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Novi Sad Vase Stajića 9 Srbija

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MAXILLOFACIAL TRAUMA IN THE EMERGENCY DEPARTMENT

URGENTNO ZBRINJAVANJE MAKSILOFACIJALNIH POVREDA

Aleksandar KIRALJ

Maxillofacial injuries are frequently found in the practice of emergency medicine. Over 50% of patients with maxillofacial injuries have injuries of other organs that require the cooperation between physicians of various specialties: emergency physician, maxillofacial surgeon, plastic surgeon, otolaryngologist, ophthalmologist, trauma surgeon. Maxillofacial trauma requires special attention of a physician. This anatomical region contains the organ systems with important functions: seeing, hearing, smelling, breathing, eating and talking, and all these structures in the head and neck are closely related. Facial bones are most frequently exposed to trauma because of their anatomical location, which is especially prevalent in the lower jaw.

Nowadays facial trauma is most frequently caused by traffic accidents, assaults, industrial accidents and gunshots. Over the past ten years (2004-2014), out of 1994 patient with facial trauma who were treated at the Department of Maxillofacial Surgery Clinical Centre of Vojvodina in Novi Sad, 806 patients had the lower jaw fractures, 319 had the upper jaw fractures, 725 patients were with the zygomatic bone fractures, 310 patients had the orbital floor fractures and 144 patients had the nasal bone or frontal process of the upper jaw fractures. The most common causes of injuries were traffic accidents (41%), assaults (37%), falls (18.7%), industrial accidents (2.2%) and gunshot injuries (1.1%). These data are different in different countries and trauma centers, therefore statistical data in literature vary.

The maxillofacial region is a specific anatomical region and it can be divided in 3 regions:

1. The region of the upper face (frontal bone and frontal sinus)
2. The region of the midface:

(a) The upper midface (zygomatic bone, nasal bone, ethmoid bone, non-tooth-bearing part of the upper jaw)

(b) The lower midface (alveolar ridge of the maxilla, teeth and palate)

3. The region of the lower face (mandible).

Rich vascularization of the maxillofacial region is often the cause of massive hemorrhage, but is also the advantage in primary treatment of soft tissue wounds because it allows treatment of the wound even 72 hours after injury using proper antibiotic prophylaxis. Wound debridement of soft tissue must be very limited in order to avoid iatrogenic injury (injuries of the facial nerve). It is necessary to remove devitalized tissue carefully.

In 1978 the Advanced Trauma Life Support (ATLS) guidelines were set up as a gold standard in treatment and care of emergency. The premise of the ATLS program is to treat the greatest threat to life first. Management of the maxillofacial injuries has its place in these trauma guidelines. Maxillofacial injuries can occur isolated, but in most cases they are associated with the injuries of other organs. There is a significant association between maxillofacial injuries and concomitant brain injuries.

The primary survey is the first part of the assessment of patient with trauma. During this period the life-threatening injuries are diagnosed and the resuscitation begins simultaneously. The primary survey includes the evaluation of the traumatized patient's condition (history of injuries, examination of the patient and assess the severity of injury). The goal of the primary survey is to bring the patient into a condition in which it is possible to make additional diagnostics and provide further surgical care.

The first stage of the primary survey is to assess the airway. Maxillofacial trauma represents the risk for the airway because of the traumatic displacement of the tissues, edema, bleeding or foreign bodies in the airway (loose teeth in the airway). It is important to ensure patency of the airway in the traumatized patient. The control of airway must be ensured as follows: if the patient is conscious and

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Abbreviations
ATLS – Advanced Trauma Life Support
OPT – orthopantomogram
CT – computerized tomography

without spinal injuries, we can allow the patient to sit up and ensure airway patency without intubation; providing jaw thrust is also a good way to open the airway but if the airway is not secured by using the basic methods (jaw thrust, chin lift and oxygenation) the definitive airway should be made early (the emergent endotracheal intubation). If the endotracheal intubation is not possible, the surgical airway should be performed (cricothyroidotomy is the quickest surgical method for providing the airway patency). Tracheostomy is not used generally in the emergency because of the complexity and duration of the procedures. Emesis, which can occur in the patients who are under the influence of alcohol and drugs, brain injuries and ingested blood, can also compromise the airway. These patients require suctioning. It is important to remember that if the patients cannot protect their own airway, the definitive airway should be performed in the form of endotracheal intubation.

Hemorrhage is the predominant cause of preventable post-injury deaths (30-40%). Hypovolemic shock is caused by significant blood loss. Two large intravenous lines must be established in the traumatized patient and a crystalloid solution may be given. If the person does not respond to this, s/he can be given type-specific blood, or O-negative blood. Maxillofacial hemorrhage is rarely life-threatening, but it requires instant intervention because it can be very dramatic. It infrequently causes hypovolemia. The bleeding from the maxillofacial region is readily apparent. In case of the significant hemorrhage, the imperative is to achieve rapid hemostasis. It can be done externally by direct pressure, sutures or staplers. The internal control of the hemorrhage can be achieved by packing the oral or nasal cavities, balloon tamponade, reduction and stabilization of the facial fractures, intermaxillary immobilization or ligation of the external carotid artery. When the hemorrhage is under control, it is not always necessary to perform the urgent reparation of the maxillofacial injuries. After the temporary stabilization of the patient is achieved, the resuscitation, prioritization of the injuries and planning the further treatment can begin.

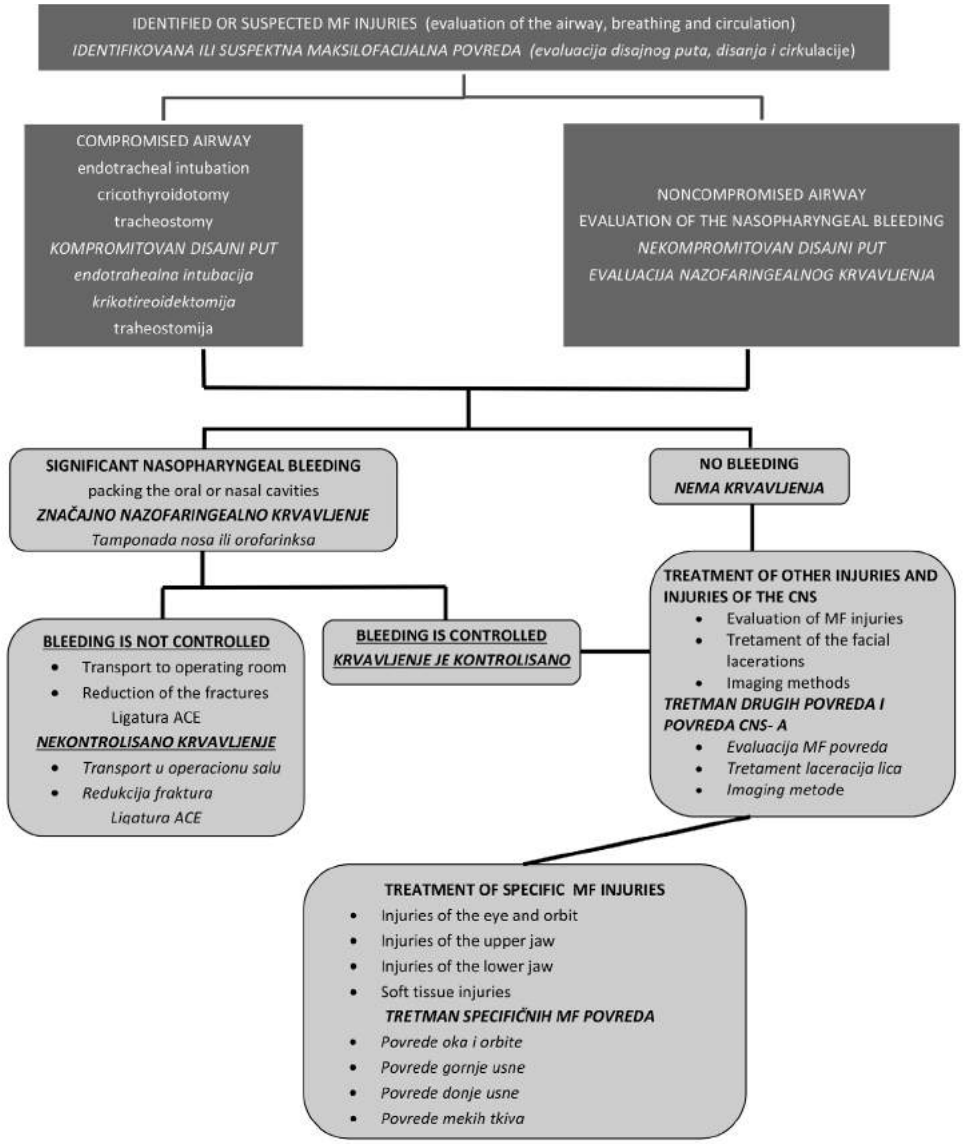
The basic neurological assessment is made during the primary survey (alert, verbal stimuli response, painful stimuli response, or unresponsive). Thus the patient's level of consciousness, pupil size and reaction, lateralizing signs, and spinal cord injury level are established.

The Glasgow Coma Scale is a method to determine the level of consciousness and severity of head trauma with the involvement of neurocranium, and it is predictive of the patient's outcome (15 is normal, 13-14 is associated with the mild head injury, 8-12 is associated with the moderate head injury, and under 8 is associated with the severe head injury). All patients with the trauma of the maxillofacial region should be considered at high-risk for C-spine injuries **(Table 1).**

The secondary survey is a head-to-toe evaluation of the trauma patient, including the complete history and physical examination. Each region of the body must be thoroughly examined. Injuries of the maxillofacial region can be divided into soft tissue injuries and injuries of facial bones.

Table 1. Glasgow Coma Scale
Tabela 1. *Glazgovska skala kome*

Best eye response (E) *Najbolji odgovor očiju*	Spontaneous-open with blinking at baseline/*Spontano otvaranje sa treptanjem*	4
	Opens to verbal command, speech or shout/*Otvaranje na verbalnu komandu, govor*	3
	Opens to pain not applied to face/*Otvaranje na bolan nadražaj*	2
	None/*Bez odgovora*	1
Best verbal response (V) *Najbolji verbalni odgovor*	Oriented/*Orijentisan*	5
	Confused conversation but able to an answer questions *Konfuzan ali sposoban da odgovara na pitanja*	4
	Inappropriate responses, words discernible/*Neodogovarajuće reči koristi*	3
	Incomprehensible speech/*Nerazumljivi zvuci*	2
	None/*Bez odgovora*	1
Best motor response (M) *Najbolji motorni odgovor*	Obeys commands for movemant/*Izvršava na verbalnu komandu*	8
	Purpaseful movement to painful stimulus/*Odgovarajući odgovor na bolni stimulans*	5
	Withdraws from pain/*Povlači se na bol*	4
	Abnormal: (spastic) flexion, decorticate posture *Abnormalna (spastična) fleksija, dekortikaciona postura*	3
	Extensor (rigid) response, decerebrate posture *Ekstenzorni (rigidni) odgovor, decerebraciona postura*	2
	None/*Bez odgovora*	1



Schema 1. Algorithm in the treatment of maxillofacial injuries
Shema 1*. Algoritam u lečenju maksilofacijalnih povreda*

Injuries of the soft tissues of the face can cause significant damage of the important anatomical structures (lacrimal duct, parotide duct, main vascular structures and nerves). The debridement of the tissue must be limited and the foreign bodies should be removed with lavage. The healing of the face wound is excellent because of the good vascular supply.

