value was detected in the BOP = 0 group within the second control. All these differences were not statistically significant. Analysis of individual, serial samples showed a significant IL9 concentration change in the DGS = 0 group (I/0 $p = 0.0481$).

Frequency of IL9 increament in response to type of dental filling used

In the groups treated with various dental filling materials the percent of patients that had IL9 increament in samples comparing with the previous time interval was estimated (Table 3). So, the frequency of IL9 stimulation was estimated within the first control point relative to the basal level, before the treatment (I/0), the second comparing to basal (II/0) and the second comparing with the first control point (II/I).

The most frequent IL9 increase was detected in GCF samples of the patients treated with D, F and than E and C types of dental materials, in more than a half within the first time interval, after 15 days. At the second chek point, IL9

Table 2

Statistical analysis of differences in the interleukin 9 (IL9) concentration in the investigated groups treated with various dental fillings[#]

Check points	A/B	A/C	A/D	A/E	A/F	B/C	B/D	B/E	B/F	C/D	C/E	C/F	D/E	D/F	E/F
I	ns	***	**	ns	ns	***	**	ns	ns	ns	**	*	ns	ns	ns
II	ns	**	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

(*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$); ns – no significant difference; I – control I; II – control II.

[#]A – zinc polycarboxilate cement; B – amalgam; C – Tetric EvoCeram; D – Beautifill; E – zinc phospate cement; F – glass ionomer cement.

Table 3

Frequency of interleukin 9 (IL9) increament (%) in response to the type of dental filling used[#]

Check points	A	B	C	D	E	F
I / O	29	29	50	67	53	57
II / O	12	27	44	33	31	38
II / I	12	27	33	27	36	27

[#]A – zinc polycarboxilate cement; B – amalgam; C – Tetric EvoCeram; D – Beautifill; E – zinc phospate cement; F – glass ionomer cement.
O – before dental filling; I – control I; II – control II.

was frequently increased in C and F types material treated teeth, but the percentage was notably lower comparing to those after the first 15 days. The pattern of IL9 elevation was the same after we compared the second to the first time interval, around one third of those teeth filled with E and C types material had the increase in IL9.

Based on this observation it could be concluded that the materials C, E and F induce local production of IL9 in most GCF samples, and that the A and B materials are IL9 inducers of low potency.

Discussion

The predominant cause of local inflammation in dental pulp is the presence and activity of bacteria originating from oral flora. Interaction of bacterial products with dental pulp immune cells realized through dental tubules results in the induction of local immune reaction by dental carious lesion [25]. The consequent inflammation is the product of mediators produced and released by various immune and non-immune cells in dental pulp, such as TNFa, IFNg, IL1b, IL6, IL10 and NO [26–28]. Deep invasion of bacteria into tooth structures induces a significant mononuclear infiltration of dental pulp. Microbial products, probably through toll receptors, stimulate dental pulp fibroblasts to produce chemoattractants needed for inflammatory cell accumulation. Takahashi et al. [29] report that CCL20 mRNA is highly expressed in inflamed comparing to healthy pulp, on fibroblasts, endothelial cells and macrophages. Generally, it could be expected that the size and the duration of dental lesion correspond to the level of local dental pulp inflammation. Karapanou et al. [7] show that GCF samples of caries affected teeth could be valuable in the assessment of staging acute pulpitis. The level of CXCL8 in GCF was sensitive biological inflammatory marker, which highly correlates with pulpitis and subjective feel of pain that had a high value even in adjacent teeth to the affected one, and had decreased GCF values in those patients who received local anesthesia before sampling.

To our knowledge there has been no published data concerning IL9 in GCF till now. Innate lymphoid cells (ILC2 type) together with Th2 and Th9 lymphocytes are considered as main producers of IL9, along with the so-called type 2 cytokines IL4, IL5 and IL13 [30, 31]. In physiological conditions these cytokines coordinately control epithelial barrier functions, inducing goblet cells proliferation and production of mucus. They also induce polarization and activation of certain functional macrophage types, important for tissue repair. Since data on IL9 in pulp or gingival tissue are seldom, all the results of our study could be interpreted with speculation. It is reasonable to suppose that dental caries that lasts long and which is extensive enough induce a significant pulp inflammation [7, 29]. In our study, larger dental lesions that needed more than 1.00 g of dental filling were accompanied with low concentrations of IL9 GCF. This finding indicates that more extensive dental caries is mediated with cytokines that down-regulate local IL9 production, or *vice versa*, that the presence of IL9 in GCF could implicate the capability to confine destruction of dental tissue.

According to the accepted view, physiological role of IL9 is represented in local response of innate lymphoid cells type 2 (ILC2) to IL33 and IL25 produced after damage of epithelial tissue with viruses, helminthes, and alergens [24]. Locally produced IL9 induce other ILC and T to produce IL5 and IL13 and mediate in restoration of epithelial integrity. Since there is no correlation of IL9 and IL13 values in GCF of our patients (unpublished data), it is hard to assume that the same mechanism of IL9 is operative in tooth microenvironment.

The importance of IL9 is now recognized in allergic and chronic inflammation, so the other speculation would be that IL9 GCF levels correspond to the degree of inflammatory process, both in the pulp and gingiva. In the samples of our patients, IL9 values correlated with the degree of gingival index and the depth of gingival sulcus, being higher with more advanced gingivitis and more pronounced anatomical changes in tooth ledge [32, 33]. The patients with most intensive gingivitis hade the highest average IL9 GCF values 30 days after filling procedures, contrary to those without any signs of gingival inflammation, where the average IL9 level was significantly reduced. Clearly, inflammation that takes place in gingiva and those happening only in dental pulp could have completely different mechanisms. While intensive inflammation in gingiva would be mediated with T lymphocytes, macrophages and neutrophiles, mild dental pulp inflammation would include odontoblasts, dental pulp fibroblasts and rare immune cells, which will generate different mediator profile. There also could be a possibility that a certain type of oral microorganism could selectively induce local IL9 production in susceptible person, like *Lactobacilus casei* that induce a strong IL10 response, *P. alactolyticis* that induces predominantly type 2 cytokine local production and *S. mutans* that induce IFNg mediated response in early pulpitis [34–36].

Horst at al. [8] show that caries induces strong response in pulp and odontoblast layer, represented by the expression of various cytokine and chemokine genes. It is important that each microenvironment, pulp and odontoblast layers, has a different dominant profile of mediators. While the pulp of carious teeth was rich with expression of various chemokines and IL1, cytokine production in odontoblast layer was dominated by IL8, IL1a, IFNa, IL9, IL9R, IL13 and chemokines. This was in concordance with the authors' hypothesis that primary role in local tooth immune response is carried by odontoblasts, which use and are governed by these cytokines to produce antibacterial proteins. In line with this attitude, our results indicate that IL9 GCF could be accepted as a measure of odontoblasts response to the extensity of dental caries.

The results of our study show that different filling materials exert various local IL9 responses. Zink polycarbonate cement and amalgam fillings induced a significant and long-lasting local IL9 decrement, while the use of tetric evoceram and GMA-BISK significantly increased IL9 levels at both check points. The frequency of patients who responded with IL9 GCF increase was highest in the Tetro EvoCeram group, but even the average IL9 level was insignificantly elevated, almost 40% of zink polycarboxilate cement treated patients showed IL9 elevation.

There are no data on direct influence of Tetric EvoCeram on cytokine production, while there are reports on fluoride release from tetric evoceram dental fillings, which was significantly associated with local mediator micro environment. Naoum et al. [37] show that the 4 different materials tested *in vitro* (Beautifil II, Tetric EvoCeram, Gradia Direct X, and Fuji IX Extra) differ in their mechanical stability, and ability to release or recharge fluoride. There are several lines of evidence based on *in vitro* experiments on ameloblast cell lines that showed profound influence of fluoride on cytokine production and cell functions. Riksen et al. [38] showed that exposing of cells to sodium fluoride for various time induced reduced cell proliferation, decreased production of VEGF, MCP1 and IP10 and decreased mRNA expression of structural enamel proteins (amelogenin, ameloblastin, enamelin, enamel protease MMP-20). Kubota et al. [39] show that fluoride concentration higher than those in drinking water caused endoplasmic reticulum stress in cultivated ameloblasts. Few animal experiments pointed out that even a 7-day fluoride supplementation given through drinking water resulted in systemic effects on the whole organism, reflected in increased levels of serum cytokines IL2, IL6 and TNFa [40]. The influences of mineral trioxide aggregate (MTA), calcium hydroxide (Life) and zinc oxide eugenol based materials were assessed on human osteosarcoma cell line (U2OS) through evaluation of cell attachment and cytokine production. The best degree of osteosarcoma cells attachment was to MTA, together with the higher levels of IL4 and IL10 produced [41]. The TEC group in our study showed the highest average IL9 GCF value, both at 7 day and 30 day controls.

Restoration of amalgam dental filling with other materials could even have systemic effects. Bjorkman et al. [42] reports that the patients with amalgam fillings have increased serum values of IL12, IL7, IFNa, IL6, GM-CSF and IL2R comparing to the controls. The use of different dental filling materials instead of amalgam in these patients induced reduction of serum cytokine levels. Immunocytochemical analysis of cultivated fibroblasts from periodontal ligament after exposure to various dental materials showed the highest collagen expression after 24 h incubation with MTA, but the group exposed to Portland cement demonstrated the highest late (7 days) production of collagen, fibronectin and TGFb [43]. In this system, amalgam showed the weakest influence on connective structures. Modified Portland cement and MTA did not exhibit any cytotoxic activity on mouse fibroblast cell line L929 [44]. Both materials induced IL1b cytokine production after a short-term culture (24 h), without differences between them.

The type of material used for dental fillings could profoundly alter biological function of gingival and pulpal cells. Materials with more rough surfaces induced, at least *in vitro* on macrophage cell line, transformation of M2 like phenotype, with increased MCP1 and MIP1a production and without arginase 1 and NOS expression [45]. These data indicate that some materials could even enhance wound repair by modulating macrophage activation.

Conclusion

The obtained results indicate that IL9 in GCF could be regarded as a measure of odontoblasts' response to extensity of dental caries. The type of material used for dental fillings could profoundly alter biological function of gingival and pulpal cells. Also, the results obtained in this study suggest that some materials could even enhance wound repair by modulating macrophage activation.

Acknowledgements

This study was supported by the grants from the Ministry of Education, Science and Technological Development, Republic of Serbia (Projects No. III41018, 41008 and 173056) and by the Ministry of Defence of the Republic of Serbia (Project No. MMA/06-10/B.3).

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Received on February 27, 2014.
Revised on May 26, 2015.
Accepted on May 27, 2015.
Online First March, 2016.

ORIGINAL ARTICLE

UDC: 159.9:616-057
DOI: 10.2298/VSP140715062G

Work motivation and job satisfaction of health workers in urban and rural areas

Radna motivacija i zadovoljstvo poslom zdravstvenih radnika u urbanim i ruralnim sredinama

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Abstract

Background/Aim. Motivated and job satisfied health professionals represent a basis of success of modern health institutions. The aim of this study was to investigate whether there was a difference in work motivation and job satisfaction between health workers in urban and rural areas in the region of Central Serbia. **Methods.** The study included 396 health professionals from urban setting, and 436 from a rural area, employed in four randomly selected health facilities. An anonymous questionnaire was used for data gathering. Statistical analysis was performed using χ^2, Student *t*-test, Spearman's correlation coefficient, and logistic regression analysis. **Results.** Urban health professionals were significantly more motivated and job satisfied than respondents from rural area. In relation to work motivation factors and job satisfaction of health professionals in urban and rural areas, there were no significant differences in working conditions and current equipment, and in terms of job satisfaction there were no significant differences in relation to income either. **Conclusion.** In order to increase the level of work motivation and job satisfaction of health workers in rural areas, apart from better income, they should get more assistance and support from their supervisors, and awards for good job performance; interpersonal relationships, promotion and advancement opportunities, managerial performance and cooperation at work should be improved; employment security should be provided, as well as more independence at work, with professional supervision of health workers.

Key words:
motivation; job satisfaction; health; physicians; health personnel; serbia; surveys and questionnaires; urban health services; rural health services.

Apstrakt

Uvod/Cilj. Motivisani zdravstveni radnici, zadovoljni poslom, predstavljaju osnov uspeha savremenih zdravstvenih ustanova. Cilj rada bio je da se ispita da li postoji razlika u radnoj motivaciji i zadovoljstvu poslom između zdravstvenih radnika zaposlenih u urbanim i ruralnim sredinama centralne Srbije. **Metode.** Istraživanjem je obuhvaćeno 396 zdravstvenih radnika u urbanoj i 436 u ruralnoj sredini, zaposlenih u četiri zdravstvene ustanove, koje su izabrane metodom slučajnog izbora. U istraživanju je korišćen anonimni upitnik. U statističkoj analizi podataka korišćeni su χ^2 test, Studentov *t*-test, Spirmanov koeficijent korelacije i logistička regresiona analiza. **Rezultati.** Zdravstveni radnici u urbanoj sredini bili su značajno motivisaniji i zadovoljniji poslom, nego u ruralnoj. U odnosu na faktore radne motivacije i zadovoljstvo poslom zdravstvenih radnika u urbanoj i ruralnoj sredini nije bilo značajne razlike u uslovima na radu i savremenosti opreme za rad, u vezi sa zadovoljstvom poslom ni u odnosu na visinu novčanog iznosa mesečne zarade. **Zaključak.** U cilju povećanja nivoa radne motivacije i zadovoljstva poslom zdravstvenih radnika zaposlenih u ruralnim sredinama, pored novčane zarade, potrebno je obezbediti bolju pomoć i podršku u radu od strane rukovodilaca, dodeljivati nagrade za dobro obavljen posao, unaprediti međuljudske odnose, omogućiti napredovanje i usavršavanje, poboljšati performanse rukovodilaca, obezbediti veću kooperativnost u radu, osigurati zaposlenje, omogućiti veći stepen samostalnosti u radu i sprovođenje stručnog nadzora nad radom zdravstvenih radnika.

Ključne reči:
motivacija; posao, zadovoljstvo; zdravlje; lekari; zdravstveno osoblje; srbija; ankete i upitnici; zdravstvene službe, gradske; zdravstvene službe, seoske.

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Introduction

Health workers are the primary developmental resource of health institutions, therefore understanding their motivation and job satisfaction represents a basis of success, actual effectiveness, efficacy and quality of work of modern health institutions [1–3].

Job satisfaction is defined as individuals' cognitive (assumptions and beliefs about work), affective (emotions about work) and evaluative (job assessment) reactions towards their job [4]. There are several key determinants of the organization and performed work related to job satisfation (perceived quality control, system of rewarding, level of work and social stimulation, power decentralization, pleasant working conditions) [4]. Apart from these, there are also personal factors that affect job satisfaction (personal characteristics, employee status, personal interests, years of experience and general satisfaction with life) [4]. Although there are various subjective factors and individual expectations in different professions which influence job satisfaction, factors affecting job satisfaction also interact and cannot be generalized [5, 6].

Job satisfaction of health professionals is an element of health care quality, which includes job expectations and attitudes to health care services, having an impact on the productivity, quality of the realized health service, better results of health institution functioning, as well as costs of health care [1, 5, 6]. Researches have shown that gender, age, educational level, years of experience, training opportunities, interpersonal relationships, support by supervisors, organization of work, working conditions, income, working hours, promotion expectations and other factors are important for the feeling of job satisfaction of health workers [7–14]. Place of work can also be a significant factor that affects job satisfaction of health professionals [15]. Studies show that working in an urban area is not a necessary prerequisite for higher level of job satisfaction [15, 16].

Work motivation, as one of the factors of efficiency and effectiveness, influences the feeling of job satisfaction [2, 3]. Motivation, being the widest notion, represents the process of initiating human activities directed towards achieving particular goals [17]. By an efficient management of human resources managers of health care institutions should motivate their employees adequately aiming at achieving effectivenes as well as quality of health care which is the ultimate goal of these institutions [17, 18].

So far, no investigations have been conducted on work motivation and job satisfaction of health workers in urban and rural areas in the Republic of Serbia.

The aim of this study was to investigate whether there was a difference in work motivation and job satisfaction between health workers in urban and rural areas in the region of Central Serbia.

Methods

A cross-sectional study was conducted in the period from December 2010 to March 2011 among health professionals in two urban health facilities (Belgrade, with approximately 1.8 million inhabitants) and in two rural health facilities (environment of the town Valjevo, with approximately 86,000 inhabitants), which were randomly selected. The study comprised 71.5% of all employees, namely 832 health workers (135 physicians and 261 nurses from urban setting and 91 physicians and 345 nurses from rural area). Data gathering was performed *via an* anonymous questionnaire, designed by the author (M.G.). The questionnaire was self completed by the respondents. Questionnaires were distributed and collected by the researcher. The survey was voluntary and anonymous. To ensure confidentiality and anonymity, questionnaire envelopes were personally handed over to respondents, and upon completion of questionnaires the envelopes were returned to the researcher without any identification. The questionnaire consisted of three parts. The first part examined demographic characteristics of health professionals, the second work motivation factors, and the third part assessed job satisfaction.

To evaluate the significance of particular work motivation factors, 15 factors were defined. Work motivation factors were measured using a five-level Likert scale ranging from 1 = it does not motivate me at all, 2 = it motivates me a little, 3 = I am not sure, 4 = it motivates me a lot, to 5 = it motivates me the most.

In order to evaluate the level of satisfaction regarding certain work motivation factors, the questionnaire included 15 statements/attitudes. The level of satisfaction (job satisfaction) by fulfillment of particular work motivation factors was also assessed by the application of five-level Likert scale ranging from 1 = I strongly disagree, 2 = I partially disagree, 3 = I am not sure, 4 = I partially agree, to 5 = I strongly agree.

Work motivation of urban and rural health workers was assessed as follows: respondents who rated all 15 work motivation factors with 4 = it motivates me a lot, or 5 = it motivates me the most were considered motivated, while those who rated all 15 work motivation factors with 1 = it does not motivate me at all or 2 = it motivates me a little were considered to be unmotivated. In this way, a new, dichotomous variable was created referred to as "motivational category".

Statistical analysis was performed using χ^2, Student *t*-test, Spearman's correlation coefficient test, and logistic regression analysis.

Logistic regression analysis (stepwise data entry) was used to examine the influence of demographic characteristics such as gender, age, profession, years of experience and place of employment − urban or rural area, on the motivation of all respondents, respondents employed in urban area and respondents employed in rural area. The outcome (a dependent variable) in the logistic regression models was the motivational category. The respondents who rated all 15 work motivation factors with 3 = I am not sure, were not included into logistic regression analysis.

The Statistical Package for the Social Sciences (SPSS) (version 17) was used to analyze statistical data of this research.

Results

In regard to urban health workers, among health workers in rural area there were significantly more males

(17.2% *vs* 7.3%), under the age of 40 years (41.0% *vs* 28.8%), and younger on the average (43.2 ± 9.5 years *vs* 45.2 ± 9.7 years).

Urban health professionals were significantly more motivated than rural health workers by the following work motivation factors: goals of my institution (health promotion, disease prevention, early diagnosis and treatment of patients), professional recognition, good interpersonal relationships, promotion and advancement, personal qualities of immediate supervisors, income, cooperative working environment, training opportunities, job security, support by supervisors, autonomy in the workplace, rewards for exceptional work (verbal or written awards, days off, financial bonuses and so on) and professional supervision (Table 1).

In regard to rural health professionals, urban health workers were significantly more satisfied with the management support, recognition they received from their managers, good interpersonal relationships, support from supervisors to get a promotion or a better job, good personal qualities of their immediate supervisors, cooperative working environ-

Table 1

Urban/rural distribution of health workers in the region of Central Serbia (n = 832) in terms of work motivation factors

Work motivation factors	I am motivated by	Urban area		Rural area		*p*
		n	%	n	%	
Goals of my institution	No	55	13.9	91	20.9	< 0.001
	I am not sure	58	14.6	93	21.3	
	Yes	283	71.5	252	57.8	
Professional recognition	No	88	22.2	142	32.6	< 0.001
	I am not sure	44	11.1	68	15.6	
	Yes	264	66.7	226	51.8	
Good interpersonal relationships	No	47	11.9	103	23.6	< 0.001
	I am not sure	47	11.9	52	11.9	
	Yes	302	76.2	281	64.5	
Promotion and advancement	No	100	25.2	144	33.0	0.005
	I am not sure	80	20.2	103	23.6	
	Yes	216	54.6	189	43.4	
Personal qualities of immediate supervisors	No	55	13.9	91	20.9	0.019
	I am not sure	67	16.9	78	17.9	
	Yes	274	69.2	267	61.2	
Income	No	159	40.2	225	51.6	< 0.001
	I am not sure	38	9.6	52	11.9	
	Yes	199	50.2	159	36.5	
Working conditions	No	101	25.5	132	30.3	0.204
	I am not sure	70	17.7	82	18.8	
	Yes	225	56.8	222	50.9	
Cooperative working environment	No	58	14.6	93	21.4	0.002
	I am not sure	74	18.7	103	23.6	
	Yes	264	66.7	240	55.0	
Training opportunities	No	77	19.4	135	31.0	< 0.001
	I am not sure	68	17.2	89	20.4	
	Yes	251	63.4	212	48.6	
Job security	No	35	8.8	70	16.0	0.002
	I am not sure	57	14.4	74	17.0	
	Yes	304	76.8	292	67.0	
Support by supervisors	No	49	12.4	106	24.3	< 0.001
	I am not sure	59	14.9	68	15.6	
	Yes	288	72.7	262	60.1	
Autonomy in the workplace	No	45	11.4	77	17.7	0.027
	I am not sure	63	15.9	73	16.7	
	Yes	288	72.7	286	65.6	
Current equipment	No	77	19.4	95	21.8	0.553
	I am not sure	64	16.2	76	17.4	
	Yes	255	64.4	265	60.8	
Rewards for exceptional work	No	85	21.5	176	40.4	< 0.001
	I am not sure	55	13.9	63	14.4	
	Yes	256	64.6	197	45.2	
Professional supervision	No	68	17.2	112	25.7	< 0.001
	I am not sure	87	22.0	121	27.7	
	Yes	241	60.9	203	46.6	

ment, opportunities for continuous improvement provided by their institution, job security, support from immediate supervisors, independence in routine tasks, rewards for exceptional work and professional supervision (Table 2).

Urban health professionals were significantly more motivated than job satisfied concerning all work motivation factors, except for promotion and advancement, personal qualities of their immediate supervisors, autonomy in the workplace and professional supervision (Table 3). Urban health workers were significantly less motivated by work motivation factors – professional supervision in relation to the level of its fulfillment by the institutions. According to Spearman's correlation coefficient test, the level of work motivation of urban health professionals was higher if the level of fulfillment (job satisfaction) provided by their institutions was higher. Rural health professionals were significantly more motivated than job satisfied concerning all work motivation factors, except for professional recognition, personal qualities of their immediate supervisors and autonomy in the workplace (Table 4). According to Spearman's correlation coefficient test, the level of work motivation of rural health professionals was higher if the level of fulfillment (job satisfaction) provided by their institutions was higher.