The fractures of the lower jaw are most frequent. These injuries are very painful because the mandible is the only mobile bone of the facial skeleton. These fractures can be easily diagnosed. The patients complain of the malocclusion and pain on the site of the fracture. The mandibular condyles must be carefully examined in cases of the blow or laceration of the chin. The intraoral examination is important and every intraoral laceration, fracture of the tooth crown and a missing tooth should be noticed. The paresthesia of the lower lip and chin can be present because of the injury of the mandibular nerve. Plain radiographs are the first line imaging method in diagnosing fractures of the lower jaw: orthopantomogram (OPT) and posteroanterior (PA) mandibular radiograph. Computerized tomography (CT) can be applied if the patient has clinical signs of fracture and X ray appears normal. These fractures are usually treated in the first 24 hours after injury because of the pain and discomfort and in order to avoid infection of the fracture site. These fractures can be treated with closed (interdental wiring) and open (open reduction and internal fixation with titanium miniplates) surgical methods. If the treatment of the fracture is delayed, the antibiotic prophylaxis is recommended.

The basic knowledge of the anatomy of the zygomatic bone and orbital cavity is important for understanding the fractures of the orbitozygomatic complex. The orbit as a part of the zygomatic complex is included in the majority of zigomatic fractures. Regular clinical examination of the patients with injuries of orbitozigomatic complex must include the eye examination (visual acuity, pupillary light reflex and ocular movements) so as not to miss the retrobulbar hemorrhage, traumatic optic neuropathy and white eye blowout fractures. In the patients with orbitozygomatic injuries, the clinical findings can include a palpable bony step-off in the area of infraorbital margin, paresthesia of the infraorbital nerve, depression of the malar eminence, diplopia, limited mouth opening (in the zygomatic arch fractures), eyelid swelling after blowing the nose, subconjunctival hematoma, etc. The CT scan with axial and coronal views is the gold standard in the examination of injuries of the orbitozygomatic region. The treatment of these injuries is not immediate, it can occur 4-7 days after injuries (in case of the fracture of the floor of the orbit it may be delayed up to 14 days after injury).

The maxillary and midface fractures usually occur along the lines of weakness in the midface bones (Le Fort I, II and III). They are characterized by bilateral symmetrical swelling of the face and racoon eyes (bilateral periorbital hematomas), flattening and elongation of the midface. Maxillary mobility is tested during clinical examination. The bilateral paresthesia of the infraorbital nerve can occur in this type of fractures. CT scan is the gold standard, but if it is not accessible, the OPT, occipitomental projection or submentovertical projection can be useful.

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The fracture of the anterior table of the frontal bone is often followed by a cosmetic defect that requires surgical reduction of the bone fragments. These fractures can be reduced 4-7 days after surgery. The fractures of the posterior table are less common and involve the cranial cavity, and therefore must be treated by a maxillofacial surgeon and neurosurgeon.

The panfacial fractures include all the mentioned fractures of the facial bones. These fractures are serious injuries and require initial assessment and management according to the ATLS guidelines. The CT scan with "in space" reconstruction is the gold standard in diagnosis of these fractures. These fractures require complex and precise surgical repositioning of bone fragments. Injuries of the cervical spine, cerebral injuries and cerebrospinal fluid leak can be associated with the panfacial fractures.

The tertiary survey includes a careful and complete examination followed by serial assessments in order to recognize missed injuries, allowing definitive care management **(Shema 1).**

Maxillofacial injuries are serious injuries, especially nowadays with the increased rate of traffic accidents. The percentage of mortality and serious disability and deformity resulting from these injuries is high. During the treatment of these injuries it is necessary to follow the basic postulates of surgery and to make proper and precise diagnosis. It is important not to forget the importance of proper assessment and interventions in urgent management of maxillofacial trauma. The best survival rate of the traumatized patients is obtained when the multidisciplinary trauma team reacts on time. Because of the specifics of maxillofacial injuries maxillofacial surgeon must be a part of such a team.

ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

Clinical Centre of Serbia, Belgrade, Department of Eye Diseases[1]
University of Belgrade, Faculty of Medicine[2]
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PHARMACOLOGICAL INTRAVITREAL TREATMENT FOR MACULAR EDEMA IN BRANCH RETINAL VEIN OCCLUSION – THREE-MONTH RESULTS

FARMAKOLOŠKO INTRAVITREALNO LEČENJE EDEMA MAKULE KOD OKLUZIJE GRANE CENTRALNE VENE RETINE – TROMESEČNI REZULTATI

Jelena KARADŽIĆ[1], Igor KOVAČEVIĆ[1,2], Jelena LJIKAR[3], Zorka GRGIĆ[3,5] and Gordana DEVEČERSKI[4,5]

Summary

Introduction. Macular edema is the main cause of visual loss in patients with branch retinal vein occlusion. Macular edema is initially reversible, but over time, permanent loss of vision occurs from structural damage to the macula. For this reason, there is a need for more rapid and effective treatments than laser photocoagulation which has been established as a gold standard. There are several pharmacologic agents which have changed the management of macular edema. **Material and Methods.** Twenty eyes of 20 consecutive patients of the Department of Eye Diseases, Clinical Center of Vojvodina, in Novi Sad, were enrolled in this prospective, randomized and consecutive study conducted from January 2012 to January 2013. The patients were randomly assigned into two treatment groups, and they were given an intravitreal injection of bevacizumab 1.25 mg/0.05 mL (Avastin®), or triamcinolone acetonid injection 4 mg/0.1mL (Kenalog®). Reinjections were performed according to the following retreatment criteria a loss of visual acuity or increase in central retinal thickness. **Results.** Both intravitreal bevacizumab and triamcinolon-acetonid were very effective in reducing macular edema and improving visual acuity in the eyes with macular edema secondary to retinal vein occlusion. The effect of the treatment was more pronounced if it started early after the onset of macular edema. The reported temporary effects of intravitreal triamcinolon-acetonide and bevacizumab could be explained by their clearance from the eye. **Conclusion.** The short-term results of our clinical trial showed that pharmacological intravitreal agents, such as bevacizumab and triamcinolon-acetonid, lead to rapid resolution of macular edema and significant improvement of visual acuity.

Key words: Macular Edema; Intravitreal Injections; Retinal Vein Occlusion; Treatment Outcome

Sažetak

Uvod. Edem makule se smatra glavnim uzrokom gubitka vida kod pacijenata sa okluzijom grane centralne vene retine. Edem makule je u početku reverzibilan, međutim tokom vremena dolazi do trajnog gubitka vida kao posledica strukturalnih promena u makuli. Zbog toga postoji potreba za bržim i efikasnijim tretmanom u odnosu na laserfotokoagulaciju, koja je dugo godina bila zlatni standard u lečenju edema makule. Postoji nekoliko farmakoloških agenasa koji su promenili način lečenja edema makule. **Materijal i metode.** Dvadeset pacijenata, koji su bili lečeni na Klinici za očne bolesti, Kliničkog centra Vojvodine u Novom Sadu, u periodu od januara 2012. do januara 2013. godine, bilo je uključeno u ovu prospektivnu, randomizovanu kliničku studiju, Pacijenti su podeljeni u dve grupe kojima je inicijalno bila data po jedna doza intravitrealno triamcinolon-acetonida, 4 mg/0.1 ml, ili bevacizumaba, 1.25 mg/0.05 ml. Reaplikacija se vršila po prethodno ustanovljenim kriterijumima: ponovno smanjenje vidne oštrine ili povećanje centralne debljine retine. **Rezultati.** Intravitrealne injekcije oba leka su veoma efikasne i dovode do značajnog poboljšanja vidne oštrine i smanjenja centralne debljine retine kod edema makule nastalog nakon okluzije grane centralne vene retine. Efekat ovih lekova je bolji ukoliko se sa lečenjem počne ranije, pre nego što dođe do strukturalnih oštećenja makule. Efekat intravitrealno aplikovanih lekova je privremen, i povezan je sa njihovim klirensom iz oka. **Zaključak.** Kratkotrajni rezultati ove naše studije su pokazali da farmakološki intravitrealni agensi kao što su bevacizumab i triamcinolon acetonid dovode do brze rezolucije edema makule i značajnog poboljšanja vidne oštrine.

Ključne reči: Makularni edem; Intravitrealne injekcije; Okluzija retinalne vene; Ishod lečenja

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Abbreviations

BRVO – branch retinal vein occlusion
ME – macular edema
TA – triamcinolone acetonide
IVBe – intravitreal bevacizumab group
IVTA – intravitreal triamcinolon-acetonid group.
OCT – optical coherence tomography
FA – fluorescein angiography
CRT – central retinal thickness
BCVA – best-corrected visual acuity
IOP – intraocular pressure
VEGF – vascular endothelial grown factor
RVO – retinal vein occlusion

Introduction

Branch retinal vein occlusion (BRVO) is a common retinal vascular occlusive disorder with the incidence of 2.14/1000/year in individuals over 40 years of age [1]. It may cause sudden vision loss because of blood nonperfusion and retinal hypoxia. In later stages, it is often complicated with macular edema (ME) which may cause an additional visual reduction that often exceeds the previous ischemic damage, and thus macular edema represents an important treatment target [2].

Macular edema is considered to be the major reason of visual impairment in BRVO [3, 4]. ME is initially reversible, but over time, permanent loss of vision occurs due to structural damage to the macula. Treatment options for the ME have changed through the years. Branch Vein Occlusion Study Group reported in 1984 that grid laser photocoagulation was superior in improving visual acuity compared to the observation. However, most patients had moderate visual acuity improvement after laser treatment [4]. In addition to possible complications associated with laser photocoagulation [5–9], the presence of intraretinal hemorrhages in the macula postpones the beginning of the laser treatment for several months [10], which compromises the functional outcome of this treatment. For this reason, there was a need for more rapid and effective treatments that could provide better functional and anatomic outcome [11].

In recent years, intravitreal pharmacologic agents have been used with increasing frequency in the treatment of retina vein occlusion and have changed the approach in dealing with ME [12]. Their anti-inflammatory and anti-angiogenic effects target vascular permeability, reduce ME and thus improve the vision [13]. Currently, there are several pharmacological agents used for ME caused by BRVO. Some of them are approved by the United States Food and Drug Administration (USFDA), including intravitreal dexamethasone implant (Ozurdex®, Allergan) and ranibizumab (Lucentis®, Genentech), while intravitreal bevacizumab (Avastin®, Genentech) and triamcinolone acetonid, (Kenalog®, Allergan) have been used off label [12].

Several studies have reported the effectiveness of intravitreal injection of triamcinolone acetonide (TA) [14–16] and of anti-vascular endothelial growth factor (VEGF) agents, such as bevacizumab, in dealing with ME caused by BRVO [17, 18]. Considering these promising preliminary results the aim of our study was to compare the effectiveness and safety of intravitreal bevacizumab (Avastin®) 1.25 mg/0.05 ml and intravitreal triamcinolone acetonide (Kenalog®) 4 mg/0.1ml in the eyes with macular edema due to branch retinal vein occlusion.

Material and Methods

Twenty eyes of 20 consecutive patients of the Department of Eye Diseases, Clinical Center of Vojvodina, in Novi Sad were included in this prospective, randomized and consecutive study between January 2012 and January 2013. The patients were randomly assigned into two treatment groups. In one group, the patients were given an intravitreal injection of bevacizumab 1.25 mg/0.05 mL (Avastin®), while the second group patients were administered a triamcinolone acetonid injection 4 mg/0.1 mL (Kenalog®). We named group one as intravitreal bevacizumab (IVBe) group, and group two as IVTA (intravitreal triamcinolon-acetonid) group.

All patients underwent complete baseline ophthalmological examination including medical history, visual acuity assessment (measured by Snellen chart), applanation tonometry, slit lamp examination, dilated fundus examination with indirect ophthalmoscopy with 90D lens, optical coherence tomography (OCT), fluorescein angiography (FA) and biochemical investigations such as complete blood count, prothrombin time, partial thromboplastin time, random blood sugar, renal function tests, liver function tests and erythrocyte sedimentation rate. The diagnosis of ME was confirmed by OCT and FA.

The inclusion criteria were: the patients with ME caused by BRVO, and no disc or retinal neovascularization. The exclusion criteria were: previous laser photocoagulation, intravitreal injections or vitrectomy, significant media opacity, and contraindications for bevacizumab or TA. The patients were initially followed up at the first post-injection day and then at four, six and twelve weeks after injection. Re-injections were performed according to the following retreatment criteria: the loss of visual acuity or increase in central retinal thickness (CRT) on OCT, compared with the best values after the initiation phase. All patients were observed for 12 weeks for further status and additional treatments. Informed consent was obtained from each patient after discussing about the benefits and possible risks of these two drugs. The study was approved by the Ethics Committee of the Clinical Center of Novi Sad. The main outcome measures included changes in the best-corrected visual acuity (BCVA) and the central retinal thickness (CRT) during follow-up examinations, and postoperative complications.

Data were analyzed using SPSS 15.0. Baseline demographic and clinical parameters were compared between the two groups using independent-samples T-test for numerical variables (such as changes in BCVA

Table 1. The baseline characteristics of two treatment groups with regard to patients' sex, age, time until the first injection, pretreatment visual acuity and retinal thickness
Tabela 1. *Osnovne karakteristike dve terapijske grupe u odnosu na pol, starost, vreme do prve injekcije, preterapijsku vidnu oštrinu i centralnu debljinu retine*

	IVBe grou *IVBe grupa*	IVTA group *IVTA grupa*	p value *Vrednost p*
Number of patients/*Broj pacijenata*	11	9	
Gender (M:F)/*Pol (M : Ž)*	8:3	4:5	0.205
Age (years)/*Starost (godine)*	61.545±7.679	59.33±7.257	0.541
Time until the 1st injection (month)/*Vreme do 1. injekcije (meseci)*	3.454±2.270	4.333±1.4907	0.356
Pretreatment BCVA/*Predtretman*	0.4±0.112	0.355±0.177	0.527
Pretreatment/CRT (μm) *Predtretman*	416.54±67.906	442.77±102.201	0.523

BCVA - okluzija grane centralne vene retine; CRT - centralna debljina retine; IVBe - intravitrealna injekcija bevacizumata; IVTA - intravitrealna injekcija triamcinolon-acetonida

and CRT). A probability value (p) of less than 0.05 was considered to be statistically significant.

Results

The baseline characteristics by groups are matched and presented in **Table 1.** As shown, there was no statistically significant difference between the groups with regard to the patients' age, gender, time from vascular attack until first injection, baseline best corrected visual acuity, and baseline central retinal thickness. The study involved a total of 20 patients (12 men and 8 women) who fulfilled the inclusion criteria. There were 11 patients in IVBe group (55%), and 9 patients in IVTA group (45%). The mean age of patients in the IVBe group was 59.33±7.257 years and 61.545±7.697years in the IVTA group, (p=0.541). The time from the BRVO appearance until the application of the first intravitreal injection was 3.454±2.270 months in the IVBe group, and 4.333±1.4907 in the IVTA group (p=0.356). There were ten patients in IVBe group (90.90%) and nine patients in IVTA group (100%) who had a history of hypertension, and were treated with oral systemic anti-hypertensive drugs. Two patients in IVBe and four patients in IVTA group (63.63% vs. 77.77%) had diabetes mellitus.

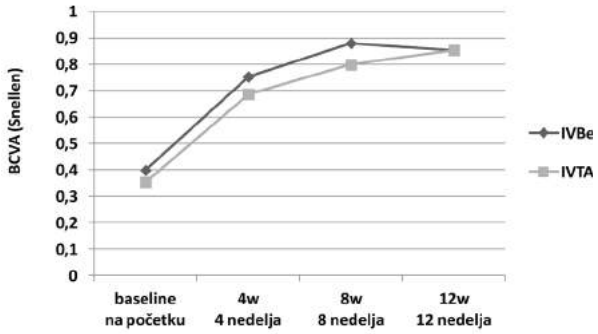
In the IVBe group, the best corrected visual acuity improved significantly (p< 0.001) from 0.4±0.112 pre-injection to 0.75±0.137, 4 weeks after the first injection. Visual acuity was still improved 0.881±0.140 8 weeks after the treatment, but the mean BCVA decreased slightly to 0.845±0.130 12 weeks after the treatment although it was still significantly better compared with initial BCVA (p<0.001). In the IVTA group, visual acuity measurements also improved significantly (p<0.001) from 0.35±0.177 pre-injection to a final BCVA of 0,68±0,196, 0.8±0.1563 and 0.855±0.157, 4, 8 and 12 weeks after injection, respectively. Changes in the BCVA did not differ statistically significantly between two treatment groups (F = 0.606, p = 0.614) (**Graph 1**).

In the IVBe group, ME demonstrated by foveal thickness on OCT improved after treatment (p<0.001). The mean foveal thickness was 416.54±67.906 μm before injection, but after injection, the central retinal thickness decreased significantly to 240.36±49.0 μm and 193.00±26.94 μm four and eight weeks after injection, respectively (-176.18 μm and -223.55 μm, respectively; p<0.001 each). The mean CRT was 203.90±44.11 (-212.64 μm, p<0.001) 12 weeks after treatment, which was little higher than the CRT after eight weeks but yet significantly below compared with the initial CRT (p<0.001). In the IVTA group, the changes of the foveal thickness measured between baseline and postoperative data also showed significant resolution (p< 0.001). The foveal thickness was 442.77±102.201 μm before injection, while 4, 8 and 12 weeks after injection, the foveal thickness was 267.44±57.12, 232±49.83 and 220±45.22 μm, respectively. Between-group comparisons with respect to changes in the foveal thickness showed no statistically significant differences (F = 0.225, p = 0.879) **(Graph 2).**

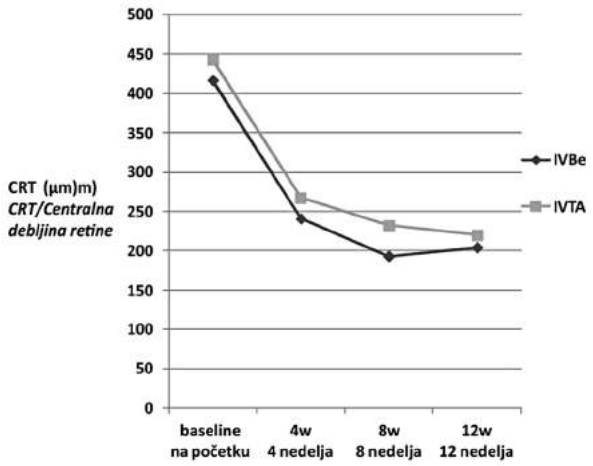
During the follow-ups, some of the patients showed recurrence of intraretinal edema which was, besides the loss of vision, criterion for re-injections. In the IVBe group, ten patients received re-injection of bevacizumab once (90.9%), five patients (45.4%) received re-injections twice, and two patients (18.1%) received re-injection three times within the 12 weeks of the follow-up period. None of the patients in the IVTA group received a re-injection during the 12 week follow-up. In this study, five patients (55.55%) in the IVTA group had transient elevated intraocular pressure (IOP>22 mmHg). All five patients with increased IOP were successfully treated and controlled with topical anti-glaucoma medication by the end of the study. There was no case with increase in IOP after intravitreal injection of bevacizumab. Both treatment procedures were well tolerated. There was no other severe ocular (inflammation, retinal tears or detachment, traumatic cataract) or systemic adverse event in this study.

Discussion

The short-term results of our clinical trial have shown that pharmacological intravitreal agents for macular edema such as bevacizumab and TA lead to rapid resolution of CRT and significant improvement



Graph 1. The change in BCVA (Snellen) between the two treatment groups at baseline and after 4, 8, and 12 weeks
Grafikon 1. *Promena u najbolje korigovanoj vidnoj oštrini (po Snelenu) između dve terapijske grupe na početku, u 4, 8. i 12. nedelji lečenja*



Graph 2. The changes in central retinal thickness (CRT) between the two treatment groups at baseline and after 4, 8 and 12 weeks
Grafikon 2. *Promena u centralnoj debljini retine između dve terapijske grupe na početku i u 4, 8. i 12. nedelji lečenja*

of visual acuity. Several treatment modalities for ME have been investigated and compared in the last years, including laser treatment, intravitreal injections of steroids and anti-VEGF drugs and surgery [19].

In BRVO, the aqueous levels of VEGF and interleukin 6 are related with the extent of retinal ischemia and the severity of ME. Thereby, inhibition of VEGF could have its role in dealing with ME [20]. The most frequently used doses of bevacizumab were 1.25 mg and 2.5 mg, although the published papers suggest that there are no significant differences in efficacy between these two doses [21]. Intravitreal TA injection is commonly used in treating ME of different etiologies [22–24] because TA has potent anti-permeable, anti-VEGF and anti-inflammatory role [25–28]. The exact dose of TA is still unclear although it has been reported that doses from 4 mg to 25 mg are effective [20]. Several retrospective [14, 29] and prospective studies [15, 16] have evaluated the therapeutic effect of 4-mg intravitreal TA for the patients with ME secondary to BRVO. These studies have shown a significant anatomical and functional improvement after intravitreal injection of TA, i.e. a reduction in ME and improvement of visual acuity. The findings obtained in this study are in agreement with previously published results. Pai et al. first used intravitreal bevacizumab as a treatment for ME related to BRVO [30]. Thereafter, there have been several retrospective case series and prospective comparative studies [31–33] examining the effects of bevacizumab in the patients with RVO. The available studies showed the results which were similar to our study, i.e. they demonstrated that intravitreal bevacizumab was very effective in reducing ME and improving visual acuity in the eyes with ME secondary to retinal vein occlusion [12].

The time between occlusion and the beginning of the treatment is a critical factor which determines the therapeutic effect of intravitreal medication. The studies which have included and treated patients shortly after the onset of vascular attack might find better response to treatment than trials including old RVO with chronic ME [13]. Kriechbaum et al. found that short duration of disease had a better visual prognosis than longstanding pathology [32]. Immediate treatment is likely to prevent macular tissue damage from chronic edema by more rapid resolution of intraretinal fluid [34]. Hence, it could be concluded that the effect of treatment is better if the treatment starts soon after the onset of ME, before the macular damage occurs.

The reported temporary effects of intravitreal TA and bevacizumab could be explained by their clearance from the eye [11]. Beer et al. showed that the half-life after 4mg of intravitreal injection of TA was 18.6 days in non-vitrectomized eyes [34], while Krohne et al. said that the half-life of 1.5 mg intravitreal injection of bevacizumab was 9.82 days in non-vitrectomized human eyes [35]. In the current study, during the 12 week follow up, approximately 90% of the patients who had received intravitreal bevacizumab needed repeated injection. No additional treatments were required during the initial 12 weeks after the first injection of TA. This difference was probably due to a short follow-up period and different clearance time of these agents from the eye. Longer clearance time of intravitreal TA from the eye seems to reduce the numbers of re-injections compared to intraviteal bevacizumab [11].