Table 2

Urban/rural distribution of health workers in the region of Central Serbia in terms of job satisfaction

Statements related to the level of job satisfaction	I agree	Urban area		Rural area		*p*
		n	%	n	%	
The manager supports me to reach my professional goals	No	87	22.0	120	27.5	0.013
	I am not sure	68	17.2	95	21.8	
	Yes	241	60.9	221	50.7	
The manager gives me credit when it is necessary/appropriate	No	92	23.2	129	29.6	0.001
	I am not sure	74	18.7	110	25.2	
	Yes	230	58.1	197	45.2	
Interpersonal relationships are good in my institution	No	75	19.0	143	32.8	< 0.001
	I am not sure	96	24.2	116	26.6	
	Yes	225	56.8	177	40.6	
The manager supports my personal promotion	No	105	26.5	163	37.4	< 0.001
	I am not sure	100	25.3	117	26.8	
	Yes	191	48.2	156	35.8	
My immediate supervisor has good personal qualities	No	46	11.6	110	25.2	< 0.001
	I am not sure	74	18.7	82	18.8	
	Yes	276	69.7	244	56.0	
I am satisfied with my income	No	291	73.5	329	75.5	0.307
	I am not sure	43	10.9	54	12.4	
	Yes	62	15.6	53	12.1	
My institution provides good working conditions	No	125	31.5	159	34.1	0.110
	I am not sure	93	23.5	112	24.6	
	Yes	178	45.0	165	41.3	
There is a cooperative working environment in my institution	No	78	19.7	137	31.4	< 0.001
	I am not sure	125	31.6	132	30.3	
	Yes	193	48.7	167	38.3	
My institution provides me opportunities for continuous improvement	No	99	25.0	165	37.8	< 0.001
	I am not sure	104	26.3	108	24.8	
	Yes	193	48.7	163	37.4	
My institution guarantees job security to employees	No	70	17.7	123	28.2	0.002
	I am not sure	117	29.5	113	25.9	
	Yes	209	52.8	200	45.9	
The manager provides me constant support at work	No	68	17.2	127	29.1	< 0.001
	I am not sure	82	20.7	105	24.1	
	Yes	246	62.1	204	46.8	
The manager allows me independence in routine tasks	No	43	10.9	83	19.1	< 0.001
	I am not sure	57	14.4	86	19.7	
	Yes	296	74.7	267	61.2	
My institution provides current equipment	No	108	27.3	128	29.4	0.525
	I am not sure	99	25.0	95	21.8	
	Yes	189	47.7	213	48.8	
My institution rewards employees for exceptional work	No	210	53.0	279	64.0	0.003
	I am not sure	90	22.7	86	19.7	
	Yes	96	24.3	71	16.3	
The manager is qualified to supervise my work	No	54	13.6	106	24.3	< 0.001
	I am not sure	74	18.7	81	18.6	
	Yes	268	67.7	249	57.1	

Table 3

Correlation between the significance of work motivation factors of urban health workers (n = 396) and the level of their fulfillment (job satisfaction) provided by their health institution

Work motivation factors of urban health workers	The mean significance/ motivation score ($\bar{x} \pm SD$)	The mean fulfillment/ satisfaction score ($\bar{x} \pm SD$)	*t*-test (p)*	Spearman's ρ (p)†
Goals of my institution	3.90 ± 1.18	3.58 ± 1.33	4.845 (< 0.001)	0.382 (< 0.001)
Professional recognition	3.66 ± 1.39	3.48 ± 1.39	2.427 (0.016)	0.425 (< 0.001)
Good interpersonal relationships	4.01 ± 1.18	3.56 ± 1.19	6.865 (< 0.001)	0.347 (< 0.001)
Promotion and advancement	3.40 ± 1.42	3.27 ± 1.35	1.838 (0.067)	0.381 (< 0.001)
Personal qualities of immediate supervisors	3.83 ± 1.21	3.89 ± 1.17	1.104 (0.270)	0.485 (< 0.001)
Income	3.13 ± 1.67	1.90 ± 1.28	14.133 (< 0.001)	0.302 (< 0.001)
Working conditions	3.46 ± 1.40	3.13 ± 1.36	4.880 (< 0.001)	0.506 (< 0.001)
Cooperative working environment	3.75 ± 1.18	3.37 ± 1.14	7.037 (< 0.001)	0.525 (< 0.001)
Training opportunities	3.67 ± 1.37	3.31 ± 1.33	5.071 (< 0.001)	0.427 (< 0.001)
Job security	4.11 ± 1.13	3.48 ± 1.20	10.658 (< 0.001)	0.415 (< 0.001)
Support by supervisors	3.92 ± 1.20	3.64 ± 1.22	5.115 (< 0.001)	0.531 (< 0.001)
Autonomy in the workplace	3.93 ± 1.18	3.97 ± 1.14	0.742 (0.459)	0.437 (< 0.001)
Current equipment	3.66 ± 1.33	3.20 ± 1.35	6.965 (< 0.001)	0.484 (< 0.001)
Rewards for exceptional work	3.70 ± 1.46	2.45 ± 1.43	15.644 (< 0.001)	0.357 (< 0.001)
Professional supervision	3.63 ± 1.24	3.84 ± 1.20	3.442 (0.001)	0.483 (< 0.001)

***Level of significance *p* – Student *t*-test for associated samples; †Level of significance *p* – Spearman's rank correlation coefficient.**

Table 4

Correlation between the significance of work motivation factors of rural health workers (n = 436) and the level of their fulfillment (job satisfaction) provided by their health institutions

Work motivation factors of rural health workers	The mean significance/ motivation score ($\bar{x} \pm SD$)	The mean fulfillment/ satisfaction score ($\bar{x} \pm SD$)	*t*-test (p)*	Spearman's ρ (p)†
Goals of my institution	3.52 ± 1.24	3.29 ± 1.41	3.448 (0.001)	0.454 (< 0.001)
Professional recognition	3.25 ± 1.49	3.17 ± 1.45	1.189 (0.235)	0.499 (< 0.001)
Good interpersonal relationships	3.60 ± 1.41	3.00 ± 1.33	9.763 (< 0.001)	0.510 (< 0.001)
Promotion and advancement	3.09 ± 1.43	2.86 ± 1.38	3.469 (0.001)	0.498 (< 0.001)
Personal qualities of immediate supervisors	3.59 ± 1.33	3.48 ± 1.43	1.854 (0.064)	0.588 (< 0.001)
Income	2.74 ± 1.62	1.76 ± 1.16	11.908 (< 0.001)	0.320 (< 0.001)
Working conditions	3.25 ± 1.35	2.89 ± 1.33	5.652 (< 0.001)	0.487 (< 0.001)
Cooperative working environment	3.45 ± 1.28	2.99 ± 1.24	8.087 (< 0.001)	0.516 (< 0.001)
Training opportunities	3.23 ± 1.42	2.89 ± 1.40	5.000 (< 0.001)	0.475 (< 0.001)
Job security	3.80 ± 1.25	3.21 ± 1.33	10.063 (< 0.001)	0.523 (< 0.001)
Support by supervisors	3.52 ± 1.39	3.18 ± 1.38	6.027 (< 0.001)	0.612 (< 0.001)
Autonomy in the workplace	3.64 ± 1.26	3.61 ± 1.32	0.609 (0.543)	0.480 (< 0.001)
Current equipment	3.52 ± 1.34	3.18 ± 1.35	6.208 (< 0.001)	0.588 (< 0.001)
Rewards for exceptional work	2.99 ± 1.58	2.07 ± 1.30	12.314 (< 0.001)	0.421 (< 0.001)
Professional supervision	3.53 ± 1.32	3.49 ± 1.43	3.881 (< 0.001)	0.474 (< 0.001)

***Level of significance *p* – Student *t*-test for associated samples; †Level of significance *p* – Spearman's rank correlation coefficient.**

There were significantly more motivated respondents among urban health professionals (91.6%), and unmotivated among rural respondents (26.8%) (Table 5).

The logistic regression model among all health workers, which proved to be statistically significant, included profession, years of experience and place of employment (Table 6). The probability of being unmotivated was four times higher in nurses compared to physicians [OR 4.051, CI 95% (1.306, 12.568), $p = 0.015$]. With each year of employment the probability of being unmotivated increased by 1.062 [CI 95% (1.016, 1.110), $p = 0.008$]. The probability of being unmotivated was 3.835 times higher in rural health workers than in urban health professionals [CI 95% (1.602, 9.182), $p = 0.003$]. Gender and age were not statistically significant predictors of motivation. The logistic regression model which included only health workers from urban area did not show a statistically significant impact of independent variables (gender, age, profession, years of experience) on the motivation of health workers. The logistic regression model which included only health workers from rural area showed that only years of experience had a statistically significant effect on the motivation of health workers (Table 7). With each year of employment the probability of being unmotivated in rural health workers increased by 1.057 [CI 95% (1.004, 1.113), $p = 0.033$].

Discussion

Our investigation shows that in regard to rural health professionals, urban health workers of Central Serbia were significantly more motivated by all examined work motivation factors except for working conditions and current equipment. The results of the study conducted by Mathauer and Imhoff [19] show that place of work is an important factor that influences work motivation factors of health workers. The same study confirms that non-financial benefits and other tools of human resource management in practice (work supervision, recognition and respect from the supervisors, education and professional advancement opportunities, participation in decision making and teamwork promotion) play an important role in improving work motivation of health workers in rural areas [19]. The study conducted in urban and rural areas in Mali shows that factors which affect motivation of health workers are: responsibility, income, further training, responsibility taking and appreciation [20]. The most common reasons for the lack of motivation are: lack of supplies and recognition, difficult living conditions, no job description, subjective performance appraisal [20]. The study performed in the rural area of Papua New Guinea shows that the most important predictors of job satisfaction among rural nurses are work environment and supportive supervisors, confirming the importance of personnel management in maintaining motivation of rural health workers and thus providing high quality health care as well [21]. Researchers conducted in Slovenia (Maribor, Celje, Slovenj Gradec and Murska Sobota) show that job satisfaction of nursing professionals is most affected by the following motivation factors: good interpersonal relations, followed by pay, favorable supervisor feedback, advancement and education opportunities, supervisor support, good working conditions, a responsible and

Table 5

Urban/rural distribution of health workers in the region of Central Serbia in terms of motivation

Motivational category	Urban area		Rural area		Total	
	n	%	n	%	n	%
Motivated	98	91.6	60	73.2	158	83.6
Unmotivated	9	8.4	22	26.8	31	16.4
Total	107	100.0	82	100.0	189	100.0

$\chi^2 = 11.485$; $p < 0.001$.

Table 6

Dependent variables and their impact on the motivation of health workers regardless of the place of employment

Dependents variables	B	*p*	OR	95% CI for OR lower limit−upper limit
Profession	1.399	0.015	4.051	1.306−12.568
Years of experience	0.060	0.008	1.062	1.016−1.110
Place of employment	1.344	0.003	3.835	1.602−9.182
Constant	-4.625	0.000	0.010	

OR – odds ratio; CI – confidence interval.

Table 7

Dependent variables and their impact on the motivation of health workers in rural area

Dependents variables	B	*p*	OR	95% CI for OR (lower limit−upper limit)
Years of experience	0.056	0.033	1.057	1.004−1.113
Constant	-2.109	0.001	0.121	

OR – odds ratio; CI – confidence interval.

challenging job, autonomy at work, and more free time [22]. The results of a research conducted at the Clinical Center of Banja Luka, show that factors that managers could apply in order to motivate employees to make an extra effort at work include better pay, adequate rewards, better working conditions and less stress; recognition and appreciation of expertise; better organizational climate and understanding; better organization, teamwork and adequate workload; fair work environment; adequate equipment and space; education, personal development and advancement; managerial competencies [23]. In the town of Niš, job satisfaction of health workers depends, among other things, on personal characteristics (opportunities to make friends and meet people) [24].

In our study, in relation rural health professionals, urban health workers were significantly more satisfied with the management support, recognition they receive from their managers, good interpersonal relationships, support from supervisors to get a promotion or a better job, good personal qualities of their immediate supervisors, cooperative working environment, opportunities for continuous improvement provided by their institution, job security, support from immediate supervisors, independence in routine tasks, rewards for exceptional work and professional supervision. Place of work is an important factor that affects job satisfaction of health workers [15]. Studies show that working in urban areas is not a necessary prerequisite for higher level of job satisfaction among health professionals [15, 16]. According to the study conducted in China, health professionals are most satisfied with their professional relationships, followed by patients' appreciation, relationship with the management, working conditions, environment, workload, awards and training opportunities [25]. Data on health workers employed at health centers in Belgrade show that they are satisfied with cooperation within their services, cooperation with colleagues from other departments, training and advancement opportunities, working conditions and work organization, extent to which their work is appreciated, their professional contributions to the institution, being informed about current issues at their departments, as well as with the possibility of presenting their ideas and questions to their supervisors [26]. The most common reasons for job dissatisfaction included low income, and to a lesser extent status at the department, the amount of paperwork and poor interpersonal relations [26]. Nikić et al. [5] conducted a survey at the Clinical Center Niš that shows that most health workers found their job to be stimulating and interesting, but that they work very hard. The same research shows that health workers are dissatisfied with their influence on the organization of work and working conditions [5]. Most health workers taking part in the survey say they have adequate cooperation with colleagues in the team [5]. In health care facilities of the Kolubara District employees are most satisfied with direct collaboration with colleagues and autonomy at work, and most dissatisfied with their monthly income [27]. The results of a study conducted by the Institute of Public Health of Serbia show that about half of the health workers employed in health institutions of the Republic of Serbia are satisfied with their job [28]. Employees are least satisfied with the equipment, opportunities for training and promotion, and monthly salary [28]. The highest job satisfaction is found in health workers in Kosovo and Metohija, then in Central Serbia and Vojvodina, while employees of health institutions in Belgrade show lowest job satisfaction [28]. The study conducted in Slovenia shows that nurses are most satisfied with their job and collaboration with colleagues and least satisfied with their salary and care for employees [22]. Another study conducted in Slovenia shows that nursing managers often use inappropriate management methods, pointing out that only managers who can adjust their way of work with current situations and employees are effective and successful [29]. Skela-Savič and Pagon [30] point out that doctors and nurses in Slovenia assess their level of involvement in teamwork as very low, pointing to the need for greater involvement of health professionals in teamwork. In the city of Split, the total job satisfaction of physicians is not high [31]. The same study shows that physicians are most satisfied with the management of institutions, then working conditions, their superiors, working hours and wages, while they are least satisfied with their free time, opportunities for professional advancement and job security [31].

Results of our research show that urban health professionals were significantly more motivated than job satisfied concerning the following work motivation factors: goals of my institution, professional recognition, good interpersonal relationships, income, cooperative working environment, working conditions, job security, support by supervisors, current equipment and rewards for exceptional work. Rural health professionals were significantly more motivated than job satisfied concerning the following work motivation factors: goals of my institution, good interpersonal relationships, promotion and advancement, income, cooperative working environment, working conditions, training opportunities, job security, support by supervisors, current equipment, rewards for exceptional work and professional supevision. The study conducted in Germany and the USA confirms that if average work motivation levels are compared with the average level of their fulfillment, physicians are significantly more motivated by several work motivation factors in regard to the level of their fulfillment (job satisfaction) by their health facilities [3]. Their gathered results show that physicians in Germany are significantly more motivated by reducing time-related work burden, financial incentives, participation in organization of health care processes, furthering academic careers, cooperation with the management and administration, continuous medical education, career opportunities, cooperation with nursing staff, job security and work environment in regard to the level of their fulfillment [3]. The same study shows that physicians in the USA are significantly more motivated by financial incentives, cooperation with the management and administration, reducing time-related work burden, administrative activities, work environment, cooperation with nursing staff, state-of-the-art equipment, participation in integrated delivery approaches, participation in organization of health care processes and nonfinancial incentives, than they are satisfied with fulfillment of these factors (job satisfaction) by their institutions [3]. A research conducted in the Tuzla Health Center [32] compares the most important motivational fac-

tors to health care workers and the level of their fulfillment by the institution they work for. The results of this study show that the most important work motivation factors are least satisfied by their institution: good salary, job security, career advancement and autonomy in workplace [32]. This study suggests that the Tuzla Health Center does not fully meet certain motivational factors, mostly basic to the employees (good salary, job security, career advancement, autonomy in workplace), and it is necessary to create work motivation strategies, since only motivated workers can achieve the goals of health facilities (quality health care and user satisfaction) [32].

Our study has several limitations. It was a cross-sectional study, examining the current situation, preventing us from studying changes over time and making causal conclusions. Also, limitations of this study are associated with the instrument used for data collection. The researchers point out that during investigating work motivation and job satisfaction in health care facilities, one of the most common problems in practice is employees' fear from unwanted consequences (to get into an uncomfortable or undesired position by answering work-related questions) [33, 34]. Given that evaluation of job satisfaction is a challenging test for institutions, particularly for the management, including opinions and attitudes of employees on specific aspects of work, researchers have tried to reduce the fear of unwanted consequences by emphasizing the anonymity of the questionnaire, and promise that the results will be used only for research purposes and will not be available to managers [33, 34]. However, the reliability of answers cannot be determined [33]. We also used anonymous questionnaire in our research, but we are sure that we did not get completely honest answers, given that even the overall opinion on work motivation and job satisfaction in an institution represents some kind of danger to employees in terms of their relations with the management [35]. Also, by using subjective measuring instruments, reality is perceived from the perspective of the participants, and not as objective reality. Respondents were asked to complete a 5-point Likert scale on the significance of work motivation factors and the level of job satisfaction, so another limitation is the central tendency bias, as respondents avoid extreme response categories, and gave answers somewhere towards the middle of the scale. Finally, a limitation of the study is the fact that it included health professionals from two health centers in urban area and two health centers in rural area, so the results cannot be generalized to all health workers in the Republic of Serbia.

Aiming at monitoring and improving the quality of work in health care facilities and increase patients' satisfaction, it is of essential importance to continuously study job satisfaction and work motivation factors of all health professionals. This has to be performed on a representative sample of health workers, in urban as well as in rural areas of the Republic of Serbia, with constant result analysis. It is of utmost importance to undertake measures to improve employees' work motivation and job satisfaction and implement continuing education for all management levels in health care institutions in the field of human resource management.

Conclusion

Urban health professionals are significantly more motivated and job satisfied than rural health workers. In order to increase the level of work motivation and job satisfaction of health workers in rural areas, apart from better income, they should get more assistance and support from their supervisors, and awards for good job performance; interpersonal relationships, promotion and advancement opportunities, managerial performance and cooperation at work should be improved; employment security should be provided, as well as more independence at work, with professional supervision of health workers.

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Received on July 15, 2014.
Revised on April 28, 2015.
Accepted on April 30, 2015.
Online First April, 2016.

ORIGINAL ARTICLE

UDC: 57.085.2::616.314-089.843
DOI: 10.2298/VSP141208041M

Effect of surgical drill guide and irrigans temperature on thermal bone changes during drilling implant sites – Thermographic analysis on bovine ribs

Uticaj hirurškog stenta i temperature irigansa na termičke promene u kosti tokom preparacije ležišta implantata – termografska analiza na govođim rebrima

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Abstract

Background/Aim. During drilling implant sites, mechanical energy is converted into thermal one resulting in transient rise in temperature of surrounding bone. The temperature of 47°C exeeding one minute impairs osseointegration, compromises mechanical properties of the local bone and could cause early implant failure. This *in vitro* study aimed to assess the effect of surgical drill guide and temperature of irrigans on thermal changes of the local bone during drilling implant sites, and to test the influence of irrigans temperature on the temperature of surgical drill guide. **Methods.** A total of 48 specimens obtained from bovine ribs were randomly allocated to four experimental conditions according to the 2 × 2 factorial design: drill guide (with or without) and saline (at 25°C or 5°C). Real-time infrared thermography was used as a method for temperature measurement. The primary outcome was bone temperature change during drilling implant sites measured at 3 osteotomy depths, whereas the second one was change in the temperature of the drill guide. Data were analyzed by Brunner and Langer nonparametric analysis and Wilcoxon test. **Results.** The effect of drill guide on the changes of bone temperature was significant at the entrance of osteotomy, whereas the effect of saline temperature was significant at all osteotomy levels ($p < 0.001$). No significant interaction was found ($p > 0.05$). Guided surgery and irrigation with saline at 25°C were associated with the highest bone temperature increase. Increase in drill guide temperature was significantly higher when saline at 25°C was used ($p < 0.001$). **Conclusion.** Guided implant site preparation generates higher temperature of the local bone than conventional drilling, not exceeding the threshold for thermal bone necrosis. Although saline at room temperature provides sufficient heat control during drilling, cooled saline is more effective regardless the use of surgical drill guide.

Key words:
dental implants; irrigation; temperature; bone and bones; stents.

Apstrakt

Uvod/Cilj. Tokom preparacije ležišta za implantat mehanička energija pretvara se u toplotnu, što dovodi do prolaznog povišenja temperature okolne kosti. Temperatura od 47°C tokom više od jednog minuta narušava oseointegraciju, mehaničke osobine lokalne kosti i može dovesti do ranog neuspeha implantata. Cilj ove *in vitro* studije bio je da se ispita uticaj hirurškog stenta i temperature irigansa na termičke promene u kosti tokom preparacije ležišta za implantat, kao i uticaj temperature irigansa na temperaturu hirurškog stenta. **Metode.** Ukupno 48 uzoraka dobijenih od govođih rebara bilo je podeljeno metodom slučajnog izbora u četiri grupe prema 2 × 2 faktorskom dizajnu: prisustvo hirurškog stenta (da/ne) i temperatura fiziološkog rastvora (25°C/5°C). Temperatura je merena infracrvenom termografijom u realnom vremenu. Primarni ishod bio je promena temperature kosti tokom preparacije ležišta implantata merena na tri dubine ležišta, a sekundarni ishod promena temperature hirurškog stenta. Podaci su analizirani Bruner-Langer neparametrijskom analizom i Vilkoksonovim testom. **Rezultati.** Uticaj hirurškog stenta na promenu

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temperature kosti bio je značajan na ulazu u ležište za implantat, dok je uticaj temperature irigansa bio značajan na svim dubinama ležišta ($p < 0,001$). Međusobni uticaj ispitivanih faktora nije bio značajan ($p > 0,05$). Upotreba hirurškog stenta i ispiranje fiziološkim rastvorom temperature 25°C bili su praćeni najvišim porastom temperature kosti. Porast temperature hirurškog stenta bio je značajno viši kada je korišćeno ispiranje na temperaturi od 25°C ($p < 0,001$). **Zaključak.** Tokom kontrolisane preparacije ležišta za implantat došlo je do većeg zagrevanja kosti u poređenju sa standardnom preparacijom, ne premašujući temperaturu kritičnu za termičku nekrozu kosti. Iako ispiranje na sobnoj temperaturi obezbeđuje dovoljno hlađenja kosti tokom preparacije ležišta za implantat, ohlađeni rastvor za ispiranje je efikasniji bez obzira na primenu hirurškog stenta.

Ključne reči:
implanti, stomatološki; lavaža; temperatura; kost; stentovi.

Introduction

During drilling implant sites, mechanical work energy is converted into thermal resulting in transient rise in temperature of the surrounding bone [1]. The response of bone tissue to the generated heat depends on the temperature achieved and time of exposure [2]. The temperature of 47°C exceeding 1 minute impairs osseointegration, compromises mechanical properties of the local bone and therefore, it is considered to be a factor of early implant failure [3–6].

The use of surgical drill guides increases the accuracy of implant placement in a required 3D position and reduces the surgical error; however, it generates higher local bone temperature than conventional drilling [7–11]. Bone temperature increase is particularly emphasized when guided surgery for dental implants is associated with flapless approach or reused drills [9,10].

Irrigation of the bone-drill interface with sterile saline is a central strategy in the prevention of bone overheating during drilling implant sites [12]. It eliminates heated bone chips from the osteotomy and reduces friction during drilling, thus contributing to decreased generation of the frictional heat [13]. Saline at room temperature can provide sufficient cooling during conventional drilling, although in dense cortical bone or at high rotational speed deleterious bone temperatures might be generated [14]. Cooled saline is proved to be more effective when drilling without the surgical guide [15].

The effect of saline temperature on heat control in guided surgery is unknown. Inability of direct irrigation of the active drill tip together with friction between metal sleeve and drill periphery seems to contribute to great heat generation expected when drill guide is used. It might be hypothesized that cooled irrigans would reduce conduction of frictional heat generated at the drill-sleeve interface to the adjacent bone more than irrigans at room temperature and therefore lower bone temperature increase could be expected. The aim of this *in vitro* study was to assess the effect of surgical drill guide and temperature of irrigans on thermal changes of the local bone during drilling implant sites, and to test the influence of irrigans temperature on the temperature of surgical drill guide.

Methods

This *in vitro* study was performed at the Faculty of Dentistry, University of Belgrade, Serbia in June and July 2014 after receiving permission from the authorized Ethical Committee (No. 36/9).

Bone specimens

Bovine ribs, obtained from male animals 9 months old and 180 kg weight, were used to simulate human jaw bone. All specimens were collected from the local butcher shop and were of already slaughtered animals. Samples with the same thickness (2 mm) of cortical bone and overall height of at least 15 mm were selected to provide uniform experimental conditions [16]. The residual soft tissue was removed and bovine ribs were cut into 25 mm length blocks that were numbered. A total of 48 specimens were obtained from 4 bovine ribs. Two factors, each with 2 levels, were tested in this experiment: surgical drill guide (with or without) and saline temperature (at room temperature of 25°C or cooled at 5°C). Each rib was divided into 3 parts and each part was cut into 4 specimens which were randomly assigned to 1 of 4 experimental conditions using computer generated random numbers. For 24 specimens that simulated guided surgical approach, surgical drill guides were made. Impression of bone specimen was taken using silicone material and plaster cast was prepared. It was coated by 2 mm layer of red wax that simulated soft tissue. Surgical drill guide was made from the self-curing acrylic material designed for surgical templates (3D-resin, Bredent, Senden, Germany). This material was adopted over the wax layer and inner sleeve with diameter of 2.39 mm (SKYplanX drill sleeve, Bredent, Senden, Germany) was locked into outer guiding sleeve and together were embedded into a guide, at a constant distance of 5 mm from the bone specimen periphery as measured by the calliper (Figure 1). The remaining 24 control specimens were covered by only 2 mm thick layer of red wax to simulate soft tissue in flapless surgical approach. To maintain the thermophysical properties, specimens not used within few hours were prepared according to the guidelines established by Sedlin and Hirsch [17], i.e. the specimens were kept moist in saline solution and stored at 10°C.

Temperature measurement system

Real-time infrared thermography was used as a method of bone temperature measurement. Bone temperature was measured by the infrared thermographic camera Varioscan R high resolution 3021 (Jenoptik, Dresden, Germany) (Figure 2).
It detected infrared radiation from the surface of the bone that was directed by the lens system toward the photo-sensor where its energy was transformed into electrical impulses that provided visualization of bone temperature values on the

Fig. 1 – Bone specimen – cross-sectional view of the specimen simulating guided surgery.

Fig. 2 – Experimental set-up – cross-sectional specimen's surface exposed to infrared camera.

display as a range of colours. The thermal resolution of camera was ± 0.03°C, temperature range from -40°C to 1,200°C and spectral range 8–12 µm. The range of temperatures on the thermogram was shown as a band with different shades of different colours. The obtained thermograms were processed by IRIBIS software [18] (Figure 3).

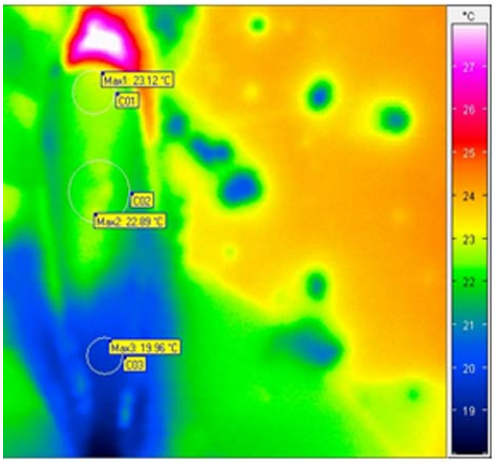

Fig. 3 – Thermogram processed by IRIBIS software. The range of temperatures on thermogram shown as a band with different shades of different colours.

Experimental protocol

All measurements were realized at the cross-sectional area of the specimen, 5 mm away from the drill sleeve. This surface of specimen was covered with a layer of graphite spray of 0.95 emissivity in order to annul the difference between the cortical and spongy bone layers. Each prepared specimen was fixed in a clamp with cross-sectional surface exposed to infrared camera that was at a distance of 0.8 m (Figure 2). The surface that was used for the measurement was isolated from the irrigans by cofferdam since a fluid might mask the real temperature readings. A bottle of saline was kept during the entire experiment in the thermostable bag to maintain the temperature of the solution. Cardboard shield was used to eliminate the background thermal radiation. All measurements were performed in the same, controlled environmental conditions with a temperature of the operating room between 22°C and 24°C.

In order to eliminate variability in operator-related factors affecting bone temperature during drilling, particularly the applied hand pressure, the same operator performed all the drillings. Conventional dental handpiece (W&H, Burmoos, Austria) was used. Temperature was measured during implant site preparation by pilot drill, designed for computer guided implantology, with the diameter of 2.35 mm and intraosseous length of 13 mm (SKYplanX, Bredent, Senden, Germany). Drill was inserted through corresponding metal sleeve in an intermittent fashion under copious irrigation with saline at the flow rate of 50 mL/min. Excessive saline was aspirated near the site of preparation. The temperature of the saline was adjusted to the experimental condition. The drill speed was 600 rpm. The same drilling parameters were used for osteotomies in the control specimens (conventional drilling).

Temperature measurement started prior to drilling (baseline) and continued up to osteotomy completion. Bone temperature was measured along the entire length of the implant site – especially during drilling at 3 site levels: entrance, middle and bottom. The primary study outcome was bone thermal change counted by subtracking the baseline value from the maximum value recorded during drilling and was calculated for all 3 implant site levels. The secondary study outcome was change in the temperature of the drill guide calculated as the difference between the maximum value recorded during drilling and the baseline value. The outcome assessor was blind to the temperature of the saline but not to the surgical approach (guided or conventional) since the outline of the stent could be visualized on thermograms. Statistician was completely blind to the allocation of the intervention.