The intravitreal injections of bevacizumab or TA are both relatively well tolerated with no frequent severe side effects [37]. In our study, five of nine BRVO patients without preexisting glaucoma developed steroid-induced elevated IOP after intravitreal TA injection and all were successfully controlled with topical anti-glaucomatous eye drops and none of the patients required surgical intervention. In the IVBe group, the IOP was normal after intravitreal injection. Therefore, intravitreal bevacizumab was safer than intravitreal TA in terms of IOP elevation [38].

Today, it is widely accepted that the quality of life and treatment satisfaction are the measures of the

outcome of every medical treatment [39]. For that reason, present and new instruments for the assessment of the vision quality of life and treatment satisfaction should be applied in the future clinical trials in dealing with macular edema caused by BRVO.

Conclusion

For a long time, a laser photocoagulation was the gold standard for treating macular edema caused by branch retinal vein occlusion. Recently, the introduction of pharmacological intravitreal agents has changed the approach to macular edema treatment. The necessity for a more rapid treatment and better anatomical and functional success completely replaced long-accepted laser treatment by intravitreal pharmacological agents (corticosteroids and anti- vascular endothelial growth factor agents) as the first line treatment. Our study showed that both intravitreal agents were very effective in treating the patients with macular edema during the period of three months. However, future randomized controlled clinical trials with larger study samples, longer follow-up periods, and standardized protocols with an appropriate control group are required to compare specific intravitreal agents as well as to determine retreatment strategies for branch retinal vein occlusion related macular edema.

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COMPARISON OF STANDARD COAGULATION TESTS AND ROTATIONAL THROMBOELASTOMETRY FOR HEMOSTATIC SYSTEM MONITORING DURING ORTHOTOPIC LIVER TRANSPLANTATION - RESULTS FROM A PILOT STUDY

POREĐENJE STANDARDNIH KOAGULACIONIH TESTOVA I ROTACIONE TROMBOELASTOMETRIJE ZA PRAĆENJE HEMOSTAZNOG SISTEMA TOKOM ORTOTOPIČNE TRANSPLANTACIJE JETRE – REZULTATI PILOT-STUDIJE

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Summary

Introduction. During liver transplantation, continuous laboratory monitoring of complex changes of the hemostatic system is necessary. The aim of this study was to compare two methods of monitoring: standard coagulation tests and rotational thromboelastometry. **Material and Methods.** The study included 17 patients who had undergone orthotopic liver transplantation in the Clinical Centre of Vojvodina, Serbia in the period from June 2008 to October 2012. The coagulation parameters (platelet count, activated partial thromboplastin time, prothrombin time and fibrinogen level) were compared with the thromboelastometric parameters (coagulation time, clot formation time and maximal clot firmness). **Results.** The results showed a statistically significant correlation between the platelet count and maximum clot firmness of the intrinsically ($r=0.51$, $p<0.001$) and extrinsically activated thromboelastometric assays ($r=0.64$, $p<0.001$). The fibrinogen level and maximum clot firmness of the fibrinogen thromboelastometric test correlated significantly as well ($r=0.44$, $p=0.002$). No significant correlations were found among the activated partial thromboplastin time, prothrombin time, coagulation time and clot formation time. **Conclusion.** For an adequate perioperative monitoring of the dynamic intraoperative hemostatic changes and the optimal use of blood derivatives during liver transplantation, the combined application of standard coagulation tests and rotational thromboelastometry should be considered whenever possible.

Key words: Blood Coagulation Tests; Thromboelastography; Liver Transplantation; Hemostasis; Blood Chemical Analysis

Sažetak

Uvod. Tokom transplantacije jetre neophodno je kontinuirano laboratorijsko praćenje kompleksnih promena u hemostaznom sistemu. Cilj studije je poređenje dve metode praćenja: standardnih koagulacionih testova i rotacione tromboelastometrije. **Materijal i metode.** Ispitivanjem je obuhvaćeno 17 bolesnika kojima je urađena ortotopična transplantacija jetre u Kliničkom centru Vojvodine, Srbija, u periodu jun 2008−oktobar 2012. godine. Koagulacioni parametri: broj trombocita, aktivirano parcijalno tromboplastinsko vreme, protrombinsko vreme i nivo fibrinogena poređeni su sa tromboelastometrijskim parametrima: vreme koagulacije, vreme formiranja ugruška i maksimalna čvrstina ugruška. **Rezultati.** Rezultati ukazuju na postojanje statistički značajne korelacije između broja trombocita i maksimale čvrstine ugruška u testu unutrašnjeg ($r = 0,51$, $p < 0,001$) i spoljašnjeg puta koagulacije ($r = 0,64$, $p < 0,001$). Nivo fibrinogena i maksimalne čvrstine ugruška značajno koreliraju u fibrinogen-tromboelastometrijskom testu ($r = 0,44$, $p = 0,002$). Nije utvrđena značajna korelacija između aktiviranog parcijalnog tromboplastinskog vremena, protrombinskog vremena, vremena koagulacije i vremena formiranja ugruška. **Zaključak.** Za adekvatno perioperativno praćenje dinamičkih promena u hemostaznom sistemu i optimalnu primenu derivata krvi tokom transplantacije jetre treba razmotriti kombinovanu primenu standardnih koagulacionih testova i rotacione tromboelastometrije kad god je to moguće.

Ključne reči: Koagulacioni testovi; Tromboelastografija; Transplantacija jetre; Hemostaza; Hemijske analize krvi

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Introduction

All components of the hemostatic system are altered in liver diseases due to impaired synthetic and excretory functions of the liver, decreased platelet count, and alterations in the hemostatic balance [1, 2]. These changes are proportional to the degree of impairment of liver function. In addition, portal

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Abbreviations
OLT – orthotopic liver transplantation
SCTs – standard coagulation tests
ROTEM® – rotational thromboelastometry
PLT – platelet count
aPTT – activated partial thromboplastin time
PT – prothrombin time
FBG – fibrinogen
CT – clotting time
CFT – clot formation time
MCF – maximum clot firmness
INTEM – intrinsically activated ROTEM® assays
EXTEM – extrinsically activated ROTEM® assays
FIBTEM – fibrinogen thromboelastometry test

hypertension that develops in hepatic insufficiency increases the risk of bleeding, whereas endothelial dysfunction and increased levels of the von Willebrand factor stimulate platelet adhesion [3], and increase the risk of thromboembolic complications. The changes in the physiological balance of hemostasis that increase the risk of bleeding include thrombocytopenia, platelet dysfunction, decreased levels of coagulation factors, plasmin inhibitors and thrombin-activatable fibrinolysis inhibitor**,** and increased levels of tissue plasminogen activator. The changes increasing the risk of thromboembolic complications, such as increased coagulation factor VIII levels, decreased activity of natural coagulation inhibitors and plasminogen levels occur at the same time [4].

Liver transplantation is an efficient treatment of patients with end-stage liver disease and irreversible impairment of liver function. During liver transplantation, most patients show multifactorial dysfunction of the hemostatic system [5] due to the drop in the levels of coagulation factors, natural coagulation inhibitors and antifibrinolytic factors [6], as well as quantitative and qualitative changes in procoagulation and anticoagulation factors and platelets [7, 8]. Orthotopic liver transplantation (OLT), during which the native liver is removed and replaced by the donor organ, is divided into the following phases: preanhepatic, anhepatic and postanhepatic. The preanhepatic phase reflects the preoperative condition of the diseased liver [9]. The anhepatic phase is characterized by a decrease in the levels of coagulation factors and dysfunction of the fibrinolytic system due to hyperfibrinolysis. During the postanhepatic phase, an increased fibrinolytic potential persists [10], as well as a thrombocytopenia and platelet dysfunction [11].

Continuous laboratory monitoring of changes in the function of the hemostatic system during OLT enables fast diagnosing of the dominant disorder at a given moment and administration of appropriate substitution therapy. There are two methods of monitoring the function of the hemostatic system during OLT: standard coagulation tests (SCTs) and rotational thromboelastometry (ROTEM®), and it is therefore necessary to analyze the correlation between the results obtained by these different methodologies. ROTEM® is routinely used in operating rooms, intensive care units and is also being introduced in the work of clinical laboratories.

The aim of the current study was to assess the correlation between coagulation and thromboelastometric parameters during OLT through monitoring the function of the hemostatic system using SCTs and ROTEM®.

Material and Methods

The study included 17 consecutive patients (5 women and 12 men), who had undergone OLT at the Clinical Centre of Vojvodina in Novi Sad, Serbia, in the period from June 2008 to October 2012. The most frequent etiology of liver insufficiency was viral hepatitis B and C, found in 10 patients. Both demographic and clinical characteristics of the patients are presented in table **(Table 1)**.

During the OLT, four to eight blood samples were analyzed for each patient, meaning at least one sample for each transplantation phase, depending on the patient's clinical status and laboratory findings as well. Blood samples were taken by cubital vein puncture; using the 3 ml tubes containing an-

Table 1. Demographic and clinical characteristics of the patients
Tabela 1. *Demografske i kliničke karakteristike pacijenata*

Mean age (years)/*Prosečna starost (godine)*	51.3
Mean follow-up (years)/*Prosečna dužina praćenja (godine)*	9
Diagnosis (pts)/*Dijagnoza (pacijent)*:	
hepatitis B/*hepatitis B*	6
hepatitis C/*hepatitis C*	4
– hepatocellular carcinoma/*hepatocelularni karcinom*	4
– autoimmune/*autoimuni*	3
Gender (pts)/*Pol (pacijent)*:	
– female/*ženski*	5
– male/*muški*	12
Variceal bleeding (pts)/*Varikozno krvarenje (pacijent)*	1
Thromboembolic events (pts)/*Tromboembolijske događaji (pacijent)*	1

Legend: pts - patients

Table 2. Intraoperative levels of coagulation parameters during phases of the transplantation
Tabela 2. *Intraoperativne vrednosti koagulacionih parametara tokom faza transplantacije*

		Coagulation parameters/*Koagulacioni parametri*			
		PLTx10^9/L (N 140-400)	aPTT (R) (N 0.83-1.30)	PT (R) (N 0.83-1.30)	FBG (g/L) (N 2.2-4.96)
Phases of OLT *Faze OLT*	PAH	78 (50-129)	1.14 (1.08-1.50)	1.39 (1.21-1.74)	1.91 (1.45-2.82)
	AH	73 (54-106)	1.21 (1.08-1.39)	1.32 (1.22-1.56)	2.28 (1.97-2.75)
	POSTAH	94 (57-112)	1.51 (1.37-1.80)	1.46 (1.38-1.69)	2.02 (1.82-2.51)

Legend: PAH - preanhepatic phase; AH - anhepatic phase; POSTAH - postanhepatic phase
Legenda: OLT – ortotopična transplantacija jetre; PAH – preanhepatična faza; AH – anhepatična faza; POSTAH – postanhepatična faza; PLT – broj trombocita; aPTT – aktivirano parcijalno tromboplastinsko vreme; PT – protrombinsko vreme; FBG – nivo fibrinogena

ticoagulant 5.9 mg K2 EDTA (Terumo Europe N.V., Leuven, Belgium) for determining the platelet (PLT) count and 3.2% sodium citrate (Terumo Europe N.V., Leuven, Belgium) taken in 5 ml tubes for SCTs. Citrated plasma was separated after centrifugation at 4000G for 6 minutes. PLT count was determined on the automated hematology analyzers Beckman Coulter HmX (Mervue, Galway, Ireland Inc.) and Cell Dyn Sapphire (Abbott Diagnostic, USA). An automated coagulometer ACL 9000 (Instrumentation Laboratory, Milano, Italy) was used to determine the activated partial thromboplastin time (aPTT), prothrombin time (PT) and fibrinogen (FBG), using the reagents HemosIL APTT-SP Liquid, RecombiPlasTin 2G and HemosIL Fibrinogen-C XL (Instrumentation Laboratory, Milano, Italy). The results for aPTT and PT are expressed as ratios (R) of sample clotting time and clotting time of normal control plasma (Instrumentation Laboratory, Milano, Italy). SCTs were performed in the laboratory of the Department of Thrombosis, Hemostasis and Hematology Diagnostics of the Centre of Laboratory Medicine and in the laboratory of the Emergency Centre. The following coagulation parameters were measured: PLT count, aPTT, PT and FBG levels determined by the Clauss assay [12]. The following coagulation parameters were also tested during OLT: thrombin time, euglobulin clot lysis time, D-dimer and antithrombin. Thromboelastometry was performed in the operating room, on ROTEM® (Pentapharm GmbH, Munich, Germany) using reagents obtained from the same manufacturer. Whole blood samples for ROTEM® tests were taken in 3.5ml tubes with 3.2% sodium citrate-BD Vacutainer (Terumo Europe N.V., Leuven, Belgium). The samples for SCTs and ROTEM® were taken intraoperatively during all transplantation phases according to the following schedule: prior to the preanhepatic phase, 30 minutes after clamping blood vessels in the anhepatic phase, after graft reperfusion in the postanhepatic phase and at the end of the operation. The coagulation parameters: PLT, aPTT, PT and FBG were compared with the thromboelastometric parameters: coagulation time (CT), clot formation time (CFT) and maximal clot firmness (MCF) in the following ROTEM® tests [13]: intrinsically activated ROTEM® assay (INTEM), extrinsically activated ROTEM® assay (EXTEM), and fibrinogen activity, a modified EXTEM test with additional PLT inhibitor-cytohalazine D (FIBTEM). The PLT count was compared with the MCF of the INTEM and EXTEM assays; aPTT with CT and CFT of the INTEM assay; PT with CT and CFT of the EXTEM assay; FBG with MCF of the FIBTEM assay.

The results of non-parametric tests are presented in tables as medians and interquartile ranges. The patients' data in various phases of transplantations were compared using the Friedman test and the appropriate post hoc test (Wilcoxon) if the Friedman test showed a significant difference. Spearman's coefficient was used to correlate SCTs and ROTEM® parameters, $p<0.05$ being considered statistically significant. These statistically significant correlations are presented in the graphs. Statistical analysis was performed using Statistica 12.0 software (StatSoft Inc., Tulsa, OK, USA). Laboratory

Table 3. Intraoperative levels of thromboelastometry parameters during phases of the transplantation
Tabela 3. *Intraoperativne vrednosti tromboelastometrijskih parametara tokom faza transplantacije*

		Thromboelastometry parameters/*Parametri tromboelastometrije*						
		CT (sec) INTEM (N 100-240)	CFT (sec) INTEM (N 30-110)	MCF (mm) INTEM (N 50-72)	CT (sec) EXTEM (N 38-79)	CFT (sec) EXTEM (N 34-159)	MCF (mm) EXTEM (N 50-72)	MCF (mm) FIBTEM (N 9-25)
Phases of OLT/*Faze OLT*	PAH	169 (149-179)	111 (98-187)	50 (43-60)	64 (55-71)	149 (104-211)	50 (42-60)	11 (8-17)
	AH	167 (146-185)	163 (127-181)	48 (41-55)	59 (50-69)	167 (76-203)	45 (42-59)	11 (7-16)
	POSTAH	214 (193-234)	164 (117-193)	49 (44-53)	57 (49-63)	153 (121-190)	49 (47-57)	11 (9-14)

Legend: PAH - preanhepatic phase; AH - anhepatic phase; POSTAH - postanhepatic phase
Legenda: OLT – ortotopična transplantacija jetre; PAH – preanhepatična faza; AH – anhepatična faza; POSTAH – postanhepatična faza; INTEM – ROTEM®testovi unutrašnjeg puta koagulacije; EXTEM - ROTEM®testovi spoljašnjeg puta koagulacije; FIBTEM – fibrinogen-tromboelastometrijski test; CT – vreme koagulacije; CFT – vreme formiranja ugruška; MCF – maksimalna čvrstina ugruška

parameters were correlated throughout the entire procedure and for each separate phase of OLT as well. The correlation for the entire OLT was analyzed for all values of each laboratory parameter obtained with both methods, SCTs and ROTEM®.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with the approval of the Ethical Board of Clinical Centre of Vojvodina for conducting the research.

Results

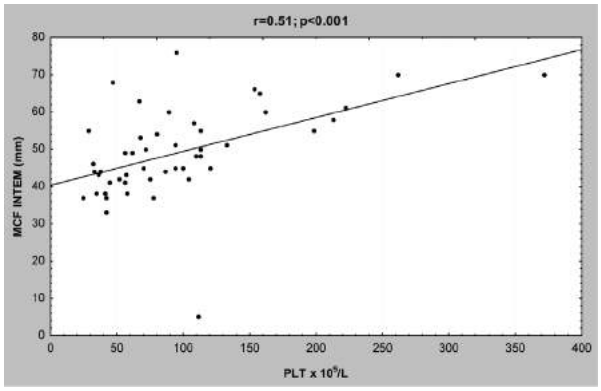
Alterations in the coagulation and thromboelastometric parameters across the different intraoperative phases of liver transplantations are shown in **tables 2 and 3**. The results of correlation of coagulation and thromboelastometry parameters are presented in **Table 4**.

The PLT count showed statistically significant correlations with MCF INTEM and MCF EXTEM in the preanhepatic phase; with MCF EXTEM in the anhepatic phase and the postanhepatic phase. The correlation was not statistically significant in the INTEM assay in either anhepatic or postanhepatic phase. During the entire procedure there was a highly statistically significant correlation between the PLT count and the MCF in both ROTEM® tests, INTEM **(Graph 1)** and EXTEM.

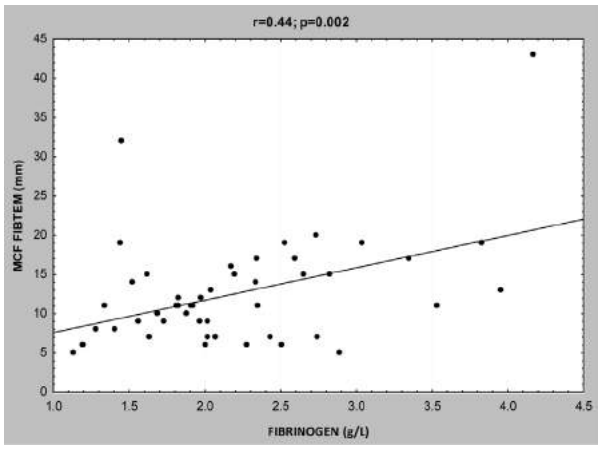
Table 4. Corellations between coagulation and thromboelastometry parameters in preanhepatic, anhepatic, postanhepatic phase and during the entire OLT
Tabela 4. *Korelacija između koagulacionih i tromboelastometrijskih parametara u preanhepatičnoj, anhepatičnoj, postanhepatičnoj fazi i tokom čitave OLT*

	PLT	aPTT	PT	FBG
MCF INTEM		/	/	/
PAH	r=0.74 p=0.001*			
AH	r=0.43 p=0.061			
POSTAH	r=0.28 p=0.271			
INTRAOP	r=0.51 p<0.001*			
MCF EXTEM		/	/	/
PAH	r=0.72 p=0.001*			
AH	r=0.63 p=0.009*			
POSTAH	r=0.59 p=0.012*			
INTRAOP	r=0.64 p<0.001*			
CT INTEM	/		/	/
PAH		r=0.30 p=0.242		
AH		r=0.16 p=0.546		
POSTAH		r=0.11 p=0.451		
INTRAOP		r=0.13 p=0.389		
CFT INTEM	/		/	/
PAH		r=0.23 p=0.375		
AH		r=0.39 p=0.121		
POSTAH		r=0.26 p=0.309		
INTRAOP		r=0.35 p=0.354		
CT EXTEM	/	/		/
PAH			r=0.20 p=0.444	
AH			r=0.14 p=0.582	
POSTAH			r=0.73 p<0.001*	
INTRAOP			r=0.20 p=0.172	
CFT EXTEM	/	/		/
PAH			r=0.52 p=0.031*	
AH			r=0.42 p=0.093	
POSTAH			r=0.12 p=0.633	
INTRAOP			r=0.23 p=0.121	
MCF FIBTEM	/	/	/	
PAH				r=0.21 p=0.424
AH				r=0.69 p=0.002*
POSTAH				r=0.01 p=0.997
INTRAOP				r=0.44 p=0.002*

Legend: PAH - preanhepatic phase; AH - anhepatic phase; POSTAH - postanhepatic phase; * - statistically significant correlation
*Legenda: OLT – ortotopična transplantacija jetre; PAH – preanhepatična faza; AH – anhepatična faza; POSTAH – postanhepatična faza; INTEM - ROTEM® testovi unutrašnjeg puta koagulacije; EXTEM - ROTEM® testovi spoljašnjeg puta koagulacije; FIBTEM – fibrinogen- tromboelastometrijski test; MCF – maksimalna čvrstina ugruška; CT – vreme koagulacije; CFT – vreme formiranja ugruška; PLT − broj trombocita; aPTT – aktivirano parcijalno tromboplastinsko vreme; PT – protrombinsko vreme; FBG – nivo fibrinogena; * − statistički signifikantna korelacija*



Graph 1. Corellation between platelet count and maximum clot firmness of intrinsically activated thromboelastometry test during transplantation
Grafikon 1. *Korelacija između broja trombocita i maksimalne čvrstine ugruška u testu unutrašnjeg puta koagulacije tokom transplantacije*



Graph 2. Corellation between fibrinogen level and maximum clot firmness of fibrinogen thromboelastometry test during transplantation
Grafikon 2. *Korelacija između nivoa fibrinogena i maksimalne čvrstine ugruška u fibrinogen-tromboelastometrijskom testu tokom transplantacije*

The correlation was not significant between aPTT and CT INTEM in the preanhepatic, anhepatic and postanhepatic phases, nor between aPTT and CFT INTEM in any of the transplantation phases, preanhepatic, anhepatic and postanhepatic phase. No significant links were found either between aPTT and CT INTEM or between aPTT and CFT INTEM during the entire procedure.

A significant correlation between PT and CFT EXTEM was observed in the preanhepatic phase, and an even more significant one between PT and CT EXTEM in the postanhepatic phase. PT was not significantly correlated with CT EXTEM in either preanhepatic or anhepatic phase, nor was PT correlated with CFT EXTEM in the anhepatic and postanhepatic phases. Throughout the entire procedure there were no significant correlations between PT and CT EXTEM, nor between PT and CFT EXTEM.

FBG showed a significant correlation with MCF FIBTEM in the anhepatic phase and no significant ones with MCF FIBTEM in the preanhepatic and postanhepatic phases. During the entire procedure a significant correlation between FBG and MCF FIBTEM was observed **(Graph 2)**.