Statistical analysis

Data were analyzed in R statistical software (The R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics was performed with a measure of central tendency (mean and median) and measure of dispersion (min, max, standard deviation). The normality of data distribution was checked by 1-sample Kolmogorov–Smirnov test.

Effects of surgical drill guide (with *vs* without), temperature of the saline (at room temperature of 25°C *vs* cooled at 5°C) and their interaction on the changes in the temperature of the local bone were assessed by Brunner and Langer nonparametric analysis of longitudinal data. One analysis for each osteotomy level was carried out. Two-sided *p*-values < 0.05 were considered as statistically significant.

The difference in changes of the temperature of the surgical drill guide during drilling with saline at room temperature of 25°C versus cooled saline at 5°C as irrigans was analysed by Exact Wilcoxon signed rank test for paired samples and previously the Cabilio-Masaro test of symmetry was run. One-sided *p*-value < 0.05 was considered as statistically significant.

A correlation between the temperature of the surgical drill guide and the temperature of bone at the implant site entrance was tested by Spearman's rank correlation coefficient.

Results

All the temperature increases recorded in this study were in the physiological range (Table 1, Figure 4). The maximal temperature increase was 7.48°C and it was recorded in one specimen at the entrance of the prepared implant site when surgical drill guide was used together with saline at room temperature. The mean increase in bone temperature was decreasing with increasing depth of the site for all experimental conditions except when conventional drilling was used under cooled saline (Figure 4).

At the entrance of the preparation, the use of surgical drill guide had a significant impact on thermal changes of the adjacent bone (ANOVA-Type Statistc = 30.952; df = 1; $p < 0.001$). Higher bone temperature increases were found when surgical drill guide was used compared to conventional drilling (Figure 4, Table 1). The effect of the saline temperature on bone heating was also significant (ANOVA -Type Statistc = 85.576; df = 1; $p < 0.001$) at this surgical site level, whereas the effect of interaction between the use of surgical drill guide and saline temperature was not significant (ANOVA-Type Statistc = 0.955; df = 1; $p = 0.328$). Irrigation of the surgical site with cooled saline reduced the increase of bone temperature regardless the use of drill guide. When cooled saline was used without drill guide, the values of bo-

Table 1

Descriptive statistics of bone thermal changes (°C) during drilling implant sites with regards to the experimental condition

Site depth	Experimental condition	x̄	SD	Median	Min	Max
Entrance	drill guide + saline at 25°C	3.54	1.87	2.86	1.69	7.48
	no drill guide + saline at 25°C	1.24	0.68	1.44	0.18	2.24
	drill guide + saline at 5°C	0.59	1.32	0.3	-1.87	2.44
	no drill guide + saline at 5°C	-0.37	0.42	-0.30	-1.21	0.31
Middle	drill guide + saline at 25°C	1.73	1.04	1.62	0.02	3.41
	no drill guide + saline at 25°C	1.10	1.16	0.67	0.04	3.40
	drill guide + saline at 5°C	0.16	0.77	-0.03	-0.86	2.05
	no drill guide + saline at 5°C	-0.12	0.36	-0.11	-0.86	0.68
Bottom	drill guide + saline at 25°C	0.95	1.77	0.37	0.00	6.37
	no drill guide + saline at 25°C	0.92	1.19	0.50	0.02	4.46
	drill guide + saline at 5°C	0.25	0.88	-0.01	-0.51	2.28
	no drill guide + saline at 5°C	0.14	1.09	-0.12	-0.69	3.54

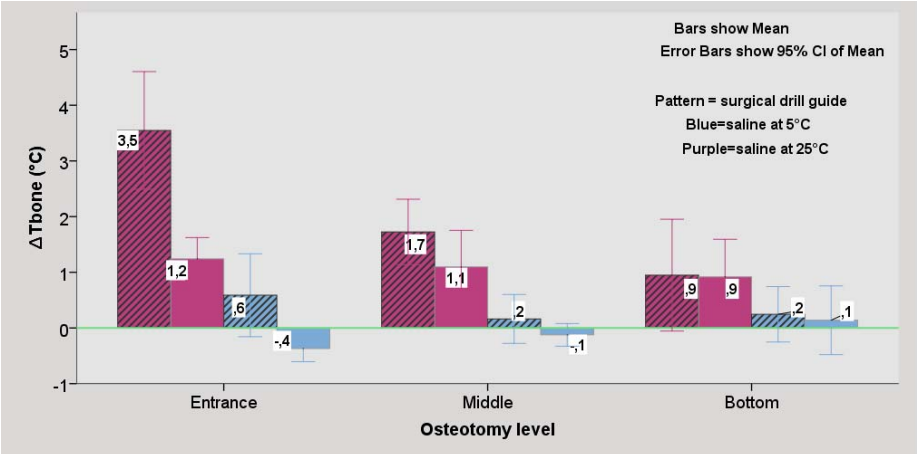

Fig. 4 – Bone termal changes during drilling implant sites with regard to the use of surgical drill guide and saline temperature.

ne temperature recorded during drilling were lower than baseline values, *ie* a decrease of bone temperature was observed (Figure 4, Table 1).

The effect of the saline temperature on bone heating remained significant at the middle osteotomy depth (ANOVA-Type Statistc = 36.814; df = 1; $p < 0.001$) whereas the effect of the surgical drill guide (ANOVA-Type Statistc = 3.637; df = 1; $p = 0.056$), or their interaction (ANOVA-Type Statistc = 0.108; df = 1; $p = 0.742$) were not. Lower bone temperature increase was recorded when irrigation was performed with cooled saline. When conventional drilling was performed under cooled saline, even a decrease of bone temperature comparing to baseline values was observed (Figure 4, Table 1).

Bone thermal changes at the bottom of the surgical site were significantly affected by temperature of the saline used as an irrigans (ANOVA-Type Statistc = 26.064; df = 1; $p < 0.001$), whereas surgical drill guide had no significant influence (ANOVA-Type Statistc = 0.072; df = 1; $p = 0.787$) neither the interaction (ANOVA-Type Statistc = 1.080; df = 1; $p = 0.298$). At this site level, bone temperature increased during drilling under all experimental conditions with the mean increase below 1°C. Lower bone temperature increase was recorded when cooled saline was used compared to saline at room temperature (Figure 4, Table 1).

The median of changes in surgical drill guide temperature during drilling was significantly higher when irrigation was performed with saline at room temperature of 25°C compared to the cooled saline at 5°C ($p < 0.001$; 95% CI for the median difference: 2.785–7.185) (Figure 5 and Table 2).

A correlation between temperature of the surgical drill guide and temperature of the bone at the surgical site entrance was significant, positive and high (Spearman *rho* = 0.868; $p = 0 < 001$). A higher increase in temperature of the surgical drill guide was associated with higher heating of the adjacent bone (Figure 6).

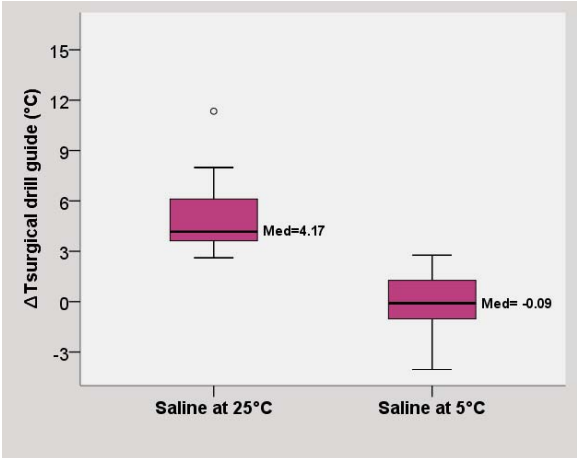

Fig. 5 – Box-plots showing changes of the temperature of drill guide as a function of saline temperature. Data were presented as the median (horizontal line), with the box representing the 75th centiles and whiskers representing the statistical range. Circle was an outlier.

Table 2

Descriptive statistics of temperature changes of surgical drill guide (°C) during drilling implant sites with regard to the temperature of the saline used as an irrigans

Experimental condition	x̄	SD	Median	Min	Max
Saline at 25°C	5.07	2.56	4.17	2.61	11.34
Saline at 5°C	0.02	1.91	-0.09	-4.04	2.77

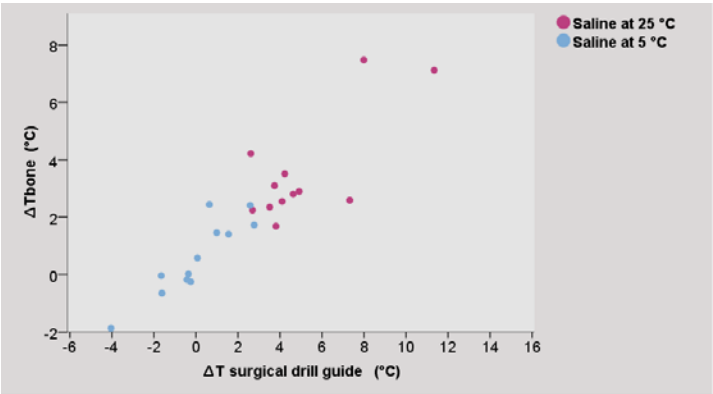

Fig. 6 – Correlation between surgical drill guide temperature and bone temperature at the surgical site entrance.

Discussion

The results of our study indicate higher heat generation during implant site preparation through guided surgical approach compared to conventional drilling. However, neither surgical technique exceeded temperature values critical for thermal bone necrosis. This is in line with data reported in several *in vitro* studies utilizing various bone models and methods of temperature measurement [8–11]. The effect of drill guide use was significant only at the superficial level of the bony walls of the prepared site. This level of the site is susceptible to higher warming than deeper parts due to prolonged exposure to friction forces and higher coefficient of friction of cortical bone layer [2]. Therefore, cortical bone at the implant site entrance requires the most intensive cooling. When no drill guide is used, the irrigans is routed directly to the drill tip where it penetrates the underlying tissues making effective control of heat generation. In the guided surgical approach, metal sleeves limit direct irrigation leading to a significant increase of the adjacent bone temperature. Further, heat generated from the friction of the metallic elements of the surgical drill guide could be conducted to the adjacent superficial bone layer, contributing to the increase of bone temperature. This is supported by a positive correlation between the temperature of the surgical drill guide and the temperature of bone at the site entrance found in our study. On the other hand, in the spongy bone layer of deeper parts of the surgical site, slight bone heating occurs that could be effectively controlled by the limited volume of saline directed through metallic sleeve in the drill guide. In contrast to our results, Misir et al. [8] found significantly higher bone temperatures at all implant site depths when it was prepared by guided drilling compared to standard method of preparation. This discrepancy could be due to exclusively cortical model or high drilling speed used in their study.

Great bone heating associated with the guided surgical approach imposes the need for an effective method of heat control when this technique for implant site preparation is used. Internal irrigation seems beneficial in guided surgery, but its efficiency can be seriously hampered by clogged irrigation point, particularly when dense cortical bone is involved. Higher jaw bone temperatures have been documented *in vitro* when guided implant site drilling was performed with combined irrigation compared to external irrigation only [8]. A forced irrigation through the drill guide using room temperature irrigans at flow rate of 500 mL/min or greater could predictably prevent overheating of the bony walls of the implant site [19]. Regarding block of irrigans flow by metal sleeves as the main concern of guided drilling, it has been recommended to modify drill guide in a way to allow easier access of irrigans to the site of cortex penetration [19]. Our study singled out the use of cooled irrigans as another strategy for the control of the heat generated during drilling implants sites through guided approach. The obtained results indicate that saline at 5°C was more efficient in cooling bony walls of the prepared implant site at all its depths compared to room temperature saline (25°C), regardless the surgical method used. When conventional drilling was used together with cooled saline, the temperature of the bone that surrounds superficial parts of the site was even decreasing to the level below the baseline values. Effective cooling of bone at deeper parts of the site when guided surgery is performed indicates that intermittent movements during drilling might compensate limited access of irrigans due to narrow space between the drill sleeve and drill itself.

According to our data, the use of irrigans cooled at 5°C during implant site drilling *via* the guided approach might be advantageous due to adequate control of adjacent bone temperature. However, when choosing a temperature of the irrigans in the clinical setting, the effect of cooled saline on nerves, vessels or other structures should also be considered [20]. Histological data [21] have shown higher osteoblast activity and greater increase in bone marrow dynamics when implant sites are drilled under saline at 4°C compared to 25°C. Rapid bone healing associated with the use of cooled saline has also been documented histomorphometrically, although irrigans temperature did not have any impact on the amount of newly formed bone [21].

Our study has several limitations. Fluid movement and water rate might dissipate some heat during drilling, but infrared thermography, limited us to measure bone temperature in dry conditions since a fluid might mask the real temperature value impairing the accuracy of measurement [22]. The difference in thermal conductivity between bovine ribs and human jaw bone, as well as between the red wax and oral soft tissues presents another limitation of this study.

We employed the flapless approach to test the effects of surgical drill guide and irrigans temperature on bone thermal changes during drilling implant sites. It was chosen because in clinical settings guided drilling is usually associated with implant placement without raising a flap, the benefit of which is minimal invasiveness of the procedure. At the same time it is the worst scenario from the thermal point of view, because there is a double barrier to fluid flow: drill guide and underlying soft tissue. Migliorati et al. [9] showed insignificant difference in temperature increase between flapless guided surgery and flap guided surgery. Bone temperature in our study was measured during drilling with the pilot drill, since its use is mandatory for guided surgery, whereas following drills, with increasing diameters, might be used after the removal of the drill guide. Also, it is expected that this drill generates the highest bone temperature increase during drilling due to small flutes that limit irrigation together with higher pressure of the drill tip on the adjacent tissue [11].

Conclusion

Guided implant site preparation generates higher temperature of local bone than conventional drilling, but not exceeding a threshold for thermal bone necrosis. Although saline at room temperature provides sufficient heat control during drilling, cooled saline was more effective regardless the use of surgical drill guide. The temperature of the surgical drill guide was reduced when cooled saline was used as an irrigans during drilling implant sites.

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Received on December 8, 2014.
Revised on May 6, 2015.
Accepted on May 18, 2015.
Online First March, 2016.

ORIGINAL ARTICLE

UDC: 613.99:618.5-089.888.61
DOI: 10.2298/VSP150428055E

Major risk factors of maternal adverse outcome in women with two or more previous cesarean sections

Faktori rizika sa najvećim uticajem na maternalni morbiditet kod žena sa dva ili više ponovljenih carskih rezova

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Abstract

Bacground/Aim. Maternal morbidity is defined as any condition that is attributed to or aggravated by pregnancy and childbirth that has a negative impact on the woman's wellbeing. In recent years, a growing trend of cesarean section rates can be seen throughout the world. The aim of this study was to assess factors that might have major impact on maternal adverse outcome in women with two or more previous cesarean sections. **Methods.** This retrospective study included women with single term pregnancy after two or more cesarean deliveries in a 10-year period (2004−2013) in the University Clinic "Narodni front" in Belgrade, Serbia. Medical records were reviewed for clinical data for maternal intraoperative and early postoperative complications regarding gestational age at delivery, the number of previous cesarean sections and mode of surgery (elective or emergency). **Results.** A total of 551 patients were included in the study. At 37 completed weeks delivered 14.1%, at 38 delivered 45.2% and at 39 completed weeks 40.7% patients. Women younger than 35 years more often delivered after 39 completed weeks compared with those over 35 years (69.2% *vs* 30.8%, $p < 0.05$). The overall rate of maternal complications in the study group was 16.5% with no statistical difference by gestational age at delivery. The overall rate of maternal adverse outcome was significantly less in the patients with three as compared with those with four or more cesareans (10.4% *vs* 66.7%, $p < 0.05$). There was a statistically significant difference between these groups of women regarding complications: scar dehiscence, the presence of adhesions, blood transfusion and admission in intensive care unit. Elective cesarean delivery was with less maternal complications compared with emergency cesarean deliveries (12.9% *vs* 27.3%, $p < 0.05$). **Conclusion.** Termination of pregnancy before completed 39 weeks does not decrease maternal morbidity. The major impact on maternal complications has the number of previous cesarean deliveries (≥ 3), as well as emergency cesarean section. Patients should be informed about potential risks for maternal health with increasing number of cesarean deliveries, especially after the first cesarean section when counseling in elective repeat cesarean *vs* trial of labor.

Key words:
cesarean section; morbidity; risk factors; obstetric labor complications; fetal development.

Apstrakt

Uvod/Cilj. Maternalni morbiditet se definiše kao svako stanje koje se pripisuje ili je otežano trudnoćom i porođajem i ima negativan uticaj na blagostanje žene. Poslednjih godina može se uočiti rastuća tendencija stope carskih rezova širom sveta. Cilj rada bio je procena faktora koji najviše utiču na maternalni morbiditet kod žena koje su imale dva ili više carskih rezova. **Metode.** Retrospektivnom studijom obuhvaćene su žene sa jednoplodnom, terminskom trudnoćom posle 2 ili više carskih rezova u desetogodišnjem periodu (1. 1. 2004 − 31. 12. 2013) na Univerzitetskoj ginekološko-akuserškoj klinici "Narodni front". Iz protokola i istorija porođaja dobijeni su podaci o intraoperativnim i ranim postoperativnim komplikacijama u odnosu na gestacijsku starost na porođaju, broj prethodnih carskih rezova i hitnost operacije. **Rezultati.** Ulazne kriterijume ispunila je 551 žena. Sa navršenih 37 nedelja gestacije završeno je 14,1% trudnoća, sa 38 nedelja gestacije 45,2%, a posle navršenih 39 nedelja gestacije 40,7% trudnoće. Žene mlađe od 35 godina značajno češće su porađane posle 39. nedelje nego žene starije od 35 godina (69,2% *vs* 30,8%, $p < 0,05$). Ukupna incidencija svih maternalnih komplikacija u ispitivanoj grupi iznosila je 16,5%. Nije bilo statistički značajne razlike u morbiditetu u odnosu na gestacijske nedelje u vreme porođaja. Žene sa trećim carskim rezom imale su značajno ređe komplikacije u odnosu na žene sa četvrtim ili više carskih rezova (10,4% *vs*

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66,7%, $p < 0,05$), a najčešće komplikacije bile su: dehiscencija ožiljka, prisustvo adhezija, transfuzije krvi i prijem na intenzivnu negu ($p < 0,05$). Elektivni carski rez bio je udružen sa značajno manje komplikacija nego hitni carski rez (12,9% *vs* 27,3%, $p < 0,05$). **Zaključak.** Završavanje trudnoće pre navršenih 39 nedelja ne snižava značajno maternalni morbiditet. Faktori sa značajnim uticajem na zdravlje majke su broj prethodnih carskih rezova (≥ 3) i hitnost operacije. Trudnice bi trebalo informisati o potencijalnim rizicima po njihovo zdravlje koji se dramatično povećavaju sa brojem carskih rezova, posebno kada se posle prvog carskog reza donosi odluka o ponovnoj operaciji ili probnom vaginalnom porođaju.

Ključne reči:
carski rez; morbiditet; faktori rizika; porođaj, akušerski, komplikacije; trudnoća, razvoj fetusa.

Introduction

The increasing number of cesarean sections (CS) in the last decade (up to 30%) and the decreasing one of vaginal births after CS (less than 10%) emphasize the problem of multiple cesarean deliveries impact on maternal morbidity [1, 2].

There are several significant maternal complications such as: uterine rupture, scar dehiscence, hysterectomy, thromboembolic disease, transfusions, wound infection, maternal death, etc, most of which increased as a trend with increasing number of repeated operations. Even half of cesarean hysterectomies are in women with one or more prior CS [3]. Besides that, as early or immediate complications, more difficult to quantify are late risks for bowel obstructions and pelvic pain from peritoneal adhesive disease, both of which increase with each successive CS [4].

The aim of this study was to determine the impact of scheduled gestational age for planned CS, the number of previous CS and unplanned, emergency CS on short-term maternal adverse outcome in women with two or more previous CSs.

Methods

This retrospective study included all patients who had repeated three or more CS in a 10-year period, from January 1st 2004 to December 31st 2013 in the tertiary medical center, University Obstetric and Gynecology Clinic "Narodni Front" in Belgrade, Serbia. We analysed the data from the patients medical records that included maternal age, parity, gestational age at delivery, neonatal birth weight and 5-minute Apgar score. Adverse maternal outcome included maternal death, the presence of adhesiones, scar dehiscence, uterine rupture, hysterectomy, placenta previa, transfusions, urinary bladder lesions, wound complications and intensive care unit (ICU) admission. Gestational age on delivery was determined in completed weeks of gestation confirmed by early ultrasound, elective CS was planned the day before and unplanned, emergency CS was performed short time after admission in patients who were admitted in labor. Hospital department policy dictated that all patients with two or more CS are ended with CS. Maternal death included only those resulting from complications related to childbirth. Uterine rupture was defined as a complete disruption or tear of the uterine muscles and serosa, while scar dehiscence was defined as uterine muscle disruption but with intact serosa. Wound infection was based on the diagnosis of superficial or deep infection involving the cesarean incision site. Placenta previa, bladder injury and adhesiones were intraoperative findings. Excluded criteria were labor before completed 37 weeks and twin pregnancies. The study group included patients with single, term pregnancies with previous two or more CS. All these patients were divided into 3 groups according to gestational age at birth: 37 to 37 + 6/7 weeks, 38 to 38 + 6/7 weeks, > 39 weeks, to assess the best timing of elective repeat CS at term on the basis of maternal adverse outcome. Maternal complications were assessed on the basis of the number of previous CS and mode of surgery (elective or emergency), as well.

All the patients had transverse, lower segment uterine incision, exept one case of classical incision in the patient with accrete placenta previa followed by hysterectomy.

The data were coded, tabulated and entered into an IBM compatibile computer. The incidence of adverse maternal outcome was calculated for each completed week of gestation at the time of cesarean delivery. Continuous variables were expressed as mean with standard deviation and compared by using the indepedenant Student *t*-test. Discrete variables were expressed as percentages and compared by χ^2 test. The test of significance was set at the 0.05 level. The statistical programs SPSS 17.0 (SPSS Inc., Chicago, IL) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for the data analysis.

The study has been approved by the Institutional Ethical Commitee.

Results

In a 10-year period, from January 1st, 2004 till December 31st, 2013, there were 67,639 deliveries in the University Obstetrics and Gynecology Clinic "Narodni front" Belgrade. In this period of time the incidence of cesarean deliveries increased from 18% in 2004 to 32% in 2013. At the same time the incidence of vaginal births after CS decreased from 13% to 8%. Out of 67,639 deliveries in this period, 16,597 (24.5%) women had cesarean delivery out of which 639 had two prevoius CS (3.85%). Excluded criteria met 76 (11.9%) women with preterm labor and 12 (1.9%) with twin pregnancies. The incidence of premature labor (< 37 weeks) was 12.1% (76/626). The study group was 551 patients with single, term pregnancy after 2 or more previous CS.

Some maternal and neonatal characteristics by gestational age are listed in Table 1. All term pregnancies were divided into 3 groups according to gestational age. In the first group (37–37+6/7) there were 78 (14.1%), in the second (38−38+6/7) 249 (45.2%) and in the third group 224 (40.7%)

Table 1

Maternal and perinatal characteristics of the study population by gestational age at cesarean delivery

Characteristics	Gestational weeks				
	37 – 37+6/7 (n = 78, 14.1%)	38 – 38+6/7 (n = 249, 45.2%)	> 39 (n = 224, 40.7%)	Total (n = 551, 100%)	*p* value χ^2 test
Maternal age (years)					
< 35	44.9 (35)	39.8 (99)	69.2 (155)	52.5 (289)	< 0.05
≥ 35	55.1 (43)	60.2 (150)	30.8 (69)	47.5 (262)	< 0.05
$\bar{x} \pm SD$	34 ± 4.3	38 ± 3.8	31.8 ± 5.4		< 0.05
Emergency cesarean section	21.8 (17)	22.5 (56)	29.5 (66)	25.2 (139)	ns
Prior cesarean delivery					
2	71.8 (56)	73.5 (183)	85.7 (192)	89.1 (491)	ns
≥ 3	23.1 (18)	8.8 (22)	8.9 (20)	10.8 (60)	ns
Birth weight (g)					
≤ 2,499	20 (16)	5 (14)	7 (16)	9 (46)	ns
2,500–3,999	67 (52)	88 (219)	81 (182)	82 (453)	ns
≥ 4,000	13 (10)	7 (16)	12 (26)	10 (52)	ns
Fetal death	0	0.5 (1)	0.5 (1)	0.3 (2)	ns
Apgar 5'					
≤ 7	6.4 (5)	4.8 (12)	2.7 (6)	4.2 (23)	ns
≥ 8	93.6 (73)	95 (244)	97 (218)	95.5 (526)	ns

Data are presented as percentage (number); $\bar{x}$ − mean value; SD – standard deviation; ns – no significant difference.

patients. There were no statistically significant differences among the 3 groups in perinatal characteristics like parity, emergency CS, birth weight, macrosomia, 5 min Apgar score, fetal death, except for maternal age. The patients under 35 years of age were significantly more often delivered after 39 completed weeks compared with those over 35 years (69.2% *vs* 30.8%, $p < 0.05$). The incidence of individual and composite adverse maternal outcomes by gestational age at delivery is shown in Table 2. There were no maternal death and only one hysterectomy in 37 plus weeks due to the accrete placenta previa with excessive bleeding. Overall incidence of maternal adverse outcome was 16.5% and there was no significant difference in composite or individual complications by gestational age at delivery. The incidence of adverse maternal outcome by the number of CS is presented in Table 3. Three or more CS had 60 (10.9%) of the patients: 54 with 3, 5 with 4 and 1 with 5 previous CS. The incidence of all adverse outcomes was much higher in the group with 3 or more CS and the difference was statistically significant (66.7% *vs* 10.4%, $p < 0.05$). Almost all individual complications were more frequent in ≥ 3 group, but a statistically significant difference was obtained in: scar dehiscence, the presence of adhesiones, blood transfusion and ICU admission. The incidence of emergency and elective CS regarding maternal adverse outcome is presented in Table 4. Emergency CS was performed in 139 (25.2%) of the patients and elective in 412 (74.8%) of the patients. The incidence of the composite adverse maternal outcome was higher in the emergency CS group and the difference was statistically significant, but no other individual outcome showed any significant difference.