Discussion

This is the first study conducted in our country that compares two methodologies of laboratory monitoring of the hemostatic system during liver transplantation. It is also the first study that has analyzed laboratory parameters of hemostasis separately for each transplantation phase.

ROTEM® is a whole blood *point-of-care* test, intended for the study of visco-elastic properties of the coagulum [14] and diagnosis and differentiation of hemostatic disorders. It enables monitoring of all coagulation phases and provides information not only on the clotting time, but also on the dynamics of clot formation, the mechanical clot stability and its lysis over time [15], as well as the degree of heparinization [16]. The disadvantages of ROTEM® are the inability to detect activity of natural coagulation inhibitors and assess thrombin activity. ROTEM® does not detect all hemostatic disorders; therefore, it is important to perform simultaneous SCTs during liver transplantation [17]. SCTs provide thorough information about the function of the extrinsic and intrinsic pathways of the hemostatic system, antithrombin levels and the degree of increase in thrombin activity [18]. However, since the tests use plasma without blood cells, which requires previous centrifugation of the blood sample and plasma separation, the time required to obtain results is longer than the test time of ROTEM®, which is about 10 minutes. Another limitation of SCTs is that FBG levels may be falsely increased due to the presence of heparin and colloid and the inability to determine mechanical stability of the clot [17].

Our results showed a highly significant correlation between PLT count and MCF INTEM and MCF EXTEM during OLT, which is similar to the results of previous studies [19, 20]. The PLT count correlated with MCF INTEM significantly in the preanhepatic phase and with MCF EXTEM in all the transplantation phases as shown in the study of Stanchev et al. [20].

The study results did not show a correlation between aPTT and CT INTEM, nor between aPTT and CFT INTEM during the entire procedure, which has been reported by other authors as well [19, 21, 22]. No statistically significant correlation was found between aPTT and CT INTEM, and aPTT and CFT INTEM in any of the transplantation phases. However, some authors showed a strong correlation between aPTT and CT INTEM during the transplantation [19].

Comparisons between PT and CT EXTEM, and PT and CFT EXTEM did not show statistically significant correlations, which is in agreement with the literature data [19–22]. PT correlated significantly with CT EXTEM in the postanhepatic phase. Tripodi et al. reported an important correlation between PT and CFT EXTEM during transplantation [7], which was found only in the preanhepatic phase, that being similar with the findings of Stanchev et al. [20].

FBG showed a significant correlation with MCF FIBTEM during transplantation, which is consistent with several previous studies [19–21]. The correlation was significant even in the anhepatic phase, as shown in the study of Stancev et al. [20].

The poor correlation found between certain coagulation and thromboelastometry parameters could be explained by the fact that different methodologies of the tests and the presence of blood cells, endothelial cells and platelets were applied during thromboelastometric testing [21].

Some studies have demonstrated the efficiency of ROTEM® in reducing transfusions of blood products [23, 24]. ROTEM® may be a useful guide for perioperative transfusion; however, it cannot be used as a substitute for aPTT and PT [21]. Substitution depends on the patient's laboratory findings and clinical condition, involving a PLT concentrate, fresh frozen plasma, cryoprecipitate, antithrombin concentrate, packed red blood cells, and antifibrinolytic therapy. ROTEM® is an appropriate method for estimation of PLT count and FBG level based on the MCF, particularly useful in afibrinogenemia, hypofibrinogenemia and dysfibrinogenemia [25]. Although certain coagulation parameters did not correlate with thromboelastometric parameters, perioperative monitoring with both SCTs and ROTEM® provides better comprehension of the complexity of rapid intraoperative changes in the hemostatic system. These changes may occur due to hemodilution [20], severe intraoperative blood loss [20], complexity of the surgical procedure [4] or pronounced fibrinolysis [20]. Timely diagnosis of this disorder enables optimal substitution therapy.

The limitation of this study is the small number of patients due to the small number of liver transplantations performed in our country. Similar studies which analyzed the correlations of SCTs and ROTEM® parameters during OLT also consisted of a relatively small number of patients (20-30), and our results correspond to the results of these studies. On the other hand, this study provides valuable information about the laboratory monitoring of patients undergoing OLT and it would be useful to continue further research by analyzing a larger number of patients.

Conclusion

Our results showed significant correlations of platelet count with maximum clot firmness of intrinsically activated rotational thromboelastometry assays and maximum clot firmness of extrinsically activated rotational thromboelastometry assays and of fibrinogen level with maximum clot firmness of fibrinogen thromboelastometry test. The results obtained indicate that maximum clot firmness may be used with a great degree of certainty to assess the function of platelet count and fibrinogen levels. No significant correlations were found between the coagulation parameters (activated partial thromboplastin time and prothrombin time) and the thromboelastometric parameters (clotting time and clot formation time of the intrinsically activated rotational thromboblastometry and extrinsically activated rotational thromboblastometry assays). A combination of standard coagulation tests and rotational thromboelastometry enables the best perioperative laboratory monitoring of the hemostatic system and the optimalal blood product substitution during liver transplantation.

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QUALITY OF LIFE AFTER BILATERAL ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTIONS

KVALITET ŽIVOTA NAKON OBOSTRANIH REKONSTRUKCIJA PREDNJEG UKŠTENOG LIGAMENTA

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Summary

Introduction. The aim of study was to analyze the influence of bilateral anterior cruciate ligament reconstructions on life quality of patients and their return to sports activities. **Material and Methods.** Thirty-two operated patients took part in this survey during the period of ten years. There were 5 women and 27 men, their average age being 30.46 years (19-55). The participants answered a modified Knee Injury and Osteoarthritis Outcome Score questionnaire set and gave data about preoperative and postoperative periods. **Results.** The participants' age and parameters of Lysholm scale did not correlate significantly with the subjective level of physical activity after the second knee surgery. After the first anterior cruciate ligament reconstruction, 4 participants (12.5%) did not return to trainings, while 28 did (87.5%); 8 patients (25%) did not return to competitions and 24 of them (75%) achieved the competition level of sports activities. After the anterior cruciate ligament reconstruction of contralateral knee, 6 (18.8%) did not return to trainings, while 26 (81.3%) did; 15 patients (46.9%) did not return to competitions, while 17 (53.1%) continued to compete without restrictions. The average values of questionnaire scores were between 95.1-98.2 points. **Discussion and Conclusion**. Resuming the same or higher level of sports activities after the first reconstruction is one of the preconditions for the same injury of another knee. An athlete looses more than two and a half years of competitions on average. Operations of additional meniscus ruptures do not play a crucial role in restitution of sports activities. Although we achieved good operative results, only every second athlete with bilateral injury has returned to sports activities without restrictions after the bilateral anterior cruciate reconstructions.

Key words: Quality of Life; Anterior Cruciate Ligament Reconstruction; Anterior Cruciate Ligament; Athletic Injuries; Postoperative Period; Questionnaires; Knee Injuries; Osteoarthritis, Knee; Lysholm Knee Score

Sažetak

Uvod. Cilj studije je analiza uticaja obostranih rekonstrukcija prednjeg ukrštenog ligamenta na kvalitet života pacijenata i povratak sportskim aktivnostima. **Materijal i metode.** U istraživanju je učestvovalo 32 operativno lečena pacijenta, tokom desetogodišnjeg perioda. Među njima je bilo 5 žena i 27 muškaraca, prosečne starosti 30,46 godina (19−55). Učesnici su popunjavali modifikovani paket *Knee injury and Osteoarthritis Outcome Score* upitnika i dali podatke o preoperativnim i postoperativnim periodima. **Rezultati.** Korelacijom starosnog doba ispitanika sa postignutim subjektivnim nivoom fizičke aktivnosti, kao i parametrima Lišolmove skale, posle druge operacije kolena nismo pronašli značajnu razliku. Posle operacije prvog kolena 4 ispitanika (12,5%) nisu se vratila u trening, dok 28 jeste (87,5%); 8 ispitanika (25%) nije se više takmičilo, dok se 24 njih (75%) i dalje takmiče. Posle operacije drugog kolena 6 (18,8%) nisu se vratili treninzima, dok se 26 (81,3%) vratilo trenažnom procesu; 15 ispitanika (46,9%) nije se vratilo u takmičenja, dok 17 (53,1%) jeste u punom obimu. Prosečne vrednosti iz KOOS upitnika iznose 95,1−98,2 poena. **Diskusija i zaključak.** Povratak na isti ili viši nivo sportske aktivnosti posle rekonstrukcije prednjeg ukrštenog ligamenta kolena jedan je od preduslova za nastanak kidanja ligamenta i drugog kolena. Sportista prosečno izgubi više od dve i po godine do povratka takmičenjima. Udružene operacije meniskusa nemaju značajnu ulogu u povratku sportskim aktivnostima. Iako su zabeleženi zadovoljavajući operativni rezultati, tek svaki drugi sportista sa obostranom povredom se vraća takmičenjima u punom obimu nakon prethodnih rekonstrukcija.

Ključne reči: Kvalitet života; Rekonstrukcija prednjeg ukrštenog ligamenta; Prednji ukršteni ligament; Sportske povrede; Postoperativni period; Upitnici; Povrede kolena; Osteoartritis kolena; Lisholmov skor

Introduction

According to various studies, the annual incidence of anterior cruciate ligament (ACL) injuries in general population ranges from 0.01 to 0.08% [1-3] and the incidence is significantly higher among sports active population (1.5-1.7%) [1–4]. The annual ACL incidence in amateur sporting groups is

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Abbreviations
ACL – anterior cruciate ligament
KOOS – knee injury and osteoarthritis outcome score

generally higher than the entire population but lower than among professional athletes [1], where it ranges between 0.15-3.7% [1–3]. The incidence of non-simultaneous bilateral ACL injuries varies from 1.1% to 14% of the total number of people with ACL rupture [4–10]. Simultaneous ACL bilateral ruptures are very rare and have been published in the literature as individual cases or small series of patients [3, 12–14].

Forty years ago it was stated that "the ACL is the most common cause of the ex-athlete", because it ended the sports career, and "represents the beginning of the end of the knee joint" [5]. It was believed that new operational techniques would stop irreversible changes in the cartilage by establishing the physiological anteroposterior displacement of tibia, but the long-term monitoring of patients led to the conclusion that this operation could not result in the prevention of arthrosis in spite of reducing the injury to the menisci [5]. The main goals of ACL surgical treatment are restoring the anteroposterior and rotary stability of the knee as well as resuming the activities before the injury. The previous level of competition is achieved in 65–88% of operated patients [4, 5, 15, 16], unless complications occur, and if they do, this level is resumed in 1–13% of patients [4, 5, 15] in case of re-rupture, and in less than 2% [17, 18] if an infection develops. ACL rupture of the contralateral knee usually happens within four years after the first surgery and can affect the return to sports competitions [5–8, 19].

According to the World Health Organization (WHO), the quality of life represents a personal perception of their own life positions in the context of the culture and value systems in which the individual lives and in relation to goals, expectations, standards and interests [20]. It consists of physical health of individuals, psychological status, financial independence, social relationships and their relation to significant environmental characteristics [21]. The concept of quality has gained a great significance and important place in the analysis of problems in a variety of clinical situations in modern medical practice over recent years [22]. The evaluation of life quality can be subjective or personal assessments or objective observer's score. Measurement scales have been designed to evaluate the extent to which a person is satisfied with the quality of life [22]. Testing the quality of life and opportunities for its improvement are particularly important and a priority not only in public health, but also in clinical disciplines bearing in mind the increasing incidence of ACL injury and injuries of surrounding structures. Knee osteoarthritis develops in 13% of people with isolated ACL rupture and 48% of people with associated meniscal injury as soon as 10 years after ACL reconstruction [5, 23]. The younger generation with osteoarthritis of knee joint is experiencing greater psychological stress than older people [24]. In addition, the chances of having the same injury are three times higher in teenagers with injured ACL, but resurgery is associated with poorer treatment outcome and a lower quality of life [25]. The quality of life related to health essentially refers to physical, social, emotional and psychological components, values and priorities in life [26–28]. The effect of rehabilitation on the quality of life can be in the form of restrictions on high-functional activities such as competitive sports and difficulties in meeting their professional obligations [29].

Bilateral ACL injuries can significantly compromise the excellent results in the sport in the span of a few years due to the long absence from training and competition, which may be perceived by the patients as a reduction in the quality of life. Since there are few data on the quality of life after injury and operative treatment of athletes, this study has been aimed at determining how the bilateral reconstructions affect the return to sports activities, and whether there is a difference in the quality of life between the patients who have undergone only anterior cruciate ligament surgery and those who had associated injuries of meniscus.

Material and Methods

Having been approved by Ethics Committee of Clinical Center of Vojvodina, this retrospective study was performed at the Department of Orthopedic Surgery and Traumatology in Novi Sad. The study sample included 32 of 50 patients operated for bilateral ACL ruptures in the period from January 01, 2003 until December 31, 2012, who had given their consent to participate in this study. The respondents were 5 women and 27 men, whose average age was 30.46 years (ranging from 19 to 55 years).

It was designed as a retrospective-prospective study. The knee injury and osteoarthritis outcome score (KOOS) questionnaire [30], entirely translated from English into Serbian and adapted for this purpose by adding questions relevant to this study was used to collect data. This questionnaire is an extension of osteoarthritis index "Western Ontarion" and "McMaster" University (WOMAC) [31] and most commonly used instrument for the assessment of the relevant effects of therapy in patients with osteoarthritis. The questionnaire has been designed to assess the short-term and long-term results after a knee injury, and is divided into five parts: the first involves the quality of life following ACL surgery; the second one relates to pain in different activities; the third is related to daily activities performed by the patient; the fourth part is related to the level of physical activity, Lysholm score [32], while the finishing, fifth part focuses on the very consciousness of the patient's quality of life and how he perceives his injury. Before surgery, all patients completed the questionnaire about the details of injuries and subjective scores. The questionnaire also represents the register of ACL injuries at the Department

of Orthopedic Surgery and Traumatology in Novi Sad and is available publicly.

The patients answered the questionnaire set and provided information about their sports activities and activities in their daily life. The following parameters were included for each patient: age, gender, height, body mass, length of training before injury, length of time from the first injury to operation, length of time from the first injury to the comeback to training, length of time from the first operation to the comeback to competition, length of time between the two injuries, length of time from the first operation and the injury of the other knee, length of time from the second knee injury to operation, length of time from the other knee injury to the comeback to training, length of time from the other knee injury to the comeback to competition, dominant leg, quantity of pain in typical activities (pivoting, extension, flexion, walking on flat surface, walking on stairs, long standing and sitting), and the achieved level of physical activities after both operations.

The quality of life questionnaire was sent to the respondents via electronic mail (e-mail). Its purpose was explained to the respondents, who then gave their consent for their answers to be used for the purposes of this study. Criteria for exclusion from the study were the patient's unwillingness to participate in the study, or failure to respond to e-mail or phone call. Standardized options were provided for answering (5 Likert's "boxes") [33], and a number of points from 0 to 4 was assigned for each question. The score of 100 indicated no symptoms, while 0 indicated extreme symptoms, and it was calculated for each dimension separately. Instructions for scoring are given in a separate "KOOS" document on scoring [33]. According to the importance of research and additional questions, our scoring is different compared to the standardized scoring method that is given in KOOS questionnaire [30], but the results are identical to the original. According to the "KOOS" scoring scale, the higher score means the better quality of life and better health condition of respondents.

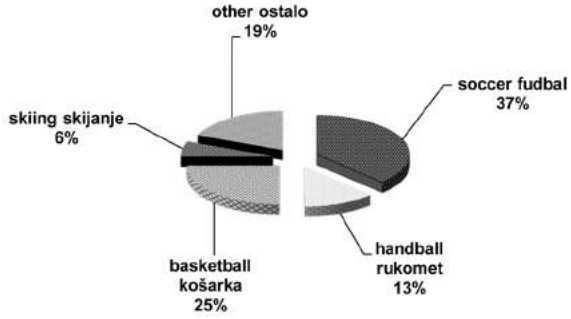
Within descriptive statistics, the following parametric values were analyzed: mean value, standard deviation, minimum and maximum, as well as the frequency of the presence of each category as a nonparametric value. Student's T-test was used to calculate the differences between groups. Pirson's χ^2-test was used to compare the differences between the tested groups for nonparametric values. Data were analyzed and shown by tables and graphs for each group.

Results

Out of 32 patients, 14 patients injured the right knee first and 16 patients injured first the left one, while both knees were simultaneously injured in two cases. The left leg was dominant in 19 patients (for jumping), and the right one was dominant in 13 patients. No statistically significant correlation was observed between the age of patients and their level of activity, nor the effect of the dominant leg on bilateral ACL injuries. The correlation of age and the activity level was F (2.29)=1.59, p=.221 (p>.05).

The periods between injuries and operations are shown in **Table 1.**

The injuries happened during sports activities in all patients: 16 (50%) got the injury in competition, 8 during the training (25%) and 8 in recreational sporting activities (25%). The associations between the type of sport and bilateral ACL rupture is shown in **Graph 1** and competition level of sports activities is given in **Graph 2.**



Graph 1. Sport that caused bilateral ACL rupture
Grafikon 1. *Vrsta sporta koja je dovela do obostrane povrede prednjeg ukrštenog ligamenta*

ACL and meniscus injuries during the first and contralateral knee injuries are shown in **Table 2.**

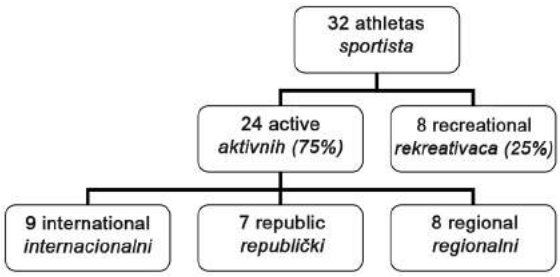
In the correlation between total Lysholm score and age of patients, lower score values were found in older patients (**Table 3**).

The average values of KOOS questionnaire ranged between 95.1 and 98.2 points.

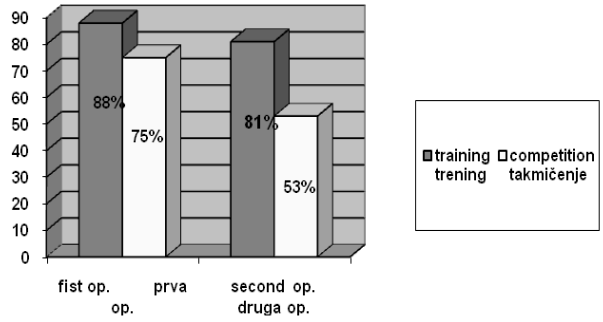
A statistically significant difference in the correlation of age and each component of KOOS questionnaire (**Table 4**) was found in the components

Table 1. Time of ACL injuries
Tabela 1*. Vreme povređivanja prednjeg ukršenog ligamenta*

	Time/*Vreme*	Average *Prosek*
1st injury-1st operation/*1.povreda-1.operacija*	25 days-7 years/*25 dana−7 godina*	10.2 months/*10,2 meseci*
1st injury-2nd injury/*1.povreda-2.povreda*	9 months-15 years/*9 meseci−15 godina*	4.34 years/*4,34 godine*
2nd injury-2nd operation/*2.povreda-2.operacija*	5 days-4 years/*5 dana−4 godine*	9.1 months/*9,1 meseci*



Graph 2. Sports activity and competition level of patients
Grafikon 2. *Nivo sportske aktivnosti i ranga takmičenja pacijenata*



Graph 3. Returning to trainings and competitions after the first and second ACL reconstruction
Grafikon 3. *Povratak treninzima i takmičenjima nakon prve i druge operacije prednjeg ukrštenog ligamenta*

Table 2. ACL and meniscus injuries during the first and contralateral knee injuries
Tabela 2. *Udružene povrede prilikom inicijalne i povrede LCA* kontralateralnog kolena*

Injury *Povreda*	Isolated ACL *Samo LCA*	Both menisci *Oba meniskusa*	Medial meniscus *Unutrašnji meniskus*	Lateral meniscus *Spoljašnji meniskus*
The first/*Prva*	15	3	6	3
The second/*Druga*	17	1	3	3

**Ligamentum cruciatum anterius*

Table 3. Correlation between Lysholm score and patient's age
Tabela 3. *Odnos Lišolmovog skora i starosti pacijenta*

		Age *Starost*	Lysholm
Age/*Starost*	Pearson correlation	1	-.390
	Sig. (2-tailed)		.029
	N	32	32
Lysholm	Pearson correlation	-.390	1
	Sig. (2-tailed)	.029	
	N	32	32

Tabela 4. Correlation between KOOS questionnaire components and patient's age
Tabela 4. *Korelacija komponenti KOOS upitnika sa godištem ispitanika*

KOOS component/*KOOS komponenta*		Age/*Dob*
Pain/*Bol*	Pearson correlation	.354
	Sig. (2-tailed)	.039
	N	32
Symptoms/*Simptomi*	Pearson correlation	.052
	Sig. (2-tailed)	.778
	N	32
Activities of daily life/*Aktivnosti dnevnog života*	Pearson correlation	-.067
	Sig. (2-tailed)	.715
	N	32
Sports activities/*Sportske aktivnosti*	Pearson correlation	-.326
	Sig. (2-tailed)	.050
	N	32
Quality of life/*Kvalitet života*	Pearson correlation	-.020
	Sig. (2-tailed)	.915
	N	31

"Pain" and "Sports activities and recreation". High scores of both tests mean that there was no significant decrease in of the patients' life quality. Thus, the thesis of our research that the quality of life after bilateral ACL injuries is lower than before them is not justified.

After the first ACL reconstruction, 4 participants (12.5%) have not returned to trainings, while 28 have (87.5%); 8 patients (25%) have not returned to competitions and 24 of them (75%) achieved competition level of sports activities. After the ACL reconstruction of contralateral knee 6 patients (18.8%) have not returned to trainings, while 26 (81.3%) have; 15 patients (46.9%) have not returned to competitions, while 17 (53.1%) of them still compete without restrictions **(Graph 3).**

Discussion

ACL reconstruction surgery is among those operations that improve the quality of life. They are not vitally indicated, but are usually performed on sports active population because the unstable knee can hardly achieve top sports results [6–8, 15, 19, 34, 35].