Table 2

Incidence of adverse maternal outcome by gestational age at cesarean delivery

Maternal complications	Gestational weeks				
	37 – 37+6/7 n = 78	38 – 38+6/7 n = 249	> 39 n = 224	Total n = 551	*p* value χ^2 test
*Composite of all adverse outcome	15.4 (12)	16.5 (41)	17.0 (38)	16.5 (91)	ns
Maternal death	/	/	/	/	/
Hysterectomy	1.3 (1)	/	/	0.28 (1)	ns
Rupture of the uterus	/	0.4 (1)	0.4 (1)	0.4 (2)	ns
Scar dehiscence	1.3 (1)	1.6 (4)	2.7 (6)	1.9 (11)	ns
Placenta previa	1.2 (1)	0.4 (1)	0.4 (1)	0.5 (3)	ns
Bladder injury	/	0.8 (2)	0.4 (1)	0.5 (3)	ns
Blood transfusion (intra- or postpartum)	3.8 (3)	2.1 (5)	3.1 (7)	2.7 (15)	ns
Wound complication	2.6 (2)	2.1 (5)	2.7 (6)	2.3 (13)	ns
Adhesions	3.8 (3)	3.6 (9)	3.1 (7)	3.4 (19)	ns
ICU admission	5.2 (4)	3.6 (9)	4.5 (10)	4.2 (23)	ns
Deep vein thrombosis	/	0.4 (1)	0.4 (1)	0.4 (2)	ns

Data are presented as percentage (number). *Composite of all adverse outcomes: maternal death, hysterectomy, rupture of the uterus, scar dehiscence, placenta previa, bladder injury, blood transfusion, wound complication, adhesions, ICU admission, deep vein thrombosis; ns – no significant difference; ICU − intensive care unit.

Table 3

Incidence of adverse maternal outcomes by number of previous cesarean sections

Maternal complications	Previous cesarean section, % (n)		
	2 89% (491)	≥ 3 10.9% (60)	*p* value χ^2 test
*Composite of all adverse outcome	10.4 (51)	66.7 (40)	< 0.05
Emergency cesarean section	26.7 (131)	13.3 (8)	ns
Maternal death	/	/	/
Hysterectomy	/	2 (1)	/
Rupture of the uterus	0.2 (1)	1.7 (1)	ns
Scar dehiscence	0.8 (4)	11.7 (7)	< 0.05
Placenta previa	0.2 (1)	3.3 (2)	ns
Bladder injury	0.2 (1)	3.3 (2)	ns
Blood transfusion (intra- or postpartum)	2.0 (10)	8.3 (5)	< 0.05
Wound complication	2.2 (10)	5.0 (3)	< 0.05
Adhesions	2.4 (12)	11.7 (7)	< 0.05
ICU admission	2.2 (11)	20 (12)	< 0.05
Deep vein thrombosis	0.2 (1)	1.7 (1)	ns

Data are presented as percentage (number). *Composite of all adverse outcomes: maternal death, hysterectomy, rupture of the uterus, scar dechiscence, placenta previa, bladder injury, blood transfusion, wound complication, adhesions, ICU admission, deep vein thrombosis;
ns – no significant difference; ICU – intensive care unit.

Table 4

The incidence of emergency and elective caesarean section

Maternal complicatins	Cesarean section, % (n)		*p* value χ^2 test
	emergency 25.2% (139)	elective 74.8% (412)	
*Composite of all adverse outcome	27.3 (38)	12.9 (53)	< 0.05
Maternal death	/	/	/
Hysterectomy	/	0.2 (1)	/
Rupture of the uterus	1.4 (2)	/	/
Scar dechiscence	2.8 (4)	1.7 (7)	ns
Placenta previa	0.7 (1)	0.5 (2)	ns
Bladder injury	0.7 (1)	0.5 (2)	ns
Blood transfusion (intra- or postpartum)	3.6 (5)	2.4 (10)	ns
Wound complication	6.5 (9)	1.0 (4)	ns
Adhesions	4.3 (6)	3.1 (13)	ns
ICU admission	6.5 (9)	3.4 (14)	ns
Deep vein thrombosis	0.7 (1)	0.2 (1)	ns

Data are presented as percentage (number). *Composite of all adverse outcomes: maternal death, hysterectomy, rupture of the uterus, scar dechiscence, placenta previa, bladder injury, blood transfusion, wound complication, ddhesions, ICU admission, deep vein thrombosis;
ns − no significant difference; ICU – intensive care unit.

Discussion

The timing of repeated CS after two or more previous CS has to be not too soon for the baby and not too late for the mother. Some studies show that neonatal morbidity associated with elective CS at term increases as gestational age at delivery decreases from 39 to 37 weeks [5, 6]. Despite these recommendations, over the third of pre-labor elective repeat CS, in a US multicenter cohort study, were delivered prior to 39 weeks [7] and this figure is as high as 50−80% in some European cohort studies [6, 8]. Concern that delivery at 39 weeks, among women with repeated CS, compared to earlier deliveries may be associated with adverse maternal outcome has been suggested as one reason for elective delivery prior to 39 weeks [9, 10]. For the last ten years, at our Clinic, 59.3% delivered prior to 39 and 40.7% after 39 completed weeks. Maternal age influenced the time of elective repeated CS, because in the third group (> 39 weeks) 70% of the patients were aged under 35 and only 30% was 35 or more years old. The highest incidence of emergency CS was in the 39 weeks group, but the difference was not statistically significant. Different results were obtained in some other studies where elective CS deliveries > 39 weeks were associated with a significant increase in the number of emergency CS [10, 11]. Among

neonatal characteristics there were no significant differences even for the 5-minute Apgar score less than 7 which was the highest rate in the 37 weeks group.

The lowest incidence of maternal adverse outcome was in the 38 weeks group, but the difference was not statistically significant. The study, that comparing maternal adverse outcome at 38 and 39 weeks in women after 2 or more CS, revealed that the lowest rate of any adverse outcome was observed when CS scheduled to 38 + 1 weeks [12]. Much bigger study revealed that elective repeat CS at 37 or 38 weeks as compared with delivery at 39 (for neonatal benefit) is not associated with decreased maternal morbidity with no apparent maternal benefit compared to elective delivery in the 39th week [13, 14]. The severe complications of repeat CS include maternal death, uterine rupture and hysterectomy [13]. In our study these complications were rare: no maternal death, two complete uterine rupture (0.4%) and one hysterectomy (0.2%) that is similar with other bigger studies [13, 15].

The overall incidence of adverse maternal outcome by the number of previous CS showed a significant difference ($p < 0.05$). Almost all individual maternal complications were more frequent in the group ≥ 3 CS, but a significant difference was obtained in scar dehiscence, the presence of adhesions, blood transfusion and ICU admission. In our study the fourth CS was associated with more potential risks for adverse maternal outcome. Cook et al. [16], from the United Kingdom Obstetric Surveillance System (UKOSS), comparing fifth or bigger number of CS with those from the second to the fourth procedure, concluded that those having five or more CS had significantly increased rates of morbidity, such as major hemorrhage rate increased 18-fold, mostly due to 18% with placenta previa or accrete syndrome, visceral damage 17-fold, critical care admission 15-fold and delivery < 37 weeks 6-fold [16]. The risk for uterine rupture after two CS was 0.2% and it was similar in patients with one previous CS (0.3%) [17]. In our study the patients with 3 or more CS incidence of uterine rupture was 1.6% and scar dehiscence 11.7%. In one previous review even 27% of patients with 3 or more previous CS had fenestration of uterine scar [18], but recent studies describe the rates ranging from 1% to 10% in women undergoing anywhere from a fifth to a ninth CS [15, 19, 20]. A systematic review and meta-analysis of 21 observational studies revealed that maternal morbidity increases in a dose-response fashion with each additional CS, especially for women with ≥ 3 CS who are at statistically significant increased risk of previa, accrete placentan and hysterectomy [2, 21]. The incidence of placenta previa in our study was 3.3% in the group ≥ 3 CS compared with 0.2 in the group 2 SC without significant difference, but the number of cases was small, although similar results were obtained in some other studies [8].

The highest rate of emergency CS was after 39 weeks, although there were no statistically significant difference. In some other studies, despite improvement in neonatal outcome, scheduling elective CS deliveries at ≥ 39 weeks is associated with a significant increase in the number of emergency CS [11, 12, 22]. In our study the rate of composite maternal complications in emergency (27.3%) compared with elective CS (12.9%) showed significant difference ($p > 0.05$), as it was obtained in the study of intraoperative surgical complications during CS [23, 24]. Possible explanation of this could be the reason for emergency CS such as uterine contractions, rupture of membranes or low station of the presenting part.

Despite the limitations of our study, the obtained data suggest that optimal timing for elective CS regarding maternal complications may be the 39th week. Since USA National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (MFMU) published that elective repeat cesarean delivery at 37 or 38 weeks compared to 39 completed weeks of gestation is associated with adverse neonatal outcomes [5, 7], therefore elective delivery prior to 39 weeks is discouraged, unless fetal lung maturity has been confirmed [25], the question is that it maybe too late for the mother regarding her complications. Our study, also, did not revealany decrease in maternal morbidity if patients delivered prior 39 weeks. Among all women undergoing pre-labor elective repeat Cesarean at term, our findings apply directly to the majority who maintain this elective status at the actual time of delivery [13].

Conclusion

The obtained data show that the factors that directly influence the adverse maternal outcome are the number of previous CS and emergency CS. The fourth CS and more are associated with more risks for maternal complications and they might be delivered prior to 39 weeks.

Because of serious complications, patients should be informed about any potential risks for their health with increasing number of CS, especially after the first CS, when counseling regarding elective repeat CS *vs* trial of labor.

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Received on April 28, 2015.
Accepted on May 18, 2015.
Online First March, 2016.

ORIGINAL ARTICLE

UDC: 615.851::[355/359:616.89
DOI: 10.2298/VSP150512083M

Posttraumatic stress disorder and art group therapy: self-expression of traumatic inner world of war veterans

Posttraumatski stresni poremećaj i grupna art terapija: samoizražavanje unutrašnjeg traumatskog sveta ratnih veterana

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Abstract

Background/Aim. Art therapy and drawings may serve as alternative means of expression and release from trauma among veterans diagnosed with posttraumatic stress disorder (PTSD). **Methods.** The retrospective clinical study of drawings of war veterans was performed. A total of 89 war veterans met the Diagnostics and Statistical Manual of Mental Disorders (DSM-IV) PTSD criteria and were consecutively admitted to the Day Hospital during 5 years. Art group therapy as part of integrative treatment was performed once a week. The group was open and heterogeneous. Qualitative analysis of drawings content and group protocols were obtained. The drawings were made by free associations. War related themes were explored and descriptive statistics were applied. **Results.** The most frequent type of common themes of combat stress presented battle and witnessing wounded and killed combatants. Less frequent were themes of graves, destroyed cities and broken trees. The veterans preferred black and red colors with association to death, blood, wounds and destroyed objects. **Conclusion.** Drawing could provide a unique, complex, visual illustration of war traumatic experiences and memories of posttraumatic stress disorder veterans. Art group discussion might enhance war veterans' verbal expression due to group support in safe setting. As adjuvant psychotherapy, art group therapy could enrich awareness and the ability of clinicians to treat hard posttraumatic stress disorder symptoms related to uncovered war trauma.

Key words:
stress disorders, post-traumatic; art therapy; veterans; psychotherapy, group; drawings.

Apstrakt

Uvod/Cilj. Art terapija i crteži mogu poslužiti kao alternativna sredstva izražavanja i oslobađanja od trauma među veteranima kod kojih je dijagnostikovan posttraumatski stresni poremećaj (PTSP). **Metode.** Izvršena je retrospektivna klinička studija crteža ratnih veterana. Ukupno 89 ratnih veterana ispunili su kriterijume *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) PTSP, i bili konsekutivno primljeni u dnevnu bolnicu u toku pet godina. Grupna art terapija kao deo integrativnog tretmana sprovodila se jednom nedeljno. Grupa je bila otvorena i heterogena. Izvršena je kvalitativna analiza crteža i grupnih protokola. Crteži su nastali prema slobodnim asocijacijama. Izvršena je analiza ratnih tema i primenjena je deskriptivna statistika. **Rezultati.** Najčešće teme borbenog stresa bile su prikazi same borbe i ranjenih i ubijenih saboraca. Ređe su bili prikazani crteži grobova, uništenih agradova i polomljenog drveća. Veterani su najčešće koristili crnu i crvenu boju asocirajući na smrt, krv, rane i uništene objekte. **Zaključak.** Crteži mogu pružiti jedinstvenu kompleksnu ilustraciju traumatičnih ratnih iskustava i sećanja veterana sa dijagnozom posttraumatskog stresnog poremećaja. Diskusija u toku grupne analize može poboljšati verbalno izražavanje traumatskih sadržaja ratnih veterana usled grupne podrške u sigurnom okruženju. Kao adjuvantna terapija, grupna art terapija može obogatiti svesnost i sposobnost kliničara da leče teške simptome posttraumatskog stresnog poremećaja koji se odnose na neotkrivene ratne traume.

Ključne reči:
stresni postraumatski poremećaji; lečenje umetnošću; veterani; psihoterapija, grupna; crteži.

Introduction

Posttraumatic stress disorder (PTSD) related to combat exposure has been associated with severe psychosocial dysfunction. War PTSD was over three times more prevalent among deployed veterans than non-deployed veterans even ten years later[1]. There were reports that approximately 7.6% to 20% of the troops deployed to Iraq and Afghanistan may require PTSD treatment[2,3].

Post-deployment early interventions may reduce risk for PTSD development, and there is a recommendation that

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all PTSD veterans receive evidence-based cognitive-behavioral therapy [3, 4]. The most recommended kinds of psychotherapy are prolonged exposure and cognitive processing therapy among cognitive behavioral therapy, then eye movement desensitization and reprocessing (EMDR) and psychodynamic psychotherapy for PTSD treatment [5].

Empirical evidences of good results for trauma treatment by art group therapy in clinical practice have been reported, but the systematic review of its effectiveness has not been established [6]. Art therapy provides an alternative means of expression and release from trauma. It may be a more profound and long-lasting procedure than standard treatment forms, so there is an urgent need for further research on art therapy and trauma [5, 6]. Treating war PTSD veterans challenges the clinicians faced with these patients, especially due to the fact that they are not fond of verbal expression of trauma events. A better inside into the inner world of veterans related to war trauma is essential for treatment tailoring and improvement.

The aim of this study was to present clinical observations of group art therapy as part of integrative treatment of war veterans with PTSD in the Day Unit and qualitative analyse of the drawing content.

Methods

The retrospective clinical descriptive study of the drawings of PTSD diagnosed combat veterans who returned from war deployment in former Yugoslavia was performed. The veterans were consecutively admitted to the Day Unit, Clinic of Psychiatry, Military Medical Academy, Belgrade, between 1992 and 1996. They were male patients who met the PTSD criteria according to DSM-IV [7] and were treated in the Day Unit for two months. The presence of co-morbid major depression, psychotic disorders and alcohol or substance harmful use or dependence were exclusion criteria. PTSD veterans with more than three months and less than two years after returning from the war were studied.

The procedure

The form and content of drawings' series and group protocols from art group therapy sessions were qualitatively analyzed. The frequency of different types of presented war trauma were analyzed. The data from medical records were obtained.

Interventions

The integrative day treatment program was applied. The general goal was not only to reduce the clients' symptoms, but to enable personality social integration, as well. The staff of the Day Unit included psychiatrists, psychotherapists, clinical psychologists, and nurses. All the patients received combined pharmacotherapy, occupational therapy, counseling, individual and group verbal therapy and group art therapy. PTSD veterans underwent homogenous group psychodynamic therapy for anxiety and stress related disorders three times a week. As adjuvant therapy art group therapy for the patients currently treated in the Day Unit was performed once a week. The group consisted from both gender, civilian and military adult participants with various mental disorder. In the first part of session the patients were drawing by free association and free choice of colors. Second part lasted 90 minutes when the patients exhibited drawings by themselves and discussed them in the setting of group analysis of drawings with therapists. The structural sessions started with giving the drawing title and discussing the feelings related to each drawing. The group was open and heterogeneous. The sessions usually consisted of 12 to 18 patients and among them 1–4 were PTSD combat veterans. The course of integrative treatment lasted two months and included on the average 7 art therapy sessions. Basic art materials, such as crayons and pastels, colored pencils, gouache paints and white paper of the same sizes, 210 × 297 mm were available.

The participants gave signed informed consent on admission and the latest release of the Helsinki Declaration was applied. Ethic approval for drawing use were obtained.

Results

Participant characteristics

There were 89 male PTSD war veterans: 72 (80.9%) active military personnel and 17 (19.1%) reserve, middle age of 35.6 years. The most were married (82%) and had on the average, 12.6 years of school.

Analysis of the drawings with war related themes

There were 553 drawings collected from PTSD war veterans (average 6.2 for each subject**).** After qualitative analysis of the drawings content and form, the war related themes were detected among 82.8% (n = 458) drawings, and were classified into five mainstream types according to the common theme. Each type of the theme was presented by some examples of PTSD veterans drawings. The each participant gave the title and described events and feeling related to the drawing during group sessions. Only 17.2% (n = 95) drawings illustrated other, war-non related themes.

The most frequent type of war-related themes among participants was illustrated as horrifying war zone traumatic events with threatened death or injury and witnessing wounded and killed combatants in 48.3% drawings (n = 267) (Figures 1–3).

The traumatic re-experience also was vividly illustrated in 14.5% of drawings entitled as Nightmares (n = 80) (Figures 4–6).

The themes of grave were frequently presented in 9.9% (n = 55) drawings (Figures 7–9).

Destroyed churches, houses, abandoned cities also were presented in 5.8% drawings (n = 32) (Figures 10–12).

The next series of drawings illustrated broken trees, stripped of leaves, with no branches, often without roots and pulled out of the ground at 4.3% drawings (n = 24) (Figures 13–15).

Fig. 1 – The Combat (A veteran who drew it described fear, horror hopelessness, death which he expirienced during the battle).

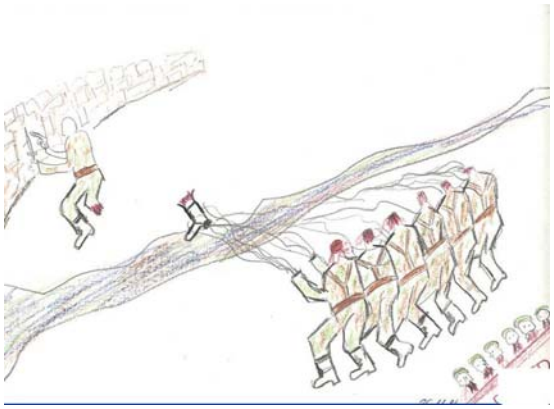

Fig. 2 – The Ultimate Combat (A scene to the combat in which all of the companions have died, while the author of the drawing has also fought and his suffered a life-threatening injury. Feelings of life endangerment, fear, sorrow because of the companions who have died, but also a will to survive and the feeling of vengeance).

Fig. 3 – The ultimate task (The description of the author refers to a sad memory of the lost companion who carried out respectably his ultimate task, during which he died in a combat, and it aroused sad memories and suffering for this lost).

Fig. 4 – The nightmare (A dream that repeats it self after the return from the battlefield. Feelings of fear, horror, helplessness because of the explosions and destructions).

Fig. 5 – An Ambush, a deadluck (A dream followed by the feeling of complete helplessness and horror of the combatant in the war, after which he wakes up drenched in sweat, terrified).

Fig. 6 – The whirpool of death (A desperate scream for help, horror, his attempt to save himself, while he sinks in the whirpool of death).

Fig. 7 – The field of the nameless graves (Instead of wood of treas, the field of the nameless cross tombstones. The sad memory of a great number of the companions who succumbed to their injuries).

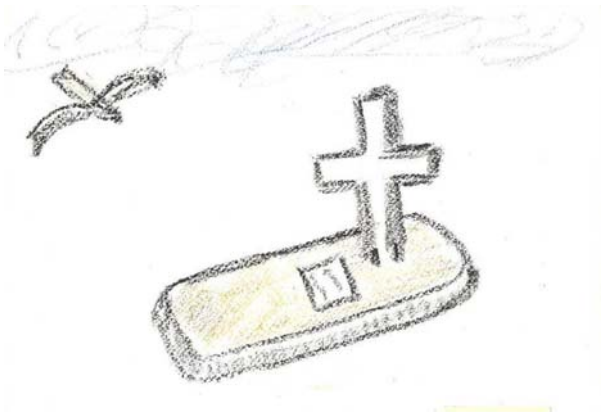

Fig. 8 – The lonely tomb (Feelings of great sorrow, emptiness devastation, complete loneliness and isolation).

Fig. 9 – After the war termination (The groves visited by the family members and companions. The grass began to grow, memories are still sad, however the life goes on).

Fig. 10 – The village in ruins (The description of destroying of the village by the hand of the enemy, feelings of devastation and sorrow).

Fig. 11 – The demolished church (The description of a burned and ruined church which was seen by a retern at the battle-field, after the withdrawal of the enemy. Feelings of sorrow and rebellion against the enemy because of the profanation of a religions sanctuary).

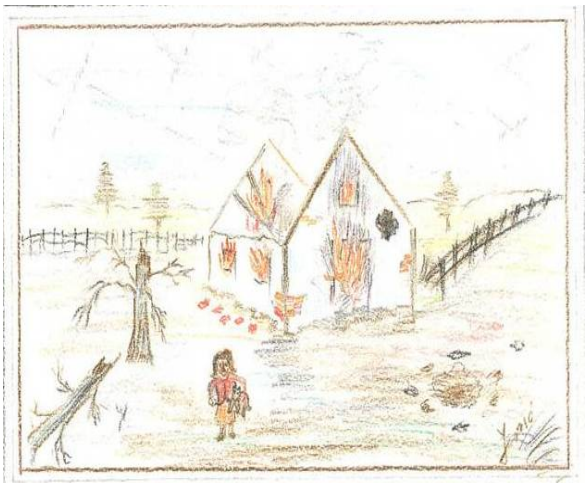

Fig. 12 – A little girl in the whirpool of the war (A memory of the village after the redemption. From a burning and ruined house only the girl has managed to escape. Feelings of devastation and sadness for the orphan, whose family and happy childhood were gone forever because of the war).

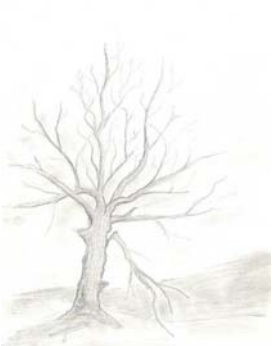

Fig. 13 – The lonely, naked tree in the field deserted by war. Feelings of despair.

Fig. 14 – A broken trunk (The only thing that's left of the robust tree in the chuck of the greyish colour. Feeling of sorrow, pain, devastation, lost).

Fig. 15 – The battlefield after the combat (Feelings of complete devastation, death, demolishment of everything possible, hopelssness).

The analysis of drawings form

Qualitative, observational analysis of the most preferred chosen colors showed that the PTSD veterans in the drawings preferred black and red colors. Black was reserved for death and fear and red for illustrating blood and wounds. Lines were sharp and quick, showing extreme tension and emotional charge.

Self-reported feelings, associations and behavior expressed during sessions

From the group protocols self-reported associations and self-descriptions of feelings related to illustrated themes expressed during sessions were obtained and analyzed. During discussion the participants verbally expressed horror, helplessness, grief, anger, guilt, loneliness and the need for forgetting anything related to exhibited drawings. They stated that they felt unpleasant when evoking memories. The patients' behavior in the group analysis was similar to their social functioning at the time: silence, negative attitude, doubting the possibility to be cured, repeating themes, and feeling that they have a "job" to do it. However, after a few sessions the most of the veterans changed their attitude, and became more interested in discussing drawings of civilian members with everyday life themes.

Discussion

The structure of the symptoms of PTSD in deployed war veterans is not known enough, but the separate four factors of re-experiencing, avoidance, dysphoria, and hyperarousal symptoms have been identified [7, 8]. In this study the veterans most frequently drew the horrifying combat traumatic events with threatened death or injury, witnessing wounded and killed combatants and nightmares as themes, which is in concordance with another reports [9]. Some new approaches to PTSD treatment refer to the interpersonal view of PTSD, and considers, estrangement feelings, guilt and protective factors, such as forgiveness and social support [10].

The themes of illustrated graves and destroyed cities and trees in war zone after combats were less frequent. Other authors reported that war deployment was associated with PTSD in terms of significantly more frequent exposure to wounded and killed and to the feeling in great danger of being killed during deployment in 20.8% *vs* 18.9% cases, respectively [11].

Psychodynamic processes became visible through "inner pictures" of the creative process of drawing that some authors suggested may be the main focus for group psychotherapy [12]. But in this paper, drawing and art group therapy did not take the central part of integrative therapy. The decision to make heterogeneous art group therapy was the result of practical reasons as it was only the adjuvant kind of therapy. The PTSD veterans were submitted to integrative treatment with the focus on homogeneous psychodynamic group psychotherapy for anxiety and stress related disorders three times a week. The veterans also could go on further discussing about traumatic themes from their drawing in homogenous group psychotherapy. Sometimes it was less painful for them to talk about trauma the next day on the verbal therapy group session.

War veterans are often socially isolated based on negative experiences they had with civilians, so participating in the group analysis of drawings was a chance to correct that experiences in a controlled and protected environment. Negative attitude was presented at starting art therapy, but after a few sessions it used to be resolved and the most of the veterans accepted this program that made them possible to experience the group support and gratification.

Our clinical experience confirmed the recommendations of another authors that art therapy interventions may uncover unknown and traumatic material while enhancing relaxation and improving communication skills through group interaction [5].

Positive effects of art therapy associated with patients with different clinical profiles as an acceptable and cost-effective treatment have been reported [6]. There is no need for expensive equipments, and drawings could help in diagnostic and therapeutic evaluation processes [13]. In the frame of multidimensional treatment of posttraumatic stress disorder visual art therapy is a unique approach and enables working on traumatic memories and integration [14].

Most of the veterans avoided talking about their traumatic experiences in front of other persons without war experiences [14]. But visual expressing and facing their drawing directly is a chance to observe it from another perspective after war [15]. The therapist and the other members of the group then helped them to synthesize the differences between war and peace time reality. There was the evidences that non-trauma focused psychotherapies less reduced PTSD symptoms compared to trauma-focused treatments with greater drop-out in treatment groups [16, 17]. Some efforts were done to promote the evidence-based psychotherapies for PTSD in mental health settings, but additional studies are needed to understand implementation of evidence-based therapy [18]. The researchers reported positive effect of art group war veteran therapy with the defined themes for each session the same for all participants according to the therapy program [19]. We preferred free associations for expression of inner world of the participants. Our findings suggest that art group therapy warm up veterans for enhancing psychodynamic group psychotherapy and other activities in the Day Unit.

The treatment goals are: reduction of anxiety, lessening of passivity, increasing of self-confidence, providing communication in positive atmosphere. During the course of day integrative treatment, these war veterans draw themes of nightmares and reminiscing war scenes with all the previously shown negative feelings. Influenced by the whole therapeutic process in the Day Unit it was observed that they gradually switched from war themes to the current social context and reality, focusing more on the "here and now" problems. They also started showing feelings of hope, with increased self-confidence in positive communication atmosphere provided.

The second part of sessions further may clarify the drawings content with the patients verbal expression of drawings during group discussion. It might enlarge the therapeutic response, trust, confidence and the group support for the participants. The important role of group psychotherapy in improving interpersonal trust in veterans with PTSD was reported [20].

The limitation of this study is that it was the retrospective descriptive analysis with clinical observations of only war- and trauma-related themes of drawings of war veterans. The heterogeneity of patients population with civilian and military persons with various mental disorders suggests the need for caution in interpreting the results of this paper. The therapists must be careful and aware of how counter-transference affects their interpretation of the drawings, even when symbolization is simple and obvious. The art group of veterans might give a unique contribution to treatment, but here it was framed into integrative day treatment and could not be evaluated and extracted from the other procedures. In this paper the focus was on the clinical experience and practice, but further studies and analyses of art therapy versus other treatments are needed to provide the evidence of its efficacy.

Conclusion

The findings of this study suggest that drawing could provide a unique and complex insight into visual presentation of uncovered war trauma experiences and memories of PTSD veterans. Group discussion might enhance self-confidence and verbal expression of each war veteran followed by group facilitation and support. As adjuvant psychotherapy the art group therapy could enrich awareness and ability of clinicians to treat hard PTSD symptoms in war veterans.

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Received on May 12, 2015.
Accepted on May 18, 2015.
Online First August, 2015.

ORIGINAL ARTICLE

UDC: 616.233/.36-08-036
DOI: 10.2298/VSP150518104R

The impact of in-hospital nutritional status deterioration on treatment outcome of adult gastroenterological patients

Uticaj intrahospitalnog pogoršanja nutritivnog statusa na ishod lečenja odraslih gastroenteroloških bolesnika

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Abstract

Background/Aim. In the current literature, data on impact of intrahospital changes in patients' nutritional status on the treatment outcome are limited. The aim of this study was to investigate the relationship between nutritional status deterioration and the treatment outcome among hospitalized gastroenterological patients. **Methods.** In 650 adult gastroenterological patients nutritional status on admission and at discharge was evaluated using the 6 nutritional status assessment parameters: body mass index, triceps skinfold thickness, mid-upper arm muscle circumference, serum albumin concentration, lymphocyte count and unintentional weight loss. The influence on treatment outcome was tested for the nutritional status on admission, nutritional status at discharge and intrahospital nutritional status deterioration. **Results.** The incidence of favorable outcome in the non-undernourished and undernourished patients on admission was in the range 93.4–97.3% and 81.2–91.2%, respectively. The incidence of favorable outcome in the non-undernourished and undernourished patients at discharge was in the range 94–97.4% and 80.8–88.1%, respectively. Favorable outcomes were obtained in 95.6–98.9% of the patients without nutritional status deterioration and in 87.1–90.3% of the patients with nutritional status deterioration. Intrahospital nutritional status deterioration significantly influenced the outcome, no matter what assessment parameter had been used ($p < 0.001$ for all the applied parameters). Furthermore, only the deterioration of nutritional status was found to be an independent predictor of treatment outcome (multivariate analysis Forward Wald, $p \leq 0.001$; relative risk (RR) = 0.104–0.350; confidence intervals (CI) = 0.037-0.186/0.297–0.657). **Conclusion.** Deterioration of nutritional status is an independent predictor of adverse outcome.

Key words:
gastrointestinal diseases; nutritional status; hospitalization; treatment outcome; adults.

Apstrakt

Uvod/Cilj. U dostupnoj litearturi postoji malo radova o uticaju promena nutritivnog statusa bolesnika tokom hospitalizacije na ishod lečenja. Cilj studije bio je da se kod hospitalizovanih gastroenteroloških bolesnika ispita odnos između pogoršanja nutritivnog statusa i ishoda lečenja. **Metode.** Kod 650 gastroenteroloških bolesnika procenjivan je nutritivni status pri prijemu i pri otpustu iz bolnice, korišćenjem šest parametara procene: indeks telesne mase, debljina kožnog nabora tricepsa, obim sredine nadlaktice, koncentarcija albumina u serumu, broj limfocita i nenamerni gubitak težine. Uticaj na ishod lečenja testiran je za: nutritivni status pri prijemu, nutritivni status pri otpustu i intrahospitalno pogoršanje nutritivnog statusa. **Rezultati.** Učestalost povoljnog ishoda kod nepothranjenih i pothranjenih bolesnika pri prijemu, iznosila je 93,4–97,3%, odnosno 81,2–91,2%. Učestalost povoljnog ishoda kod nepothranjenih i pothranjenih bolesnika na otpustu, bila je 94%–97,4%, odnosno 80,8–88,1%. Povoljan ishod bolesti dobijen je kod 95,6–98,9% bolesnika bez pogoršanja nutritivnog statusa i kod 87,1–90,3% bolesnika sa pogoršanjem nutritivnog statusa. Intrahospitalno pogoršanje nutritivnog srtatusa značajno je uticalo na ishod lečenja, bez obzira na to koji je parametar procene nutritivnog statusa bio primenjen ($p < 0.001$ za sve primenjene parametre). Osim toga, intrahospitalno pogoršanje nutritivnog statusa bilo je jedini nezavisni prediktor ishoda lečenja (multivarijantna analiza *Forwald Wald*, $p \leq 0{,}001$; relativni rizik (RR) = 0,104–0,350; interval poverenja (IP) = 0,037–0,186/0,297-0,657). **Zaključak.** Pogoršanje nutritivnog statusa je nezavisni prediktor nepovoljnog ishoda lečenja.

Ključne reči:
gastrointestinalne bolesti; nutritivni status; hospitalizacija; lečenje, ishod; odrasle osobe.

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Introduction

Malnutrition is highly prevalent among patients on hospital admission [1–4]. Previous studies have indicated that poor nutritional status (NS) in hospitalized patients is associated with many adverse outcomes, including a higher risk of complications, increased morbidity and mortality, prolonged hospital stay and increased hospitalization costs [5–10]. Some authors have determined malnutrition as a risk factor for frequent readmissions and bad outcome in a postdischarge period [11–13]. In spite of that, the problem of intrahospital malnutrition is often underestimated, and unfortunately, likelihood of nutritional depletion increases during hospital stay, even in large hospitals. Compared with the numerous studies on malnutrition prevalence on hospital admission and the impact of malnutrition on the treatment outcome, studies on intrahospital changes in NS and their association with a bad outcome, are in minority [14–18]. In Serbia, there is no data on this problem.

The aim of this study was to investigate the relationship between the nutritional status deterioration (NSD) and treatment outcome among hospitalized gastroenterological patients.

Methods

Study design and patient population

This prospective study on adult patients, admitted to our hospital, was conducted over a 15-month period. The inclusion criteria were: age ≥ 18 years, a Karnofsky score better than 40 on admission, lack of hemiotherapy, hospitalization period longer than 7 days and informed written consent to participation in the study. The patients were continuously included in the study. All the patients underwent both, diagnostic procedures and medical therapy. The ethical aspect of this study was approved by the local Ethics Committee.

Assessment of nutritional status

Nutritional status was assessed within 48 h after admission and at discharge, using the 6 nutritional status assessment parameters (NSAPs): body mass index (BMI), triceps skinfold thickness (TSF), mid-upper arm muscle circumference (MAMC), serum albumin concentration (ALB), lymphocyte counts (LYM), and unintentional weight loss (WL).

BMI was calculated as weight/height^2 (kg/m^2). Weight (nearest 0.1 kg) and height (to the nearest centimetre) were measured while the patient was standing in light clothes and without shoes. Mid-upper arm circumference (MAC) and TSF, were measured using a tape and callipers at the midpoint between olecranon processes and the acromion of the non-dominant side. The mean value of three consecutive measurements was recorded. MAMC was calculated indirectly, on the basis of the TSF and the MAC: MAMC (mm) = 10 [MAC (cm) – 0.314 x TSF (mm)].

On the basis of each of the 6 NSAPs, the patients were classified as being non-undernourished (normally nourished and obese) and undernourished [19].

NS was not assessed according to weight loss and lymphocyte counts if ascites and hypersplenism were presented, respectively. For the patients with ascites, BMI was calculated using the recommended equation [20].

Intrahospital NSD was considered if any decrease of NSAPs was present, regardless of their extent.

Factors influencing the treatment outcome

The influence on treatment outcome was tested for the NS on admission, NS at discharge and intrahospital NSD.

The parameter for the treatment outcome was the patient's objective status at the discharge from the hospital. It was evaluated on the basis of the physical examination of the patients and laboratory analysis, while ultrasound and endoscopic examinations were repeated if it was necessary. Physical examination of the patient at discharge from the hospital, was performed by the same doctor as on admission. It included general observation (state of consciousness, temperature, mobility, appearance of the skin and mucous membranes) and examination by body systems. Laboratory analysis such as erythrocyte sedimentation rate, complete blood count with differential count, blood glucosa, urea, creatinin, protien, albumin, bilirubin holesterol, triglycerides, iron and liver enzimes were measured in all patients, while additional biochemical analyses were performed depending on the underlying disease. Treatment outcome was defined as satisfactory (the patients' clinical status was better than it was on admission), or unsatisfactory (the patients clinical status was worse or the same, as it was on admission).

Statistical analysis

Data processing was performed using SPSS 11.5 for Windows software (SPSS, Inc., Chicago, IL). Average values were presented as mean value ± standard deviation (SD), and p value of < 0.05 (two-sided) was considered to be statistically significant. Characteristics between the two groups were compared by means of the Student's t- test for parametric data and by the Mann-Whitney U-test for categorical data. Binary logistic analysis was performed to test the correlation between two variables, and Forwald: Wald multivariate logistic regression analysis was used for the prediction of clinical outcome. Critical values of some parametric variable for unsatisfactory clinical outcomes were calculated on the basis of the area under the receiver operating characteristic (ROC) curve.

Results

Characteristics of the patient

A total of 989 patients were assessed for eligibility over the study period. Three hundred and 39 patients were excluded from the study: 67 patients did not meet inclusion criteria on screening, 186 patients were hospitalized for less than 7 days, 42 patients died in hospital and 44 patients were excluded for other reasons. The data were analyzed for 650

patients. The hospitalization length ranged from 7 to 45 days (13.5 ± 6.7 days, on the average). Other baseline characteristics of the series are presented in Table 1.

Influence of admission nutritional status on treatment outcome

Depending on the NSAPs applied, 68.3–92.3% of the patients on admission were non-undernourished, while 7.7–31.7% were malnourished. The incidence of favorable outcome in non-undernourished and malnourished patients on admission was 93.4–97.3% and 81.2–91.2%, respectively. Regardless of the NSAP applied on admission, the tretment outcome was always better in the patients with better NS on admission. These differences were statistically significant if the assessment parameters were WL ($p < 0.001$), BMI ($p = 0.010$), MAMC ($p < 0.001$) or albumin ($p < 0.001$), but were not if the assessment parameters were TSF and lymphocyte counts (binary logistic analysis; $p > 0.05$).

Influence of discharge nutritional status on treatment outcome

Depending on the NSAPs applied, 61.8–92% of the patients at discharge were non-undernourished, while 8–38.2% were malnourished. The incidence of favorable outcome in non-undernourished and malnourished patients at discharge was in the range of 94%–97.4% and 80.8–88.1%, respectively. Regardless of the NSAP administered at discharge, the treatment outcome was always significantly better in the patients with better nutritional status at discharge (binary logistic analysis; $p < 0.001$ for WL, BMI, MAMC, albumin; $p = 0.041$ for TSF; $p = 0.004$ for LYM).

Influence of nutritional status deterioration on treatment outcome

Depending on the NSAPs applied, NSD during hospital stay ranged from 29.1% to 57.9% in all the patients. Favorable outcomes were obtained in 95.6–98.9% of the patients without NSD and in 87.1–90.3% of the patients with NSD. Deterioration of NS during hospitalization significantly influenced the outcome, no matter of the assessment parameter used (Table 2). Among admission NS, discharge NS and NSD during hospitalization, only NSD was found to be an independent predictor of outcome, regardless of the assessment parameter applied (multivariate analysis Forwald Wald, $p \leq 0.001$; relative risk (RR) = 0.104–0.350; confidence intervals (CI) = 0.037–0.186/0.297–0.657).

The patients with favorable and unfavorable outcome of treatment had similar mean declinings of TSF, MAMC, and lymphocytes (paired-samples Student's *t*-test; $p > 0.05$), while the average declinings of body weight, BMI and albumin were significantly higher in the those with an unfavorable outcome, compared to those with a favorable outcome (paired-samples Student's *t*-test, Table 3). Reducing the body weight of 1.2 kg, or 1.4% in relation to weight at admission, reducing the BMI of 0.55 kg/m^2, and reducing the level of albumin for 2.5 g/L were critical for the occurrence of an adverse outcome (ROC curve; Table 3).

Table 1

Baseline characteristic of the patients

Patient's characteristics	OSD	HBT	Pancreas	Intestine	Total
The organ involved, n	68	224	92	266	650
Gender (men/women), n	34 / 34	114 /110	62/30	150 / 116	360 / 290
Average age (years), $\bar{x}$ ± SD	67.9 ± 12.9	59.8 ± 16.5	59.7 ± 15.4	59.2 ± 16.3	60.3 ± 16.1
Average body weight (kg), $\bar{x}$ ± SD	67.7 ± 15.2	74.3 ± 13.9	70.9 ± 11.1	72.3 ± 15.1	72.3 ± 14.3
Disease nature (malignant / benignant), n	26 / 42	42 / 182	64 / 28	104 / 162	236 / 414
Average Karnofsky score, $\bar{x}$ ± SD	92.9 ± 9.0	95.4 ± 8.9	90.7 ± 9.7	90.7 ± 9.7	94.8 ± 8.8
Average length of hospitaliz. (days), $\bar{x}$ ± SD	14.2 ± 7.1	14.5 ± 7.1	13.6 ± 5.4	12.5 ± 6.6	13.5 ± 6.7

OSD – oesophagus, stomach and duodenum; HBT – hepatobilliary tract; $\bar{x}$ – mean; SD –standard deviation.

Table 2

Favorable and unfavorable treatment outcome in patients with and without deterioration of nutritional status (NS) (binary logistic analysis)

Assessment parameter for NSD	Deterioration of NS (present)		Deterioration of NS (absent)		Statistical parameters		
	Favorable outcome	Unfavorable outcome	Favorable outcome	Unfavorable outcome	*p*	RR	CI
WL	324	35	258	3	< 0.001	0.150	0.052–0.428
BMI^d	302	40	304	4	< 0.001	0.101	0.036–0.285
TSF^d	272	36	334	8	< 0.001	0.181	0.083–0.396
MAMC^d	180	26	426	18	< 0,001	0.293	0.156–0.547
ALB^d	272	38	334	6	< 0,001	0.130	0.054–0.313
LYM^d	162	24	434	20	< 0.001	0.311	0.167–0.578

NSD – nutritional status deterioration; WL – weight loss at discharge; BMI^d – body mass index declining; TSF^d – triceps skinfold thickness declining; MAMC^d – mid-upper arm muscle circumference declining; ALB^d – albumin concentration declining; LYM^d – lymphocyte counts declining; *p* – probability; RR – relative risk, CI – confidence interval.

Table 3

Average parameters reduction during hospitalization and treatment outcome

Treatment outcome	Average parameter declining during hospitalization						
	WL (kg)	WL **(%)**	BMI[d] kg/m^2	TSF[d] mm	MAMC[d] mm	ALB[d] g/L	LYM[d] $\times 10^3$/mm^3
Favorable, x ± SD	1.0 ± 1.0	1.4 ± 1.4	0.4 ± 0.4	1.4 ± 2.0	9.8 ± 13.3	2.6 ± 2.4	0.3 ± 0.3
Unfavorable, x ± SD	2.1 ± 2.2	3.2 ± 3.4	0.8 ± 0.7	1.1 ± 0.9	9.3 ± 6.7	5.6 ± 3.1	0.4 ± 0.5
p	**< 0.001**[†]	**< 0.001**[‡]	**< 0.001**[†]	> 0.05[†]	> 0.05[†]	**< 0.001**[†]	> 0.05[†]
t	-5.730	-5.730	-5.203	-	-	-7.015	-
Critical declining[§]	**1.2**	**1.4**	**0.55**	-	-	**2.5**	-
p	< 0.001	< 0.001	< 0.001	-	-	< 0.001	-
sensitivity (%)	67.7 %	67.0 %	60.0 %	-	-	73.3 %	-
specificity (%)	65.8 %	64.1 %	71.2 %	-	-	67.5 %	-
CI	0.630–0.808	0.621–0.795	0.612–0.800	-	-	0.649–0.843	-

WL – weight loss at discharge, BMI[d] – body mass index declining; TSF[d] – triceps skinfold thickness declining; MAMC[d] – mid-upper arm muscle circumference declining; ALB[d] – serum albumin concentration declining; LYM[d] – lymphocyte counts declining; *p* – probability; CI – confidence interval;
[†]Paired-samples – Student's *t*-test; [‡]Mann Whitney test (*U* = 8136; z = -4.322); [§]Receiver operating characteristic (ROC) curve.

Discussion

The first study on the impact of malnutrition on disease outcome was published in 1978 by Mullen et al. [21]. They found that the recent loss of 10–15% of body weight increased the perioperative risk and prolonged recovery. Weight loss of 20–25% endangers a patient who is planning to go to surgery, while the loss of 30% to 35% is a sign of severe cachexia and ends lethally, if a vigorous nutritional therapy is not applied [21]. Studies carried out on the following years demonstrated that malnutrition increases morbidity, prolongs recovery period after illness and surgery and reduces the response to chemotherapy in patients with malignant diseases [22, 23]. Furthermore, malnourished hospitalized patients have a higher mortality rate (10–40%), in relation to well-nourished patients [5, 24–26].

Influence of admission and discharge nutritional status on treatment outcome

The outcome of our patients has been significantly influenced by the admission and discharge NS. Regardless of the NSAPs administered, the frequency of favorable outcome was always higher in well-nourished than in malnourished patients. This is in accordance with the results of certain other studies [27–29]. These authors demonstrated that malnutrition at admission was an independent risk factor for poor rehabilitation outcome, morbidity and mortality of hospitalized patients [27–29]. In the study by Merli et al. [30] the presence of pretransplant malnutrition was the only independent risk factor for the length of stay in the ICU after liver transplantation. Similar results were published by Yosry et al. [31]. However, none of the cited authors, investigated the dynamics of NS from admission to discharge and its impact on treatment outcome.

Influence of nutritional status deterioration on treatment outcome

In our study the frequency of favorable outcome was always higher in patients without NSD, than in patients with NSD during hospital stay. Although the outcome of our patients was significantly influenced by all the three aspects of nutritional status: NS at admission, NS at discharge and NS deterioration during hospitalization, only the deterioration of NS was an independent predictor of the treatment outcome. This result is consistent with the results published by some other authors [14, 15, 22]. Donini et al. [22] found that deterioration of NS was the main independent predictor of mortality and occurrence of adverse events in the population of geriatric rehabilitation patients. Even a mild deterioration of NS could cause an increase in the incidence of adverse events and in mortality in these patients. In the study by Hill et al. [15] deterioration in NS during radiotherapy could be associated with bad treatment outcomes in the patients with gastroenterological cancer. Braunschweig et al. [14] pointed out that patients whose nutritional status worsened during hospitalization regardless of their nutritional status at admission, had significantly higher hospital charges and a higher likelihood of complications. Accordingly, it is reasonable for physicians to pay more attention to intrahospital changes in NS, even if the patient is well-nourished on admission.

In our patients, intrahospital decrease was noticed for the values of all NSAPs, except for the LYM. This result is mostly in concordance with the results of some other studies [17, 32]. There is a slight disagreement concerning the lymphocytes values between our results and the resultes obtained in the studies of Beghetto et al. [18] and Assensio et al. [5]. Those studies demonstrated that, compared to values on admission, lymphocytes were deteriorated as well as the other NSAPs. Furthermore**,** Asensio et al. [5] found that the decrease in lymphocyte count was an independent prognostic factor for in-hospital mortality.

Affected parameter depends on the patient's age. Farré Rovira et al. [33] concluded that in patients over 40 years, the values of all NSAPs decrease during hospital stay, whereas in younger patients hospitalization changes the values of albumin, weight and BMI only. The results obtained by Fettes et al. [34] pointed to possible gender differences in the intrahospital changes in NSAPs: in their study weight loss during hospitalization was bigger in males, than in females. In addition, male lost muscle mass, while females lost subcutaneous fat.

In our study critical values of the reduction in body weight, BMI and albumin level, for the occurence of adverse outcomes, were 1.2 kg, or 1.4% in relation to weight at admission, 0.55 kg/m^2 and 2.5 g/L respectively. De Hollander et al. [35] reported that a decrease in weight, equal or more than 3.2 kg, was significantly associated with mortality risk in older hospitalized adults. In the same study, they also found a significant association between waist circumference and MUMC reduction and increased mortality risk [35]. In the study of de Luis et al. [36], each decrease of 1 g/dl of albumin caused an increase of 3.1 days in hospital stay.

There are more works reporting on the values of certain assessment parameters on admission which are significant for development of an adverse outcomes: TSF [22, 31, 37], level of transferrin and the number of lymphocytes [5], weight loss [38], and BMI [37].

Critical values of body weight reduction for the occurence of adverse outcomes, expressed in kg and in precentages, which were obtained in our study have similar sensitivity and specificity. Interestingly, the critical values of BMI reduction have the highest sensitivity, but low specificity compared with the reduction of body weight and albumin values. The best combination of sensitivity and specificity was obtained for the decrease in albumin level, but, in general, this results in clinical practice should be used with great caution. Therefore, future prospective studies, which will comprise a homogenous groups of patients, are certainly needed to test the results of the present study.

Conclusion

This study is the first one in Serbia on the impact of in-hospital nutritional status deterioration on treatment outcome of gastroenterological patients. The results point to the significance of monitoring of patients' nutritional status during hospitalization, regardless of their nutritional status at admission. Reducing the deterioration of the nutritional status we should be able to reduce its negative effects on the treatment outcome.

Acknowledgement

The authors wish to thank Mr. Zoran Roganovic for his assistance in statistical analysis and also thank their colleagues from the Gastroenterological Department, who took part in the treatment of the patients included in the study.

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Received on May 18, 2015.
Revised on August 5, 2015.
Accepted on August 7, 2015.
Online First May, 2016.

PRACTICAL ADVICES
FOR PHYSICIANS

UDC: 616-073.75::616.24-073.432.19
DOI: 10.2298/VSP150607084R

The role of lung transthoracic ultrasound in clinical practice

Uloga transtorakalnog ultrazvuka pluća u kliničkoj praksi

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Key words:
lung diseases; ultrasonography; diagnosis; diagnosis, differential; intensive care units.

Ključne reči:
pluća, bolesti; ultrasonografija; dijagnoza; dijagnoza, diferencijalna; intenzivna nega, odeljenja.

Introduction

Lung ultrasound is a relatively new area of diagnostic sonography, which came into use towards the end of the 20th century. As a matter of fact, for many years chest ultrasonography was considered unfeasible because the air in the lungs dissipates ultrasound waves. The only discernible structure in a healthy pair of lungs is the pleura, which appears as a hyperechoic horizontal line, moving synchronously with the lung during respiration. Conversely to healthy lungs, in pathological conditions such as pneumonia, heart failure, acute respiratory distress syndrome (ARDS), pulmonary fibrosis and others, the volume of air in the lungs decreases, which leads to the appearance of various images (artefacts), based on which the pathological process is diagnosed.

History

Lung ultrasound has been used for decades in diagnosing and assessing pleural effusions and as a guide in thoracentesis. However, the beginnings of ultrasound assessment of lung tissue are associated with the French authors, Targhetta et al. [1], who used this technique in 1994 to demonstrate abnormalities in pulmonary sarcoidosis. The foundations of lung ultrasound were set by another French doctor, emergency medicine specialist Lichtenstein and his coworkers [2], who introduced the concept of B-lines that appear in interstitial oedema and pulmonary fibrosis. They demonstrated the correlation between the B-lines and the computed tomography (CT) findings, thereby effectively launching a new era in the diagnostics of lung diseases. In the beginning of the new millennium, significant contribution to this area came from Italian doctors Jambrik et al. [3], Picano et al. [4] and Gargani et al. [5] who explored the application of chest ultrasound in heart diseases.

Equipment and technique

Lungs can be examined with any ultrasound device, from portable and pocket-sized imaging devices to the latest, state-of-the-art machines, using any kind of probe, from cardiac to convex and linear probes. The best images are produced by: abdominal (convex) probes, which penetrate deep and have a large field of view, but with slightly poorer image quality; linear (vascular) probes, which produce higher resolution and more detailed images, at the expense of the depth (penetration); cardiac probes, convenient due to their small footprint which allows them to scan between rib interspaces.

Examination usually starts with a 3.5–5 MHz convex probe, while a 7.5–10 MHz linear probe is used for more details. In most cases, two-dimensional image (2D) is sufficient, although colour Doppler imaging can also be used to distinguish pleural thickening from small effusions, as well as to map blood vessels that might be in the trajectory of a needle during lung biopsy. Great significance is attached to the M-mode technique, especially in diagnosing pneumothorax [6].

During examination, patient is in supine position in hospital bed, with hands placed underneath his/her head, and op-

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tionally turns to a lateral decubitus or prone position if his/her conditions allow it. If lungs ultrasonography is undertaken in the course of thoracentesis, patient sits on a chair, leans with his/her chest against the backrest of the chair and lifts his/her arms above the head to expand intercostal spaces. The probe is placed perpendicularly to the surface of the chest in the intercostal space, with the orientation marker pointed cephalad, scanning the space between two ribs. A transducer is moved from one intercostal space to another, allowing the inspection of entire lung. The right side of the image shows the lower rib, while the left side shows the upper rib. The depth of ultrasound image is usually about 5 cm [7].

Protocols

There are several lung ultrasound protocols. The most commonly conducted examination involves 6 areas of investigation in each lung: anterior zone is located between the collar bone and the anterior axillary line, from the collar bone to the diaphragm; lateral zone occupies the space between the anterior and posterior axillary lines, from the axilla to the diaphragm; and posterior zone is outlined by the posterior axillary line and the vertebral column; each of these zones is divided into the upper and the lower area (Figure 1).

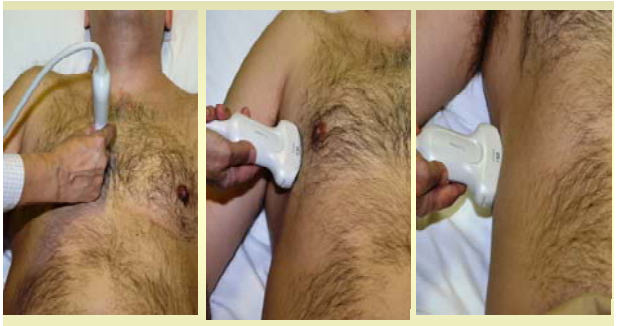

Fig. 1 – Lung ultrasound protocol with 6 areas of investigation in each lung.

Another protocol, used in semiquantitative assessment of heart failure, defines 26 areas and involves lung examination from the second to the fifth intercostal spaces on the left and right side, along the parasternal, midclavicular, anterior axillary and midaxillary lines.

A protocol in which lungs are examined in eight locations, four in the left and four in the right hemithorax, down the midclavicular and midaxillary lines, is also frequently followed.

A very practical examination of lungs is conducted by lobes on the left and right side, i.e. in three locations in each hemithorax, positioned apically on the midclavicular line, in the middle on the midaxillary line under the armpit and basally on the posterior axillary line [8].

Fundamentals of lung ultrasound exam

Ultrasonography of various organs is based on the phenomenon that an interface between two tissues reflects ultrasound back towards the probe, thus creating an ultrasound image. In the lungs, ultrasound reaches the air and passes through it, effectively generating no image due to the fact that air lets the sound waves pass through.

The presence of fluids (inflammation ARDS) or hard tissues (tumour, fibrosis, condensation) in the lungs generates artefacts, i.e. reflects ultrasound waves and creates images. Hence, ultrasound examination of pathological processes in the lungs basically means scanning of artefacts.

Normal lungs contain about 98% of air, pneumothorax 100%, pulmonary oedema 10%, atelectasis 5%, tumor 0%. During the examination, it is necessary to take into account the effects of gravity on various pathological conditions; accordingly, effusions are visible at the bases of lungs, as opposed to pneumothorax, which appears apically, or at the highest point of lying patient's lungs [9].The only visible structure in healthy lungs is the pleura, which is visualised as a hyperechoic horizontal line, moving synchronously with the lung during respiration (Figure 2).

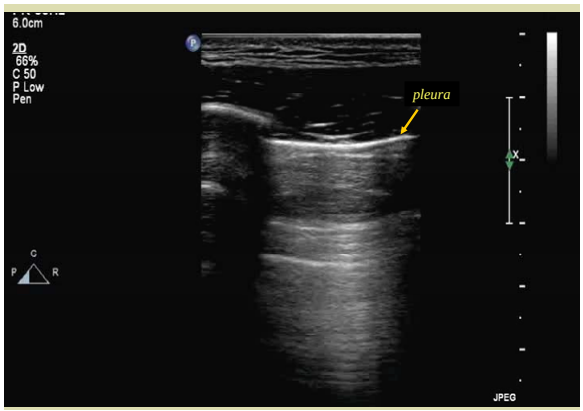

Fig. 2 – Lung ultrasound – the pleura is visualised as a hyperechoic horizontal line, moving synchronously with the lung during respiration.

Actually, when the transducer is held against the chest wall, the image reveals the following structures: skin and subcutaneous fat tissue; pectoral muscle and intercostal muscles between the ribs; ribs on both sides, casting an acoustic shadow (Figure 3).

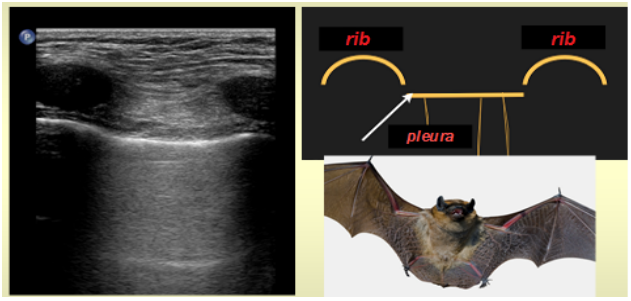

Fig. 3 – Two-dimensional ultrasound of healthy lungs. Ribs and the pleura outline the so-called "bat sign", where the pleura is the back of the bat and ribs are the wings of the bat.

The parietal and visceral pleura appear as a single, bright hyperechoic line, about 1 mm thick. In the intrapleural space there is a minimal amount of fluid, which is rarely discernible. The two layers of the pleura slide against each other synchronously with respiration, which is a very important diagnostic indication of healthy lungs [10].

Below the pleural line, scan of healthy lung tissue shows A-lines – bright echogenic lines parallel to the pleura, which are in fact artefacts created by the reflection of ultrasound from the pleura. They are about 2 cm long, located at the same distance from the pleura as the pleura's distance from the probe and they move together with it (Figure 4). Their absence may indicate excessive content of air in the lungs, i.e. pneumothorax.

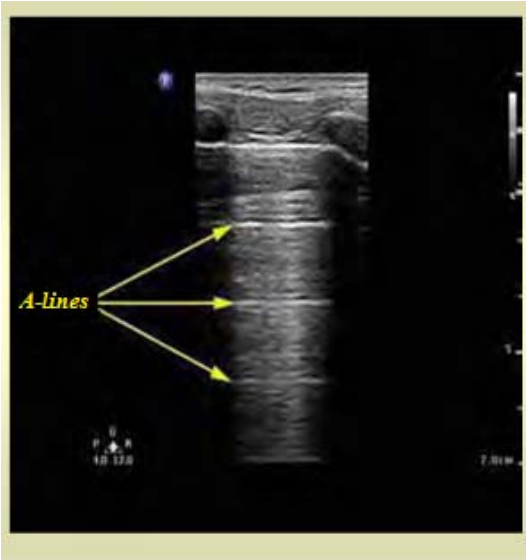

Fig. 4 – A-lines – bright horizontal lines, appearing under the pleura and standing parallel to it. They are artefacts created by the reflection of ultrasound from the pleura.

Another normal reading comes in the form of B-lines – very short hyperechoic lines, about 1 cm long, appearing immediately below the pleural line (Figure 5).

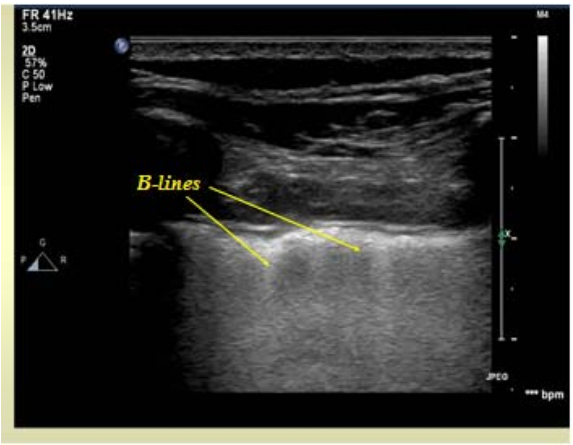

Fig. 5 – B-lines – short vertical lines under the pleura. They appear as a result of the minimum amount of fluid between the two layers of the pleura.

If we make an image of healthy lungs in the M-mode, the result will be the "seashore sign" – there are horizontal lines above the pleura, generated by the movement of the skin and muscles. These lines resemble the sky and the waves, where the skin is the sky and the muscles are the wavy ocean. Below the pleura, the sand-like grainy pattern is the result of the sliding pleura and the movement of lungs during respiration (Figure 6).

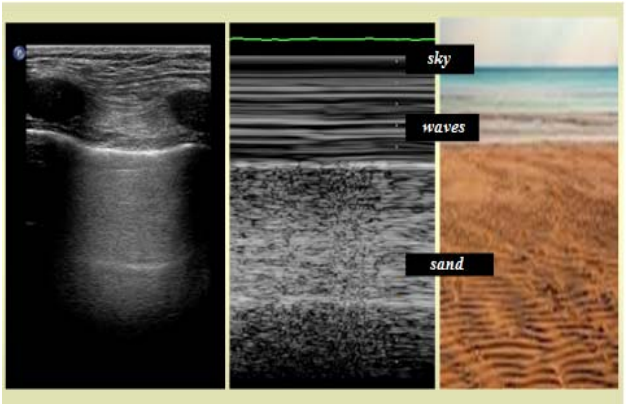

Fig. 6 – M-mode image of the lungs: seashore sign.
Above the pleura, the scan reveals wave-like lines, generated by the movement of muscles (waves) and the skin (sky).
Underneath the pleura, the image shows a grainy pattern resembling the sand, which is the result of lung sliding.

In pneumothorax, this sign is missing due to the presence of air between the pleural layers and only straight horizontal lines can be seen above and underneath the pleura [11].

Clinical implications

Lung ultrasound is often far more reliable than physical examination or radiography [12]. The advantage of ultrasound over chest radiography or CT is in the following facts: ultrasound is readily available in intensive care units or in any other place, including outdoors (street, sports facilities, etc.); examination is simple and quick; it is repeatable; it is cheap; no need to transport patients to remote parts of the hospital or across the city; it is non-ionizing; no risk of kidney damage caused by contrast dye or allergy [13].

The drawbacks of chest ultrasound: image quality and, consequently, the diagnosis strongly depend on the experience of the person performing the scan; not as good as CT in assessing pulmonary parenchyma.

Ultrasound diagnostics of lung diseases covers quite a wide range of pathological abnormalities. It is most commonly used in: interstitial oedema associated to cardiac dysfunction and acute respiratory distress syndrome [14–16], pneumothorax [17], pleural effusions [18], pneumonia [19], lung tumour [10], differential diagnosis of chronic obstructive pulmonary disease [20].

Moreover, ultrasound can be used as a guide in thoracentesis and lung biopsy [21]. It is used in procedures that were previously unsuccessful, since it detects the exact location of the effusion, much more accurately than by physical examination or chest radiography. This prevents serious injuries of the liver, spleen and kidneys, which is a very severe complication of the pleural puncture. The effusion should be at least 1 cm thick and, as a rule, the puncture is made at the point where the effusion is the thickest [22].

Conclusion

The possibility of examining lungs by means of ultrasonography, at the bedside and noninvasively, is gaining

popularity in intensive care units, pulmonology and radiology. Knowledge of the normal sonographic appearance of the lung, pleura, and chest wall facilitates accurate diagnosis of pathological processes and enables safe pleural puncture. Lung ultrasound techniques are relatively easy to learn, but they require adequate training and months of practice.

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Received on June 07, 2015.
Accepted on July 14, 2015.
Online First August, 2015.

CASE REPORTS

UDC: 616.12-08-06
DOI: 10.2298/VSP141222053D

Very late stent thrombosis of bare-metal coronary stent nine years after primary percutaneous coronary intervention

Veoma kasna tromboza metalnog stenta devet godina nakon primarne perkutane koronarne intervencije

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Abstract

Introduction. Stent thrombosis (ST) in clinical practice can be classified according to time of onset as early (0–30 days after stent implantation), which is further divided into acute (< 24 hours) and subacute (1–30 days), late (> 30 days) and very late (> 12 months). Myocardial reinfaction due to very late ST in a patient receiving antithrombotic therapy is very rare, and potentially fatal. The procedure alone and related mechanical factors seem to be associated with acute/subacute ST. On the other hand, in-stent neoatherosclerosis, inflammation, premature cessation of antiplatelet therapy, as well as stent fracture, stent malapposition, uncovered stent struts may play role in late/very late ST. Some findings implicate that the etiology of very late ST of bare-metal stent (BMS) is quite different from those following drug-eluting stent (DES) implantation. **Case report.** We presented a 56-year old male with acute inferoposterior ST segment elevation myocardial infarction (STEMI) related to very late stent thrombosis, 9 years after BMS implantation, despite antithrombotic therapy. Thrombus aspiration was successfully performed followed by percutaneous coronary intervention (PCI) with implantation of DES into the previously implanted two stents to solve the in-stent restenosis. **Conclusion.** Very late stent thrombosis, although fortunately very rare, not completely understood, might cause myocardial reinfaction, but could be successfully treated with thrombus aspiration followed by primary PCI. Very late ST in the presented patient might be connected with neointimal plaque rupture, followed by thrombotic events.

Key words:
stents; drug-eluting stents; thrombosis; myocardial infarction; angioplasty, baloon.

Apstrakt

Uvod. Tromboza stenta (ST) može se klasifikovati u kliničkoj praksi, prema vremenu nastanka, u ranu (0–30 dana nakon implantacije stenta), koju možemo dalje podeliti na akutnu, ukoliko se javi u prva 24 h, subakutnu (1–30 dana), kasnu (> 30 dana) i veoma kasnu (> 12 meseci). Reinfarkt miokarda usled veoma kasne ST kod bolesnika na antiagregacionoj terapiji javlja se veoma retko i može biti smrtonosan. Proceduralni i tehnički faktori su povezani sa akutnom/subakutnom trombozom stenta. S druge strane, neoateroskleroza u području stenta, upala, prerano prekidanje antiagregacione terapije, kao i neadekvatna apozicija stenta igraju važnu ulogu u kasnoj/veoma kasnoj ST. Neka istraživanja pokazala su da je etiologija veoma kasne tromboze metalnog stenta (BMS) u značajnoj meri drugačija od one nakon implantacije stenta obloženog lekom (DES). **Prikaz bolesnika.** Prikazali smo 56-godišnjeg muškarca sa akutnim inferoposteriornim infarktom miokarda sa elevacijom ST segmenta (STEMI) usled veoma kasne tromboze stenta, 9 godina nakon implantacije BMS, uprkos primeni antiagregacione terapije. Učinjena je uspešna tromboaspiracija, nakon čega je urađena primarna perkutana koronarna intervencija (PKI) sa ugradnjom jednog DES na mestu prethodno implantiranih stentova i tako lečili *in-stent* restenozu. **Zaključak.** Veoma kasna tromboza stenta, iako srećom retka i još nedovoljno razjašnjena, može izazvati reinfarkt miokarda, ali se može uspešno lečiti tromboaspiracijom i primarnom PKI. Ruptura plaka neointime sa posledičnom trombozom može biti uzrok veoma kasne tromboze stenta kod prikazanog bolesnika.

Ključne reči:
stentovi; stentovi, lekom obloženi; tromboza; infarkt miokarda; angioplastika, balonska.

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Introduction

Stent thrombosis (ST) in clinical practice, can be classified according to the time of onset, as: early (0–30 days after stent implantation), further divided into acute (< 24 hours) and subacute (1–30 days); late (> 30 days); and very late (> 12 months).

The procedure alone and related mechanical factors seem to be associated with acute/subacute ST. On the other hand, inflammation, premature cessation of anti-platelet therapy, as well as stent fracture, stent malapposition, uncovered stent struts play role in late/very late ST. Very late ST after stent implantation is more frequent after drug-eluting stent (DES) implantation than after bare-metal stent (BMS) implantation [1]. Moreover, the risk of very late ST after DES seems to be even higher in patients with ST segment elevation myocardial infarction (STEMI) compared with those with stable coronary artery disease [2, 3]. Consequently, professional societies have recommended the use of dual antiplatelet therapy (DAT) minimum for 12 months after DES implantation [4]. Actually, very late ST is not common in clinical practice following BMS implantation. Some findings implicate that the etiology of very late ST of BMS is quite different from those following DES implantation.

Case report

We presented a 56-year-old man with chest pain during one hour before admission, with propagation in the left shoulder, as well as fatigue and weakness. Previously, the patient had the history of dyslipidemia, high blood pressure, family history of coronary artery disease (CAD). Also, the patient was a former smoker. Nine years before he had myocardial infarction of the inferoposterior wall and underwent recanalization of the right coronary artery (RCA). Balloon NC SPRINTER 3.0 × 19 mm, two bare metals stents (BMS): JOMED 3.5 × 12 mm and JOMED 3.0 × 19 mm at 14 atm and balloon angioplasty were used for percutaneous coronary intervention (PCI) on the middle part of RCA. During further follow-up 9 years, the patient did not have any chest pain. He was on dual antithrombotic therapy (clopidogrel 75 mg and aspirin 100 mg *per* day) during the first year, followed by aspirin alone 100 mg *per* day.

Just before admission, electrocardiography (ECG) showed sinus rhythm, heart rate 73 bpm, ST segment elevation in inferior leads, marked down-ST segment depression with biphasic, dominant negative T waves from V1-V3 (Figure 1a).

In the right precordial leads there were no significant ST-segment changes (Figure 1b), that excluded signs of myocardial infarction of the right ventricular wall.

The patient was the New York Heart Association (NYHA) functional class II and had low blood pressure, 100/70 mmHg. Laboratory analyses revealed creatine kinase (CK) 797 U/L, MB fraction 50 U/L, alanine aminotransferase (ALT) 52 U/L, aspartate aminotransferase (AST) 101 U/L, lactate dehydrogenase (LDH) 386 U/L, total cholesterol 6.93 mmol/L, triglycerides 1.56 mmol/L. Other laboratory parameters were normal.

Transthoracic echocardiography (TTE) revealed normal left ventricular dimension, with hypokinesis of basal and middle segments of inferior and posterior wall with moderate to severe decreased left ventricular ejection fraction (LVEF 45%).

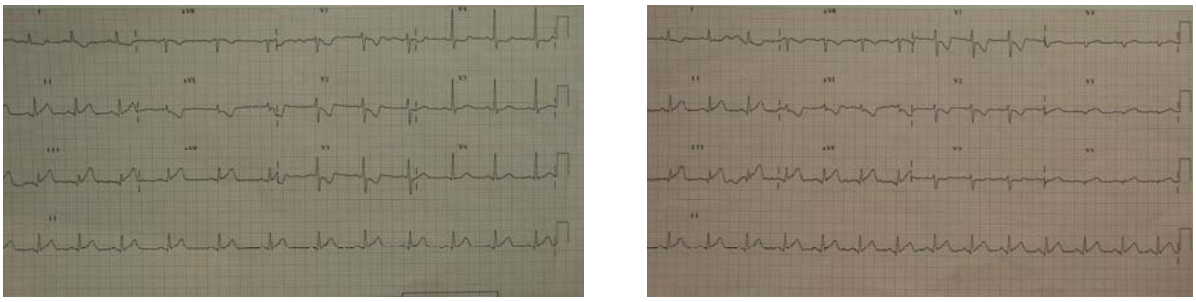
Coronary angiography was immediately performed using the right transfemoral approach and revealed the atherosclerotic left anterior descending artery (LAD), with narrow tubular stenosis diameter of 60–70% in the proximal segment and second stenosis of 80% in the middle part of the LAD. At the distal part of LAD there were 2 stenosis, one between 50% and 60%, and the second 70–80%.

The second diagonal artery had ostial stenosis of 90%. (Medina 1, 0, 1). Proximal circumflex (Cx) artery had stenosis of 40%, and without significant stenosis in the distal part (Figure 2).

Dominant right coronary artery (RCA) had stenosis of 99% in the middle segment with a huge thrombus into the previously implanted stents (Figures 3).

We decided to perform thrombus aspiration (TA) with the Export Advance Medtronic aspiration catheter as the first step of revascularization strategy. We started the procedure using 6 French JR Concierge guiding catheter for RCA. After that, ASAHI Fielder guide wire passed into the distal part of RCA to posterolateral branch, and we performed thrombus aspiration (Figures 4).

Figure 4b shows the two quite long thrombuses that indirectly implicated very late thrombosis of stents. Subsequently drug-eluting stent Coracto 3.5 × 25 mm was implanted into the middle segment of the RCA up to 14 atmosphere (Figures 5). The angiographic result was optimal, with no residual RCA stenosis.



a) **b)**

Fig. 1 – a) Electrocardiography on admission, and b) Electrocardiography of the right precordial leads.

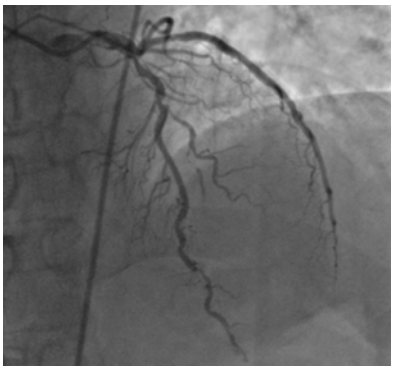
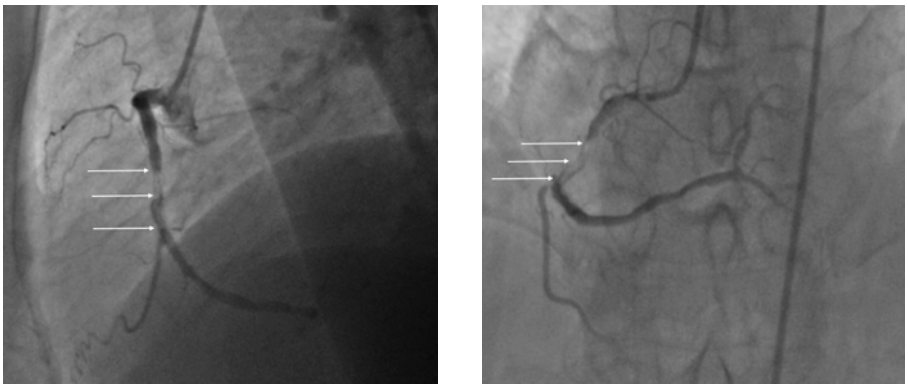
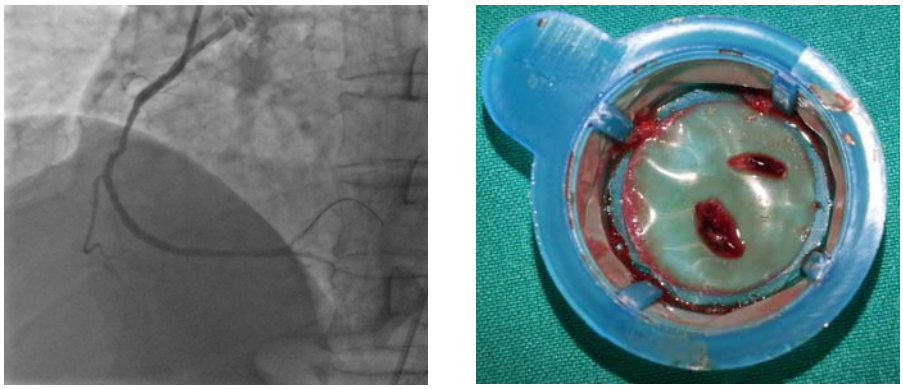


Fig. 2 – Coronary angiography of the left coronary artery.



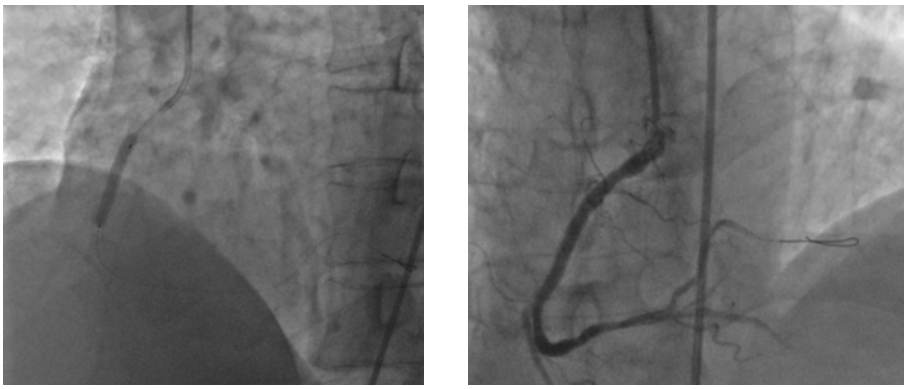
a) **b)**

Fig. 3 – a) Right coronary artery (RCA) with a thrombus (lateral view) and b) Right coronary artery (RCA) with a thrombus (cranial view).



a) **b)**

Fig. 4 – a) Right coronary artery angiography after aspiration, and b) Two large thrombuses in the right coronary artery.



a) **b)**

Fig. 5 – a) Implantation of drug-eluting stent (Coracto 3.5 × 25 mm), and b) Final results after stent implantation.

Discussion

Stent thrombosis is a catastrophic, a potentially fatal complication of stent implantation which can cause acute myocardial infarction (MI)[5], cardiogenic shock, life threatening arrhythmias and sudden cardiac death.

BMS, as well as DES, could increase and modify platelet adhesion inducing further thrombotic, inflammatory and vasoconstrictor pathophysiological reactions. Therefore, effective and longer dual anti-platelet therapy is mandatory. Late and very late ST can occur due to malapposition of stent struts, strut fractures, as well as premature cessation of antiplatelet therapy [6, 7]. In the following years stents will be covered with endothelial cells (neoendothelialization) and the need for platelet inhibition decreases due to low risk for thrombus formation inside BMS.

We presented a successful unusual results in a 56-year-old male patient with acute inferoposterior STEMI due to very late stent thrombosis (ST) despite antithrombotic therapy (aspirin + clopidogrel for one year followed by aspirin alone). The patient had myocardial infarction of the inferoposterior wall 9 years before, with PCI performed on the RCA with two BMS and balloon angioplasty of the LAD. After TA, we implanted one drug-eluting stent into the position of the previously implanted two stents to solve the in-stent restenosis.

Very late ST of BMS is quite rare, but more frequent after DES implantation due to absent endothelialization of the stent struts and delayed arterial healing [8]. DES polymer can provoke hypersensitivity and inflammatory reaction, as well as thrombus formation inside stents and new plaque rupture [8].

Neoatherosclerosis, the occurrence of atheromatous changes within neointimal tissue, is uncommon in early years after BMS implantation. It is considered to occur more frequently five years after placing BMS [9]. Recently conducted retrospective study reported that the cumulative incidence of ST after BMS implantation was 0.5% at 30 days, 0.8% at 1 year, 1.3% at 5 years, and 2.0% at 10 years [10].

The reason for very late ST in the presented patient might be connected with neointimal plaque rupture, followed by thrombotic events. Unfortunately, because of technical reasons, we could not perform intravascular optical coherence tomography (OCT) or ultrasound (IVUS) imaging which is known enable to a precise analysis of the previously stented lesion.

The results of a meta-analysis with data on 117 762 patients showed that DES are highly efficacious at reducing both the short-term risk and the long-term risk of target vessel revascularization (TVR) or target lesion revascularization (TLR), as well as stent thrombosis, compared with BMS [11]. That was the reason to implant one drug-eluting stent into the previously implanted two stents. Even more, the same meta-analysis [16] showed a significant reduction in both short and long-term risk of stent thrombosis with the newest DES (everolimus-eluting stents- EES) compared with BMS. Additionally, there were significant differences among DES types both in efficacy and safety. Evidence suggests that EES, sirolimus-eluting stents (SES), and zotarolimus-eluting stents (ZES-R), are the best regarding long-term safety and efficacy among the studied stent types [11].

Percutaneous coronary intervention, as a revascularization strategy with thrombus aspiration, as an adjunctive therapy, is class IIa recommendation for prevention and treatment of no-reflow according to the Guidelines of European Society of Cardiology [12].

In patients with ST, emergent PCI is required in order to establish normal coronary perfusion, and in two thirds of patients the procedure is successful [13]. ST has 30-day mortality rates of 10–25% [13], and every fifth patient with a first stent thrombosis experience a recurrent ST episode within 2 years [13]. Long-term follow-up of randomized DES *versus* BMS studies has reported that the incidence of ST is not likely to be increased after implantation of DES compared to BMS [14]. The total incidence of myocardial infarction and death were similar with BMS and DES [15]. Dual antiplatelet therapy (DAPT) (aspirin plus ticagrelor or presugrel) are currently recommended for the treatment of patients after PCI with either BMS or DES.

In acute coronary syndrome (ACS) patients, the incidence of ST has been reduced by replacing clopidogrel with recent and more efficient antiplatelet agents (prasugrel and ticagrelor), even though this benefit is achieved at the cost of increased bleeding according to the most recent guidelines and randomized trials [12 16, 17] .

Taking into account all the relevant facts due to this case, we decided to continue DAPT with ticagrelor 90 mg twice daily in addition to aspirin 100 mg daily and the patient remained free of symptoms or major adverse cardiac event (MACE) at 6 month follow up.

Conclusion

This is a very rare case of acute inferoposterior STEMI related to quite late stent thrombosis, 9 years after BMS implantation, despite antithrombotic therapy. We successfully performed thrombus aspiration, followed by PCI with implantation of one drug-eluting stent into the previously implanted two stents to solve the in-stent restenosis. Very late stent thrombosis, although fortunately very rare, not completely understood so far, may cause myocardial reinfaction, but can be successfully treated with thrombus aspiration followed by primary PCI with DES.

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Received on December 24, 2014.
Revised on May 18, 2015.
Accepted on May 20, 2015.
Online First March, 2016.

CASE REPORT

UDC: 617.3-089:617.58-089
DOI: 10.2298/VSP150419039R

Ilizarov method as limb salvage in treatment of massive femoral defect after unsuccessful tumor arthroplasty

Primena aparata prema Ilizarovu za spasavanje noge u lečenju masivnih defekata butne kosti nakon neuspešne tumorske artroplastike

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Abstract

Introduction. Surgical management of massive bone defects is very challenging in terms of estimating possibilities of saving the extremity and adequate method that can make it possible. Selection of methods is additionally limited in the presence of infection at site of defect. **Case report.** The female patient, diagnosed with Ewing sarcoma was treated by segmental bone resection and implantation of Kotz modular tumor endoprosthesis. After 5 years the signs of infection occured and persisted with low grade intensity. After falling, 12 years following implantation, the patient acquired periprosthetic fracture. Then endoprosthesis was removed, all along with surgical debridement of wound and application of the Ilizarov apparatus. The apparatus was applied, osteotomy of callus and the tibia performed with transport of bone segments, untill reconstruction of defect and arthrodesis of the knee was achieved. **Conclusion.** The Ilizarov apparatus offered us huge possibilities for management of massive bone defects with natural bone which has superior biomechanical characteristics comparing to the implant. The most frequent complication of this method is a prolonged treatment period that demands good patient selection and preparation and wide surgical experience.

Key words:
sarcoma, ewing; femur; infection; fractures, bone; ilizarov technique; treatment outcome.

Apstrakt

Uvod. Hirurško zbrinjavanje velikih defekata kostiju stavlja hirurga u veliko iskušenje u pogledu procene mogućnosti spasavanja ekstremiteta kao i primene adekvatne metode kojom će to učiniti. Izbor metoda je dodatno ograničen kod postojanja infekcije na mestu defekta. **Prikaz bolesnika.** Kod bolesnice zbog Ewing-ovog sarkoma učinjena je resekcija tumora i implantacija tumorske endoproteze Kotz. Posle pet godina javili su se znaci infekcije niskog intenzitetom. Nakon 12 godina, bolesnica je pri padu zadobila periprotetski prelom kada je odstranjena endoproteza, učinjena hirurška obrada i postavljen aparat prema Ilizarovu koji je, uz menjanje konstrukcije i dodatne operacije, nosila do potpune nadoknade defekta i postizanja artrodeze kolena. **Zaključak.** Aparat prema Ilizarovu pruža velike mogućnosti nadoknade defekta prirodnom kosti koja ima superiorne biomehaničke karakteristike u odnosu na implantat. Najčešća komplikacija ove metode je produženi period nošenja, što zahteva dobru selekciju i pripremu bolesnika, kao i veliku veštinu hirurga.

Ključne reči:
sarkom, juingov; femur; infekcija; prelomi; metod ilizarova; lečenje, ishod.

Introduction

Ewing sarcoma is a highly malignant tumor. In most cases its origin is in bone tissue (approximately 10% originates from tissues that are surrounding bone) [1]. Population younger than 30 years is usually affected [2]. The fact that almost 25% of this tumor are metastatic at the diagnosis time is one of the biggest problems in succesfull treatment [3]. For a

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long period amputation surgery was the only treatment for this pathology. The first announcement of possible new treatment option was made in 1950 when Buchanan [4] introduced total femur replacement. First results of reconstructive surgery were controversial comparing to amputation, a standard procedure for this pathology at that time [5]. The cardinal reason for this was a high frequency of tumor recidives. Together with improvement of adjuvant hemiotherapy and advancement in endoprosthesis design limb salvage surgery has been established as standard in this area of orthopedic oncology [6, 7]. A spectar of new complications arises comparatively with this procedure with infection and residual bone defects among most frequent ones.

There are few available options for treatment of this complication with its benefits and imperfections. One of those, used with a significant succes is the Ilizarov method. First attempts of external or extrafocal fixation originated from the first half of 19th century and were represented by a work of Malgagnie in 1843 [8]. In 1966 Russian physician Ilizarov introduced a new method of reconstruction of defects of long bones based on *de novo* bone formation between bone selvedges created by osteotomy and their latter graduated distraction. The osteosinthesis process is performed in two manners, by bilocal sinchronized compressive distraction or by alternate distraction compressive osteosinthesis [9]. At the very beggining of external fixation, the Ilizarov major aim was treating of bone infection ensued after fracture [10]. He was first who described the influence of exerted distraction in the processes of osteogenesis and suppresion of tissue inflamation reaction without use of antibiotics.

Case report

At the age of 18 the patient was diagnosed with Ewing sarcoma. The patient was treated surgically by segmental resection of the femur and reconstruction of the distal femur with the Kotz type of modular tumor endoprosthesis. Five years afterwards, the signs of low-grade infection occurred (secretion from wound and local rudiness). This was treated by occasional peroral antibiotic therapy in addition to which infection persists. Twelwe years following implantation, after falling, the patient acquired a periprosthetic fracture of the proximal femur and was referred to our hospital for the first time. After clinical processing was completed, we ascertained periprosthetic fracture and the presence of fistula with low secretion of serous pus content. Laboratory parameters for infection as well as culture results of smear were negative. As there were data about a long history of infection and significant wound secretion earlier, we decided to perform extraction of endoprosthesis and surgical debridement. Intraoperatively, we found a small amount of pus and intraoperative culture was negative. Postoperatively, the leg was immobilized with coxofemoral imobilisation. Antibiotic therapy was administered by the protocol that was apllied at that time and, meanwhile changed a lot. It consisted of the 3rd generation of cefalosporin intravenously for 10 days and continued with peroral antibiotics for 21 day. Afterwards, the patient tried to manage further medical treatment in the Ilizarov Center in the city of Kurgan, Russia, but after some time changed her mind and continued with treating at our Clinic.

Before surgery, new x-ray was obtained and healing of the fracture of the proximal femur was found. Femoral defect was estimated approximately 15 cm (on x-ray) relative shortening, while clinical (absolute) shortening of the leg was about 22 cm. After 6 months without clinical and laboratory signs of infection the Ilizarov apparatus was positioned on the thighs and lower leg, corticotomies of the tibia and fibula performed as well as osteotomy of a callus of the fractured fragment of the proximal femur. Then we started with simultaneous transport of a free femoral fragment and distraction of the lower leg aiming at arthrodesis of the knee. The dinamics of fragment transport and distraction was 0.5 mm *per* day (Figures 1 and 2). Occasionaly, we noticed cut-in of a K wire through skin and consecutive minimal skin necrosis

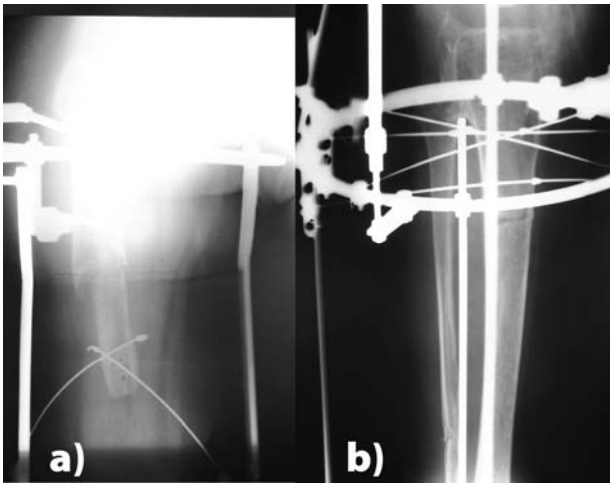

Fig. 1 – Osteotomy of calus performed, also corticotomy of tibia and fibula: transport started [a) antero-posterior radiograph; b) profile radiograph].

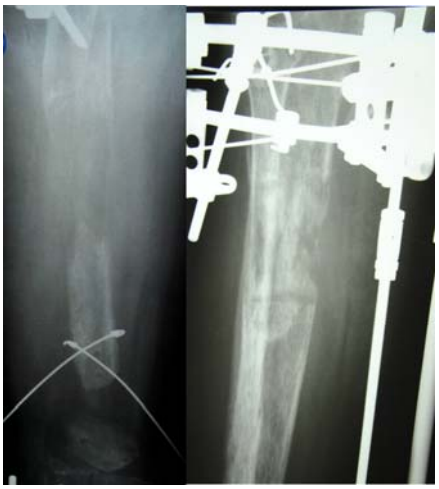

Fig. 2 – Transport of bone segments-noticeable regenerate.

which was treated by local wound cleaning and healed *per secundam*. Ankle distraction resulted in contracture, as well as equinus foot deformity, that are frequently reported as complications of this method, so we removed this construction after 6 months. Then we performed Achilles tendon elongation (Hoke) and placed construction for correction of equinus deformity. As fractured femoral fragment transport was finished, with good bone regenerate forming, two hoops were placed on the distal femur and adequate construction of the lower leg in order to aplly compression and achieve arthrodesis of the knee. This was enhanced with patellar autologous bonegrafting. This construction was successful for correcting foot deformity and Achilles tendon elongation, but unsuccessful about knee arthrodesis. After 8 months we estimated that the existing bone quality was not good for a new Ilizarov construction, so we removed the existing one and put immobilisation, that was used for next 2 years. Then, in agreement with the patient, a new construction was positioned, accompanied with osteoplastics with alografts, bone ends refreshing and graduate compression, so we reached arthrodesis in 5 months (Figure 3). After finishing surgical treatment, residual leg shortening was 1.5 cm, the patient walked without using any tool, with no pain in everyday activities. The patient restored the same level of activities as before the failed artrhoplasty. Ankle function was excellent, with submaximal range of movement and no pain (Figure 4).

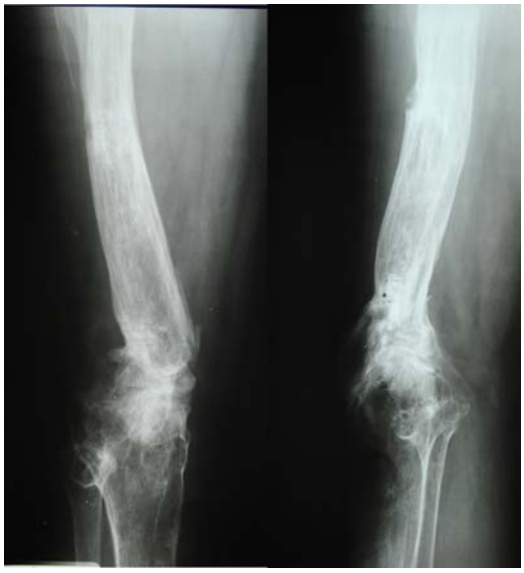

Fig. 3 – Arthrodesis of the knee achieved (Illizarov apparatus removed).

Fig. 4 – Patient 24 months after apparatus was removed.

Discussion

Managing the presented patient, the surgeon was in enviable position and in a great dilemma choosing the therapeutic approach. Amputation was a possible option, with the possibility for quick rehabilitation. As the patient was young, with no complications of primary pathology, and highly motivated for reconstructive surgery, it was decided to use the experience with the Ilizarov technique and attempted to manage the existing defect with bone transport and distraction with final knee arthrodesis. The patient was acquainted with the inevitable long period of treatment, as well as with the possibility of other complications.

Surgical treatment of bone defects following trauma, tumors, infections, failed arthroplasties or congenital anomalies can be performed with different methods: free bone grafts, vascularized fibular grafts, custom made endoprosthesis and arteficial bone substitutes. There are advantages and imperfections of each of these methods regarding defect size that can be managed, percentage of nonunion, mechanical strength, donor site comorbidity and surgeons experiance that is needed [11–14]. Autologous bone grafts can be used in treating smaller defects. Vascularized fibular grafting is an extremely technically demanding procedure and there are reports of significant incidence of pseudoarthrosis and nonunions. Song et al. [15], published a study that suggested advantage of bone transport comparing to vascularized fibular graft when it come to functional results.

The Ilizarov metod of osteodistraction is a reliable method for managing defects larger than 8 cm [13], like the one we had to deal with. The most frequently reported complications of this method are a prolonged period of treatment and pin tract infection [16–18]. Some authors suggest intramedulary nailing and bone transport over nail for the reduction of treatment time [19–21]. There is a widely accepted opinion that pin tract infection is successfully managed by local wound toilette, antibiotics administration and, eventually correction of needle position [16, 17, 22, 23]. One of the most frequently reported complications of this metod is docking site fracture in 25% of patients [24, 25].

Principal advantage of distraction osteogenesis is the possibility to achieve regeneration of live bone that has the same or closely same strength like former bone, with the possiblity of live tissue to adopt for mechanical loads in future.

Difficulties we dealt with during treatment of the presented patient are the most frequent complications of the Ilizarov method in general. At the planning phase and during

the treatment, possibilities that could reduce treatment time were considered, but we thought none of them could successfully be applied in this case. We deem that key factors for the success in such a long treatment are patient cooperability and a good relation between a patient and the doctor. If we take a look on economical side, inital expenses for amputation are much lower, but projected expenses of lifetime prosthetic works are larger [26, 27].

Conclusion

The Ilizarov method is an excellent choice for managing massive bone defects accompanied with local infection. A principal disadvantage is a prolonged treatment time, that demands good selection and preparation of patients. It is very important to mention a long learning curve and the need to plan the well-timed education.

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Received on April 19, 2015.
Revised on May 12, 2015.
Accepted on May 13, 2015.
Online First March, 2016.

CASE REPORT

UDC: 616-001.45-089::617.51/.52-089.844
DOI: 10.2298/VSP150310043M

Cranial reconstruction with prefabricated 3D implant after a gunshot injury – A case report

Rekonstrukcija defekta lobanje 3D implantatom nakon sklopetarne povrede glave

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Abstract

Introduction. Complex defects of skull bones with different etiology, still present the challenge in reconstructive surgery. The goldstandard for cranioplasty is the autologous calvarial bone graft removed during surgery which cannot be always applied, especially in gunshot wounds for sometimes complete bone destruction. Autologous reconstruction with split calvarial, rib bones or iliac bone graft is also possible. Materials routinely used for reconstructions like titanium mesh, polymethyl metacrylate (PMMA), and other have numerous disadvantages and limitations. **Case report.** We presented a patient with gunshot injury to the head with residual large bone defect in the frontal region, with involvement of the skull base, and open frontal sinus. After conservative treatment, six months after the injury, reconstruction of the residual bone defect was performed. The chosen material was computer-designed PEEK-OPTIMA® implant, manufactured on the basis of MSCT scan. This material has not been used in this region so far. The postoperative and follow-up period of the next 12 months passed without surgical complications, neurological deficit, with satisfactory functional and aesthetic results. **Conclusion.** Implanted bone replacement was designed and manufactured precisely according to the skull defect, and we found it suitable for the treatment of complex defects of the cranium. Early results are in favor of this cranioplasty method over standardized materials. Therefore, this material is expected to become a method of choice for reconstructive surgery of bony defects of the face and skull especially in complex cases.

Key words:
skull; prosthesis and implants; biocompatible materials; polyethylene glycols; polyetheretherketone; computer-aided design; reconstructive surgical procedures.

Apstrakt

Uvod. Kompleksni koštani nedostaci mogu imati različitu etiologiju i predstavljaju pravi izazov u rekonstruktivnoj hirurgiji. Zlatni standard kranioplastike je rekonstrukcija skinutom kosti lobanje, koja se u mnogim slučajevima ne može primeniti, naročito kod sklopetarnih povreda zbog destrukcije kosti. Rekonstrukcija autolognim graftom razdvajanjem kalvarija, rebrom ili ilijačnom kosti, takođe je moguća. Do sada primenjivani veštački materijali poput palakosa, titanijumskog meša i drugih, imaju brojne nedostatke i ograničenja. **Prikaz bolesnika.** Predstavljen je pacijent kome je nakon sklopetarne povrede glave ostao veliki koštani defekt frontalne regije sa zahvatanjem prednje lobanjske baze i otvorenim frontalnim sinusom. Nakon primarnog hirurškog zbrinjavanja i sprovedenog konzervativnog lečenja, šest meseci od povrede odlučeno je da se uradi rekonstrukcija nastalog koštanog defekta. Uzimajući u obzir sve relevantne medicinske faktore odlučeno je da se rekonstrukcija uradi primenom najsavremenijeg implantata od materijala PEEK-OPTIMA® koji je oblikovan na osnovu MSCT snimka u 3D tehnici. Ovaj materijal do sada nije korišćen na ovim prostorima. Neposredno i postoperativno praćenje sledećih 12 meseci pokazalo je tok bez komplikacija operativnog polja i neurološkog deficita, sa izuzetno zadovoljavajućim funkcionalnim i estetskim rezultatima. **Zaključak.** U toku primene ove nove hirurške intervencije uverili smo se da je proizveden implantat veoma precizno izrađen prema defektu i da je veoma pogodan kod zatvaranja kompleksnih i ekstenzivnih kranijumskih defekata. Naša prva iskustva idu u prilog očekivanju da će ovaj vid kranioplastike imati značajno mesto u rekonstruktivnoj hirurgiji defekata kostiju lica i glave.

Ključne reči:
lobanja; proteze i implantati; biokompatibilni materijali; polietilen glikoli; polietereterketon; kompjuterski podržan dizajn; hirurgija, rekonstruktivna, procedure.

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Introduction

Cranial defects are mainly caused by surgical intervention after various types of traumas, tumors, infections, congenital cranial anomalies and other causes. In most cases it is necessary to reconstruct them. The main objectives of cranioplasty are to restore the normal barriers protecting the intracranial structures, normalization of intracranial pressure, thus alleviating neurological deficits, but also to achieve satisfactory aesthetic results [1–3]. In cases of gunshot wounds to the head, bone is usually destructed, therefore not usable.

Cranioplasty is dating back to the prehistoric times when various materials, available at that time, were used. Historical data shows that golden and silver plates were used in some parts of the world [1]. These materials were also used in the recent history, but they are no longer in use due to low resistance even to the minimal trauma. Other materials such as steel and tantalum were discarded because of the excessive conductivity of heat and cold, weight, as well as inadequate radiopacity.

Due to its characteristics, autologous bone grafts remain still superior, despite many various synthetic materials. In some cases, it is not possible to preserve autologous bone graft, and the length of its own storage in the patient or in the bank is not unlimited. Gunshot wounds to the head lead to destruction and contamination of the calvarial bones, and, therefore, these bone defects are always a subject to delayed reconstruction.

Autologous bone graft, taken from another part of the body (calvarial bone, rib grafts, iliac bone) has many advantages like resistance to infections, growth potential, radiotransparency at no additional cost. At the same time, important downsides are two surgical fields [4, 5], and risks of incomplete take of the graft, due to resorption or infection [6–8].

Therefore, there was the need for a material that would be a suitable replacement, as similar as possible to the characteristics of the bone tissue, resistant to infection, atoxic and biologically inert.

Methyl methacrylate (MM) is the most widely applied alloplast in use, particularly suitable for small defects, and some authors report its infection rates to be lower than rates achieved with autologous bones [9], but infection rate is higher on large-size defects [10]. This material is cheap, momentarily available and easy to use. The limitations of this material are numerous when the defect is in contact with the sinuses, because of significantly increased risk of infection [11].

In addition to MM, titanium mesh is in use, which is very difficult for design of complex defects, and sharp edges can lead to decubitus wounds [12, 13], as well as the problem of application in patients who have suffered radiation treatment.

Nowadays bioactive materials such as hydroxyapatite, kryptonite and many others are in use. But so far, no large study on these materials has been published, and surgical experience with them is also modest.

Materials used so far were insufficient when it comes to large and complex defects of the skull. Modeling was difficult or even impossible, and satisfactory functional and cosmetic results were not always achieved.

PEEK OPTIMA® is polyetheretherketone, which is structurally linear, aromatic polymer, and morphologically semicrystalline. The advantages of this material are excellent biocompatibility, combination of strength, stiffness and viscosity [14], comparable to cortical bone. Manufacturers state that it has bone-like temperature conductivity of 0.4 W/Km. As for the radiological characteristics, there are no artefacts when using conventional imaging techniques such as X-Ray, computed tomography (CT), magnetic resonance imaging (MRI), and all conventional procedures for the sterilization are applicable (steam, ethylene oxide and gamma irradiation), and a resterilization is possible, as well. PEEK OPTIMA® can be additionally shaped at the operating room.

Case report

We presented a 21-year-old male patient who sustained gunshot head injury of a frontal region. He was initially treated in a local health center, where he underwent primary surgical treatment, wound debridement and removal of bone fragments. Soft tissues and dura were reconstructed, however, the reconstruction of the skull defect was not performed. After the intervention the irregularly shaped bone defect (7 × 8 cm) remained, with the defect of the skull base and opened frontal sinus.

The patient was admitted to the Clinic for Infectious Diseases of the Military Medical Academy, Belgrade, Serbia, as an emergency with signs of meningeal irritation one month after primary surgical treatment. Urgent multislice computed tomography (MSCT) revealed signs of epidural and subdural abscess and pneumocephalus causing compressive effect to the brain parenchyma after which an emergency surgery was performed, and included wound revision with the evacuation of the epidural and subdural abscess and reconstruction of the dura mater and frontal sinus. The bone defect remained for the subsequent solving. He was discharged from the hospital two weeks later, in good clinical and neurological state with an oral anticonvulsive and antimicrobial therapy (Figure 1).

One month after discharge from the Clinic for Infectious Diseases of the Military Medical Academy, the patient reported in good general clinical state, with laboratory results showing no signs of infection, nor inflammation, with no pathologic neurological finding (Glasgow Coma Scale − 15). Complex defect of the skull engaging frontal and sphenoid bones was present, compromising both functional and aesthetic purpose of the bones. Polymethyl methacrylate (PMMA) or titanium mesh reconstructions were of probable unsatisfactory result, and the decision was made to use prefabricated 3D implant which would be precisely fited to the contours of the bone to fulfill the defect as good as possible.

Surgery was scheduled for 6 months after discharge. The absence of signs of infection (both local and systemic) had to be repeatedly verified. MSCT was done (Figure 2) and the files were sent to the engineers in a “3Di company”, who had made a virtual 3D model of the patient. To design a virtual model, either an inversion or simulation model can be used. The inversion was based on the assumption that the

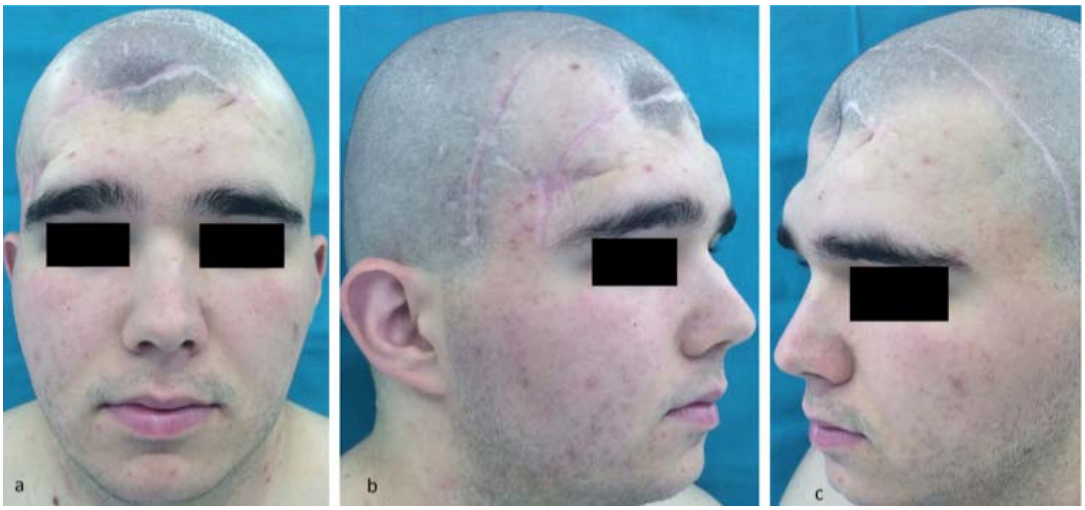

Fig. 1 – Preoperative appearance of the patient: a) *En face*; b) Right halfprofile; c) Left halfprofile.

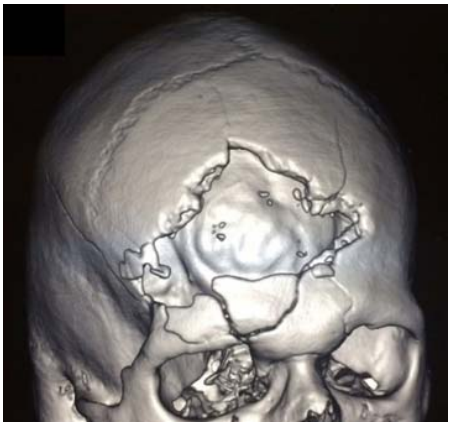

Fig. 2 – Preoperative multislice computed tomography showing a complex defect of the skull.

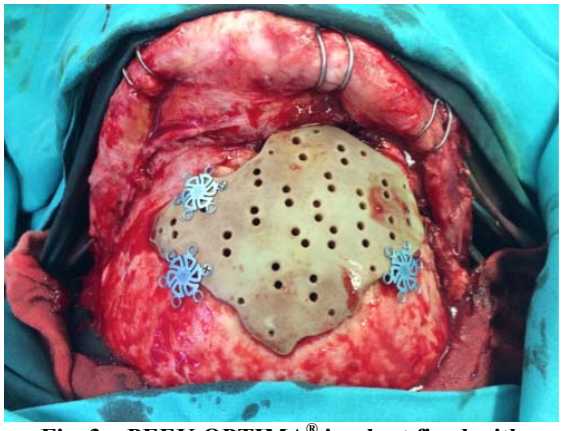

Fig. 3 – PEEK OPTIMA® implant fixed with titanium screws and stars.

human skull is almost symmetric, and the simulation model is useful in cases of asymmetrical defects, in the midface area, whenever an inversion is impossible. In this case, the simulation model was used. In this method measurements and characteristics of the scanned skull contained in a data bank, are compared to a highly precise 3D representation of the patient's corresponding defect area. After designing a virtual model, it is forwarded to the surgeon, for consultation before completion of prosthesis creation, in order to make any possible adjustment, regarding thickness and the type of fixation of the implant. Fabrication of the implant was performed with three-axis computer numerical control drilling machine using selected material. In this case, the 3D implant is made from non-resorbable thermoplastic material PEEK OPTIMA®.

After the arrival of the implant, and preoperative preparation, cranioplasty was performed with the 3D implant previously cut, characteristic for bicoronary craniotomy. Due to the open frontal sinus, cranialisation with neuropatch was required. After preparing the bone defect edges of the skull, previously sterilized implant has been created, using titanium plates, and fastened with screws. The implant is attached to the bone with three titanium stars (Figure 3). The epicranial aspiration drainage was also applied. A triple antibiotic therapy was administered to the patient after the surgery. Postoperative scan images showed that prothesis completely filled the bone deficiency (Figure 4).

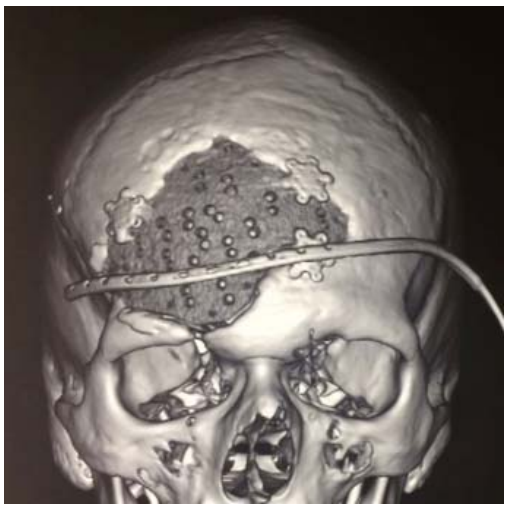

Fig. 4 − Multislice computed tomography (3D reconstruction) on the first postoperative day showing the fixed PEEK OPTIMA® implant.

The patient was discharged on the fifth postoperative day, with regular local and good overall status. At the check-up on the 12th postoperative day, stitches were removed, and the local status was very satisfactory. The patient was without neurological deficit. At the check-up one month after the operation, the patient showed himself completely satisfied (Figure 5). Postoperative follow-up the next 12 months showed the course without complications of the operative field and neurological deficits, neither was the forthcoming period expected to give any.

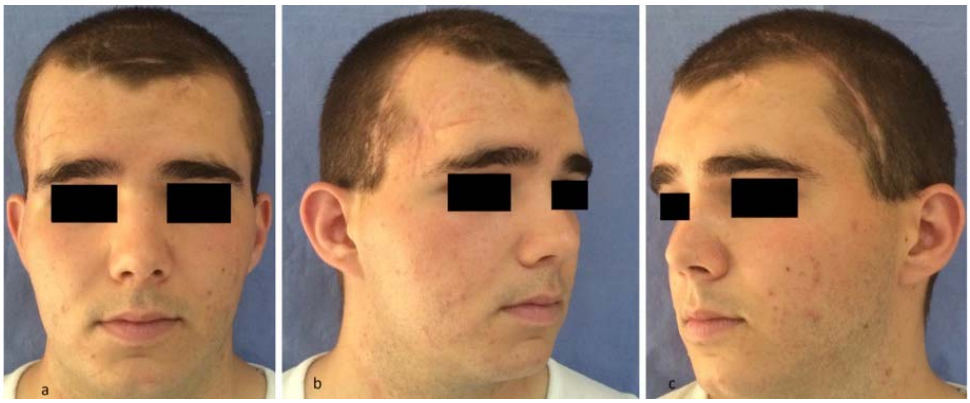

Fig. 5 – Postoperative appearance of the patient: a) *En face*; b) Right halfprofile; c) Left halfprofile.

Discussion

Cranioplasty of complex bone defects represents a real challenge for the surgeons. Many materials commonly used have many drawbacks during designing phase, so that fully satisfactory functional and aesthetic results cannot be achieved. Cranioplasty performed at early state, reduces the risk of late epilepsy, as well as complications of neuropsychological nature. War gunshot wounds to the head are specific for their extensiveness due to large projectile primary bone destruction and primary polymorphic bacterial contamination, which, together with wounded skin scaring makes cranioplasty vastly complicated. Wounding is also resulting in large epidural cavity, which makes difficult the procedure furthermore.

The golden standard of cranioplasty after craniotomy is reconstruction with the autologous bone graft. In many cases such a bone cannot be used, due to complex multifragmentary fractures with bone destruction (as is the case in civilian and war gunshot wounds), tumor destruction, poor bone quality after chemotherapy and radiotherapy, so artificial materials are being commonly used in deferred cranioplasty.

Large individual diversity of the skulls, high functional requirements, as well as high aesthetic criteria represent a major challenge for the surgeon during selection and utilization of the materials for such an intervention. Industrially manufactured implants are unable to respond to all requirements set. Consequently, all this new technology has been developed for the creation of 3D referent implants and that is based on the data according to the prepared MSCT, so that each implant is made in shape of the defect, and is specific for each patient. Materials most often used for this purpose include BIOVERIT® II and PEEK-OPTIMA®. BIOVERIT® II is glass-ceramics polymer. It was introduced in 1982 and up to nowadays it has been used for building over 2,000 specifically designed implants. The material is biocompatible, firm, suitable for modelling during the intervention, and it does not cause any artefacts in MR/CT scans. The major flaw of this material is its price. PEEK-OPTIMA® is a kind of thermoplastics with high performances, linear aromatic polymer, with similar characteristic as BIOVERIT® II. It is in use for the last 30 years. In addition, material is successfully used for intraoperative modelling, can be sterilized by any method, and repeatedly, if required. Material is often used for secondary cranioplasty following infections, with excellent results [15]. It has shown a great success with patients who has been previously exposed to radiation, and with signs of radionecrosis and osteomyelitis [16]. The method of reconstruction presented in this paper provides achieving very precise and natural model, as well as for very unreachable regions such as base of a skull [14].

The aim of skull reconstruction is adequate reconstruction of the defect without functional problems, and on the other hand as good aesthetic result as possible. Cranioplasty as a method of treatment has to be safe, fast and technically easily performed. Price quality *versus* rate of the procedure will certainly dictate further application [17].

PEEK OPTIMA® personalized implants have been in use for 10 years in western countries with great success. Simplicity of the procedure, short postoperative flow and almost complete absence of complications are the main qualities emphasized for this material.

The biggest drawback of PEEK-OPTIMA® material is the implant price. A concrete case presented here costs more than ten thousands euros, which significantly raises expenses of the operation. Compared to a titanium mash or MM, PEEK-OPTIMA® has several times higher price. Application of this material is a completely new practice for this medical center, therefore it is difficult to justify its usage according to its advantages, related to the days required for postoperative phase, and other eventual complications. However, even with high price for some complex defects, it still holds absolute indication for application, and this case represents only the beginning.

Conclusion

Experience in reconstructive skull surgery shows that complex defects represent quite a challenge for a surgeon, in order to provide good functional achievement, and satisfying aesthetic results at the same time. Each material used previously showed certain drawbacks, as discussed. During application of this new surgical intervention, it is convincing that a produced implant was made precisely according to craniotomic defect, and that it fills in completely, following anatomic shape of the skull. Implant edges meet the requirement of the defect, and are rounded, which prevents risk of decubitus wounds. At the same time, the duration of intervention is shortened, since the surgeon gets a well-prepared implant, and no additional time is necessary for modelling in the operation room. Early experiences prove that this method of cranioplasty is significantly more suitable than previous methods. As stated before, the biggest obstacle in routine application of the method is the high price of the material. There is a hope that the price will get lowered, and become available to a larger group of patients.

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Received on March 10, 2015.
Revised on May 22, 2015.
Accepted on July 24, 2015.
Online First March, 2016.

CASE REPORT

UDC: 616.13-002-036/-08
DOI: 10.2298/VSP150717092K

Relapse of Takayasu arteritis as a cause of suicidal poisoning and subsequent major ischemic stroke successfully treated with thrombolytic therapy

Pogoršanje Takayasu arteritisa sa suicidnim trovanjem i ishemijskim moždanim udarom uspešno lečenim trombolitičkom terapijom

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Abstract

Introduction. Takayasu arteritis (TA) is a rare large vessel arteritis, affecting primarily aorta and its major branches. Its clinical manifestations can vary significantly – from asymptomatic to serious vascular events. Acute neurological complications are frequent at the onset of the disease and in relapses. Anxiety and depression are more frequent in TA patients than in general population as well as during relapses. Prevalence of transient ischemic attack or ischemic stroke in TA patients is approximately 10–20%. **Case report.** We presented a patient with TA that began with a depressive episode resulting in attempted suicide by bromazepame poisoning. This was subsequently followed by major ischemic stroke caused by thrombosis of the left middle cerebral artery (probably due to aortic arch embolism) successfully treated with intravenous thrombolysis. **Conclusion.** Intravenous thrombolysis appears to be safe and effective in patients with TA and stroke.

Key words:
takayasu arteritis; recurrence; poisoning; suicide, attempted; thrombosis; middle cerebral artery; tissue plasminogen activator; treatment outcome; depression.

Apstrakt

Uvod. Takayasu arteritis (TA) je redak arteritis velikih krvnih sudova, koji prvenstveno zahvata aortu i njene velike grane. Njegove kliničke manifestacije mogu znatno varirati, od asimptomatskih do ozbiljnih vaskularnih događaja. Akutne neurološke komplikacije su česte na početku bolesti i tokom relapsa. Anksioznost i depresija su češće kod bolesnika sa TA nego u opštoj populaciji i češće su tokom relapsa. Prevalencija tranzitornog ishemijskog ataka i ishemijskog moždanog udara kod bolesnika sa TA je približno 10–20%. **Prikaz bolesnika.** Prikazana je bolesnica čija je aktivna faza TA počela depresivnom epizodom koja je dovela do pokušaja samoubistva trovanjem bromazepamom. Sledio je *major* ishemijski moždani udar izazvan trombozom srednje moždane arterije (verovatno usled embolije poreklom aortnog luka), koji je uspešno lečen intravenskom trombolizom. **Zaključak.** Intravenska tromboliza je bezbedna i efektivna kod bolesnika sa TA i moždanim udarom.

Ključne reči:
takajasu arteritis; recidiv; trovanje; samoubistvo, pokušaj; tromboza; a. cerebri media; plazminogen, aktivator, tkivni; lečenje, ishod; depresija.

Introduction

Takayasu arteritis (TA) is a large vessel arteritis, affecting primarily aorta and its major branches. Its clinical manifestations can vary significantly – from asymptomatic to serious vascular events, occurring both at the beginning of the disease and during relapses (i.e. active phase). In the presented case, relapse of the disease began with a depressive episode resulting in attempted suicide by bromazepame poisoning. Ischemic stroke occurred subsequently, also in the active phase of the disease, and was successfully treated with intravenous thrombolysis.

To the best of our knowledge, this is the first report of TA relapse manifesting with depression and attempted suicide, followed by ischemic stroke and successful intravenous thrombolysis.

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Case report

A 61-year old female was found in a state of unconsciousness, on the floor of her home with a scalp laceration. The patient was in a shallow coma, Glasgow Coma Scale (GCS) score 7 with otherwise unremarkable neurological examination, subfebrile (37.2°C) and hypotensive (80/60 mmHg) with ECG showing regular sinus rhythm at a rate of 68/min. She was initially examined in the local hospital, intravenous dopamine and normal saline were administered, and head laceration was sutured. Multislice computed tomography (MSCT) of the head was done at local hospital and no signs of ischemia, hemorrhage, or other brain lesions were noted.

Drug overdose was suspected since empty packages of prescribed medications were found in her vicinity and she was transported to the Military Medical Academy for toxicology screening. Upon admission to emergency room, benzodiazepine antagonist – flumazenil (0.2 mg *iv*) was administered with partial improvement of consciousness. She was admitted to the Toxicology Clinic in a soporous state (GCS 9), with slurred speech and unresponsive, miotic pupils. Bromazepame plasma concentration was 1.02 mg/L (levels above 0.3 mg/L are considered toxic, coma is virtually invariable above 1.0 mg/L) with serum positive for 3-OH-bromazepame metabolite (this suggests even higher blood levels of bromazepame than those detected). Toxicology screening for ramipril and amlodipine (concomitant therapy, also suspected in overdose) were negative. Laboratory analyses at this time showed marked leukocytosis of $22.1*10^9$ (normal values: $4–11*10^9$/L) and very high creatine kinase levels of 4,390 (normal 26–200 U/L). Leukocytes remained elevated throughout the course of treatment ($> 20*10^9$/L). Acute phase reactants – erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values at that time were unavailable. The patient was treated with flumazenil in the total dose of 2.3 mg during three days, rehydrated, intubated with continuous cardiorespiratory support and had good recovery further on. From day four she was fully alert and responsive, with unremarkable neurological exam. There was no record in personal medical history regarding depressive disorder or previous suicide attempts. The patient and her family denied any psychiatric symptoms prior to this. According to the patient, an argument with her daughter provoked her to act in this manner. Psychiatric exam found her to be suffering from an anxious-depressive disorder without current suicidal tendencies, and she was prescribed with trazadone 50 mg/day and lorazepame 3 mg/day. The personal history revealed that she was diagnosed with TA, at the age of 59, according to the current criteria [1]. The disease was presented a few months prior to diagnosis, with general weakness, malaise, arthralgia and low-grade fever. During hospitalization at that time, significantly elevated acute phase reactants were noted, while cardiac ultrasound showed only mild aortal sclerosis. However, position emission tomography (PET) scan showed increased accumulation of fluorine-18 fluorodeoxyglucose (18F-FDG) in the projection of all of the major aortic branches (brachiocephalic trunk, carotid and subclavian arteries) and MSCT aortography showed aortal wall thickening (4.5 mm) from descendent part to iliac arteries. Corticosteroid and azathioprine therapy was introduced as regular long lasting treatment.

Several months prior to attempted suicide, the patient on her own stoped taking recommended therapy. Besides this, she was treated with ipratropium bromide /fenoterolhydrobromide for chronic obstructive pulmonary disease, and was taking medium doses of ramipril, hydrochlorothiazide and nifedipine for arterial hypertension. The personal history also revealed the presence of fatty liver, gallbladder calculosis and chronic gastritis.

On the ninth day after admission, while still not taking immunosuppressive drugs, acute neurological impairment occurred, manifested as sensorimotor aphasia and severe right-sided weakness. National Institute of Health Stroke Scale (NIHSS) score was 13. She was normotensive, ECG showed regular sinus rhythm. MSCT of the brain showed discrete zone of subcortical hypodensity in the left operculum (Figure 1), while MSCT brain angiography showed left medial cerebral artery (MCA) occlusion (Figure 2). Besides this, a few chronic ischemic lesions in the left lentiform and caudate nucleus and right subcortical frontal regions were observed (Figure 1).

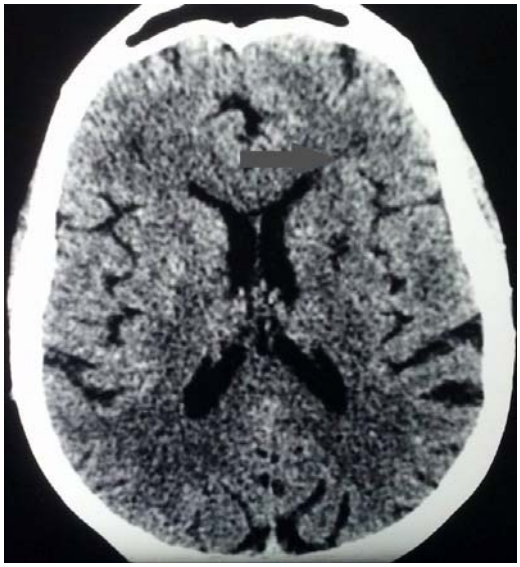

Fig. 1 – Multislice computed tomography (MSCT) axial noncontrast head scan shows left opercular hypodense lesion corresponding ischemia.

Since the patient was in therapeutic window for thrombolysis, 1 hour from symptoms onset, intravenous recombinant tissue plasminogen activator (rTPA) was administered according to standardized protocol [2, 3]. During the first 24-hour observation period, a significant clinical improvement was noted, primarily improvement of speech (minor dysphasia) and of right hand limb strength, NIHSS being 7. Control brain MSCT with angiography 24 hours after thrombolysis showed M2 and M3 segments patent, presumably through collaterals and M1 occluded. No radiological signs of acute ischemia were noted. Thrombolytic therapy was without brain hemorrhage or any other medical complication (Figure 3).

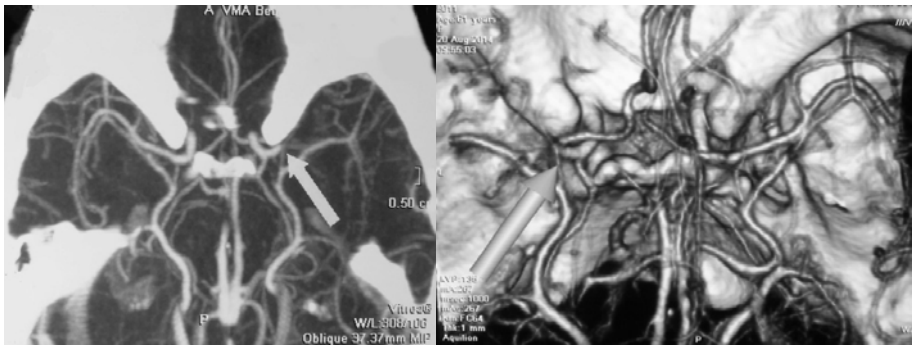

Fig. 2 – Multislice computed tomography (MSCT) brain angiography prior to *iv* thrombolysis shows occlusion of the left medial cerebral artery (MCA).

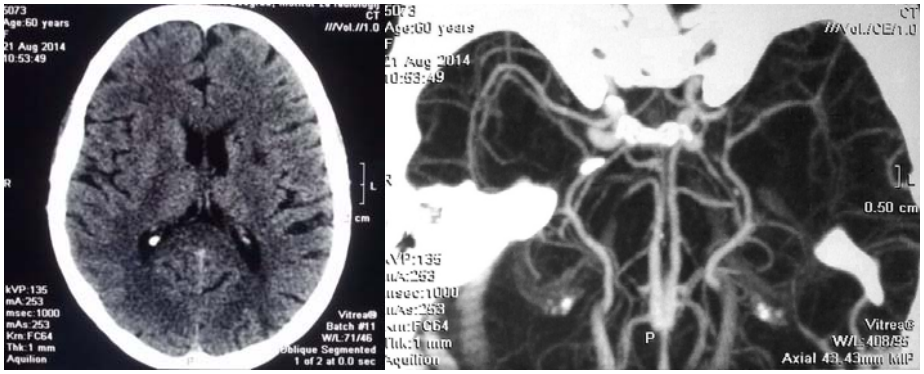

Fig. 3 – Repeated multislice computed tomography (MSCT) and MSCT angiography showing M2 and M3 postcontrast opacification of left medial cerebral artery (MCA).

A marked leukocytosis ($26.8*10^9$/L) with elevated acute phase reactants – ESR 86/h (normal value < 10/h) and CRP 195 (normal value < 3.0 mg/L), mild elevation of liver enzymes [AST 55 U/L (normal value < 37 U/L), ALT 100 U/L (normal value 7–49 U/L), LDH of 1.350 U/L (normal value 120–246 U/L)] were present in the following days. Protein C and S and antiphospholipid antibodies were negative. Serial ECGs showed sinus rhytm, with heart rates between 70 and 80/min. Polymerase chain reaction (PCR) for the most common thrombophilias-Factor V Leiden, prothrombin variance, methylenetetrahydrofolate reductase (MTHFR) and plasminogen activator inhibitor-1 (PAI-1) were negative. Carotid and vertebral Doppler sonography showed double angulation of left internal carotid artery (ICA), tortuous vertebral arteries and bilateral external carotid artery (ECA) stenosis of 20 to 25% with stable fibrolipid plaques and no other structural, nor hemodynamical significant findings. Contrast enhanced transcranial Doppler sonography showed no signs of right-to-left shunting and no microembolic signals. Transthoracic echocardiography (TTE) showed normal dimensions of atria and ventricles, preserved global and segmental kinetics, with normal blood flow and pericardium. Ejection fraction was 65%. Transesophageal echocardiography (TEE) findings were consistent with TTE findings, without additional pathology. MSCT aortography showed slight aortic arch atheromatosis with thickening (3–4 mm) of thoracic aorta wall (Figure 4).

The patient was released from hospital ten days after ischemic stroke (18 days from the attempted suicide). NIHSS upon release was 2 – a discrete right facial paresis and a minimal right hand paresis. She was advised to take aspirin 100 mg/day, atorvastatin 40 mg/day, methylprednisolone 20 mg/day for two weeks, then 15 mg/day, trazadone 50 mg/day and lorazepame 3 mg/day proscribed by psychiatrist and her usual bronchodilatative and antihypertensive therapy.

At follow-up visits, after one and six months, inflammation parameters (ESR and CRP, as well as complete blood count) were within normal range, the patient did not have new neurological, psychiatric nor any other symptoms, and overall recovery was good.

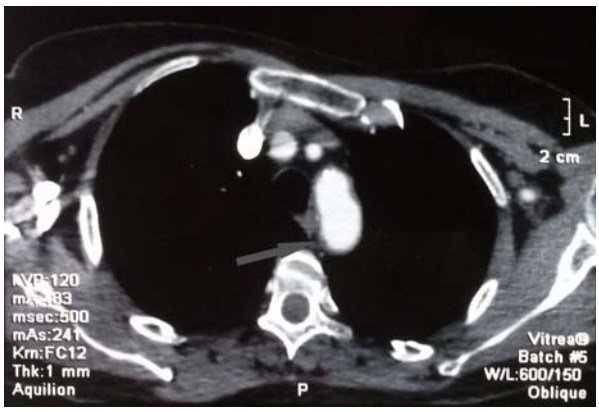

Fig. 4 – Multislice computed tomography (MSCT) aortography shows slight aortic arch atheromatiosis with thickening of the thoracic aorta wall.

Discussion

In the presented patient, relapse of TA was initially manifested as severe depression and attempted suicide with

subsequent development of major ischemic stroke, severe neurological impairment and successful thrombolytic treatment. Elevated parameters of systemic inflammation confirmed TA relapse [3]. Disease activity affects quality of life and mental and functional status in TA patients. Anxiety was found to be significantly higher in TA patients than in healthy controls [4]. Depression is twice more common in TA patients [5]. However, anxiety and depression have significantly higher incidences in active disease than in remission [5]. There are no published papers assessing incidence and prevalence of suicide attempts and suicides in patients with TA. To the best of our knowledge, this is the first published case of suicide attempt as principal manifestation of TA relapse.

Takayasu arteritis is a relatively rare systemic vasculitis with estimated incidence of 2.6 *per* million [5]. Spectrum of TA symptoms is wide, ranging from asymptomatic to serious, often psychiatric and neurological manifestations [6, 7]. Natural course is virtually unpredictable regarding initial presentation, onset of disease activity and symptom severity [8]. Asymptomatic progression is not uncommon [6–9]. The first symptoms of TA in our patient appeared at 59 years, which is rather late considering the second and the third decade of life as the usual time of TA clinical presentation [6]. Most frequent neurological symptoms are headache, dizziness, visual disturbance, transitory ischemic attacks and ischemic stroke [6, 7, 9].

Literature data regarding ischemic stroke due to TA is sparse and consists mostly of case reports and case series [10–18]. There are only few, mostly retrospective studies currently available assessing stroke in the setting of TA [9]. The prevalence of ischemic stroke in patients with TA is found to be, depending on study, between 5% and 15%, especially at the onset of the disease and during the relapses [11–16]. Etiology of ischemic stroke in patients with TA is various: artery-to-artery embolism – from aortic arch and its major branches, carotid stump syndrome, hypercoagulable state, or cardiogenic emboli due to aortic regurgitation [9]. Thrombosis of the left middle cerebral artery was the cause of major ischemic stroke in our patient, probably due to aortic arch embolism. Other possible causes of stroke were excluded – cardiogenic embolism, carotid artery embolism, thrombophilias, hypertension and atrial fibrillation.

The presence of TA is not regarded as contraindication for intravenous thrombolysis in patients with stroke according to present guidelines for acute ischemic stroke treatment [2]. Reported cases of rTPA use in TA patients with acute ischemic stroke are extremely rare and in the available literature there is only one published paper [10]. Furthermore, there are no randomized clinical trials regarding therapy of neurologic complications in TA. R-TPA application in presented case resulted in the complete recovery without complications.

Therapeutic approach in TA is oriented in general to diminishing disease activity with corticosteroids and immunosuppressants [19]. The presented patient did not take recommended corticosteroid and immunosuppressant therapy, which was a probable cause of TA relapse. Treatment of arterial hypertension and other secondary manifestations is also advised in order to decrease the incidence of end-vessel pathology [8]. Low dose aspirin use could be associated with lower frequency of repeated ischemic events in patients with TA [20], and this was our therapeutic choice as secondary prevention.

Conclusion

Acute psychiatric and neurological symptoms in patients with TA are more frequent than in general population, and tend to occur more often during relapses. This is, to the best of our knowledge, the first reported clinical case of suicide attempt caused by TA relapse, as well as one of the two reports of successful intravenous thrombolysis after ischemic stroke in a patient with TA. Intravenous thrombolysis with rtPA appears to be safe and effective in patients with TA and stroke.

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Received on July 17, 2015.
Revised on July 30, 2015.
Accepted on July 30, 2015.
Online First September, 2015.

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