In our sample, the average absence from competition was 31 months for an athlete with bilateral ACL rupture because ten months had passed in waiting for the first operation (due to untimely reporting for examination, diagnosis and losing time on the waiting list for surgery), plus another 6 months at least after that period before returning to competition after the rehabilitation. In case of contralateral ACL injuries, the patient waited for the new operation for 9 months on average and resumed competitive sports in 6 months at best. When it is known that in Serbia the first ACL injury occurs in the 26th year of life, and the second in the 30th year on average [15, 19, 34, 35], it is clear that an athlete has a dilemma about continuing or discontinuing the active sports career. In majority of foreign studies [4, 8, 36] athletes also lose between 1.5 and 2.5 years of competitions after bilateral ACL reconstructions. The difference is in fact that the time frame from the injury to operation is shorter (within two months), but those athletes have longer average period to return to competitions. Thus, as many as 89% of professional American basketball players return to active sports 11.6 months after unilateral injury (11.6 ± 4.1), which also happens in the 26th year of life (25.7 ± 3.5) on average [36]. ACL injury of contralateral knee usually happens 3-4 years after the first injury [4, 8, 19].

The most prominent risk factor for the contralateral ACL injury is the attempt to return to a high (competitive) level of physical activity [6–8,19], which is in agreement with our results because 75% of our operated patients returned to competition level of activities after the first operation, and then had another knee injury within the first 4 years after the first operation. Most authors [4, 7, 8, 19] confirm the above mentioned time frame, while Orchard et al. [38] have found that the greatest risk factor for the contralateral ACL injury is the history of an ACL reconstruction in the previous 12 months.

Intensive sports that involve movements of pivoting, forced valgus and anterior translation of tibia, during one-leg landing and sudden change of direction represent risky activities for ACL rupture [34, 37]. The fact that in our former studies [16, 34, 35] almost half of all of the patients were injured in football (soccer in the United States) only reflects sports preference of young population in Serbia due to the popularity of that sport among young professionals as well as playing football by the middle-aged population as a recreational activity. Football was the most prominent sport also in this study; the second and third place was taken by basketball and handball, respectively. Souryal et al. [9] put American football (rugby) in the first place with 25.6%, then basketball and soccer with 20.7% and 11%, respectively. This is in accordance with the findings of our studies. The difference is only in fact that rugby is more popular sport than soccer in North America. Swedish authors [5] believe that handball is a high risk sport due to the rapid change of direction movement of players and pivoting, which says more about the popularity of that sport in Scandinavian countries. Authors from Japan think that basketball and gymnastics are sports with the highest risks among women [39].

Except our four participants (13%) who have not returned to trainings after the initial injury, all others have continued to be involved in sports at the level of trainings or returned to regular competitions. According to our earlier results the most commonly injured athletes are those who take active part in sports activities for the period from 11 and 20 years, most often in competitive matches, and considerably less in friendly matches and in the sessions. The parts of competition that have the highest risk are its middle part and end of match [34]. Our results showed that the patients who were in competitive level of sports activities accounted for 50% in the structure of our participants.

Returning to trainings and competitions shows a decreasing trend in function of time **(Graph 3).** After the first ACL reconstruction, 12.5% of participants have not returned to trainings and 25% have not returned to competitions, whereas only 18.8% have not returned to trainings after the second ACL reconstruction, that being a slightly decreasing trend. However, as many as 46.9% of athletes have not returned to competitions without restrictions, which can be explained by the assumption that the average time from operation to training and competition is longer after the second reconstruction than after the first one. Longer period of rehabilitation in addition to the time factor between the first operation and the second injury (average 3.6 years; 6 months-13 years) results in a lower percentage of athletes who have returned to unlimited sports activities. Not competing for some time is irreparable for an active athlete.

According to Swedish researchers [6], the patients with contralateral ACL injuries had lower knee function, activity level and quality of life scores compared with patients who had undergone a single ACL reconstruction. The median Tegner score was 9 points before the first injury, 7 points before the second injury and 4 points during the follow-up after bilateral operations [6]. The mean Lysholm score for patients with bilateral ACL injuries was only 82 points [6]. This is a significantly lower score in comparison to primary operations that are generally above 94 points [15, 16, 35]. Even re-operated patients with complications had better results [15, 17, 18].

Motohashi et al. [39] compared the groups with bilateral and unilateral injury and concluded that the results were better in the one with unilateral injury because only 10% of the patients with bilateral injuries returned to sports activities without restriction, whereas that percentage was 35% in the group with unilateral injury. Falstrom and Ardern et al. [6, 40] and Salmon et al. [4] reported that 40-43% and 56% of those patients returned to sports, respectively. Our results are similar to the majority of others [5, 15–17, 36], showing that 75% of athletes (65-89%) returned to the competition level after the first operation. That percentage was significantly lower (53%) among our patients after the second reconstruction, but it was still higher than in the majority of other studies where it ranged between 10-40% [6, 39, 40].

A group of Japanese authors [39] classified their patients according to how they returned to sporting activities into group A, the patients who had returned to the former level of sporting activities; group B, those who had returned to sporting activities with a reduced ability; group C, those who had returned to other sports less risky for knee injuries; and group D, those who discontinued sports completely. The results of comparison of the patients with the first and second ACL reconstruction were better in the group with unilateral injury because there were three times more athletes classified in group A (that achieved the same competition level). By questioning their patients with reconstructed bilateral ACL ruptures, Ardern et al. [40] found that 60% of their operated athletes did not return to pre-injury activities more because of their subjective perception than because of lower quality of operation. The main reasons for not returning were not trusting the knee (28%), fear of a new injury (24%) and poor knee function (22%).

By correlating the associated injuries during the second knee injury and the achieved level of physical activity, it was found that meniscus ruptures did not play a crucial role in restitution of activities in this study group. Statistical parameters show that there is no statistically significant difference. The reason for such a result is again significant disproportions in the representation and associated absence of ruptures within the group, as well as the higher percentage of those participants who were not able to provide the information on associated knee injuries. Only 9.4% of the respondents had the rupture of medial meniscus, another 9.4% had the rupture of the lateral one, and 3.1% of both menisci simultaneously. As many as 25% of participants did not know if they had an injury of menisci, while 53.1% of them had an isolated ACL rupture. Faltstrom et al. [6] found ruptures of medial meniscus in 15.4% of cases during initial injuries and 31.1% during the contralateral injuries. Lateral meniscus was injured in 15.4% of initial ACL injuries and in 13.1% of contralateral. Both simultaneously injured menisci during the initial rupture happened in 4.6% of cases and in 3.3% during contralateral ACL rupture. Ardenord et al. [8] have also concluded that the previous meniscal and chondral injuries were not the predictors of future contralateral ACL reconstruction, although they noted significantly greater percentages than we did (40% menisci and 27.5% chondral lesions).

Average scores for each of the components of KOOS questionnaire show that our results are quite close to the maximum score, ranging from 95.06 to 98.21 points, which leads us to the conclusion that bilateral ACL reconstructions provided good results. Although the objective result of the operation satisfy the criteria of returning to the sports activities, we believe that athletes have their contralateral knee injured due to the unconscious sparing of initially operated knee, thus overloading the other knee. It usually takes longer than 6 months to regain the absolute neuromuscular control and proprioception of the originally operated knee, when athletes return to competitions. Sometimes it takes years, and another ACL gets injured in the meantime [5, 8, 15].

The shortcoming of this study is that the patients did not fill in the KOOS questionnaire exactly at the specified intervals starting from the initial injury, which would follow the dynamics and dependence of the questionnaire's components and aspects of postoperative period. This should be done in a future study. Getting the statistical significance of the KOOS component "Pain" could be explained by the lower level of pain tolerance which decreases with the person's age [41]. The statistical significance of an adverse effect of moderate intensity obtained in the analysis of component "Sport and recreation" means that the absence of difficulties in sporting activities decreases with age. This can be explained by the reduction of motor abilities with aging, decline in motivation and change of lifestyle [41]. The main disadvantages of the study are a small sample of patients (32) and fact that the patients had to recall specific information about activities and symptoms retrospectively, thus the subjectivity in filling in the questionnaire could not be excluded. Similar difficulties have been reported by other authors [5, 6, 41].

Conclusion

Returning to the same or higher level of sports activity after reconstruction of the anterior cruciate ligament is one of the preconditions for the rupture of contralateral ligament.

Although we recorded satisfactory results of bilateral reconstruction of the anterior cruciate ligament, 81% of the athletes returned to training, but only every second (53.1%) returned to the sport after previous operations without restrictions.

It took the athletes in our sample more than two and a half years on average to return to competitions. Operations of additional meniscus ruptures do not play a crucial role in restitution of sports activities.

Because of the methodologically small sample, the statistical correlations gave little or no statistical significance. Therefore, it is necessary to perform more detailed observation of the results obtained under different aspects of sports activities on a larger number of patients.

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THE RELATIONSHIP BETWEEN BODY MASS INDEX AND SUBJECTIVE WELL-BEING – THE MODERATING ROLE OF BODY DISSATISFACTION

RELACIJA IZMEĐU STEPENA TELESNE UHRANJENOSTI I SUBJEKTIVNOG BLAGOSTANJA – MODERATORSKA ULOGA NEZADOVOLJSTVA TELOM

Dragana BRDARIĆ, Veljko JOVANOVIĆ and Vesna GAVRILOV JERKOVIĆ

Summary

Introduction. Excess bodyweight and obesity are widespread health problems throughout the world. In Serbia, over 50% of the adult population is overweight and the Province of Vojvodina is one of the regions with the highest percentage of obesity. The relationship between obesity and health complications has been consistently demonstrated. However, research on the relationship between obesity and subjective well-being has not provided clear results. Body dissatisfaction is considered to be an important factor for understanding this relationship. The main objective of this study was to investigate the moderating effect of body dissatisfaction in the relationship between body mass index and subjective well-being. **Material and Methods.** The study sample included 731 respondents (72.6% women), with the mean age 28.93 years (SD = 8.47) from the Province of Vojvodina who had completed an online set of tests consisting of Body Shape Questionnaire, Depression Anxiety Stress Scale-21, Satisfaction with Life Scale, Scale of Positive and Negative Experience and a self-assessment of bodyweight and body height. **Results**. The results indicate that the moderating effect of body dissatisfaction in the relationship between body mass index and indicators of subjective well-being is statistically significant in both sexes. Specifically, the women with higher body mass index values who expressed lower body dissatisfaction reported lower levels of emotional distress and higher levels of pleasant emotions than those with lower body mass index. On the other hand, the men with higher bodyweight preoccupation and low body mass index reported significantly higher levels of pleasant emotions than those with higher body mass index values. **Conclusion**. These results suggest the necessity of a more detailed study of this relationship on both clinical and general population samples from Serbia.

Key words: Overweight; Obesity; Personal Satisfaction; Body Size; Eating Disorders; Body Mass Index; Health Promotion; Stress, Psychological; Questionnaires; Social Media

Sažetak

Uvod. Prekomerna uhranjenost i gojaznost predstavljaju rasprostranjen zdravstveni problem u sve većem broju zemalja širom sveta. U našoj zemlji, preko 50% odraslog stanovništva ima problem prekomerne uhranjenosti, pri čemu je Vojvodina jedna od oblasti sa najvećim procentom gojaznosti. Veza između prekomerne uhranjenosti i zdravstvenih komplikacija se dosledno pokazuje. Međutim, istraživanja o tome da li je i na koji način je gojaznost povezana sa pokazateljima subjektivnog blagostanja ne daju dovoljno jasne rezultate. Kao jedan od faktora koji se smatraju važnim za razumevanje ove relacije navodi se nezadovoljstvo telom. Osnovni cilj ovog istraživanja je ispitivanje moderatorskog uticaja nezadovoljstva telom na relaciju između telesne uhranjenosti i mera subjektivnog blagostanja. **Materijal i metode.** Istraživanjem je obuhvaćen 731 ispitanik (72,6% žena), prosečne starosti 28,93 godine (SD = 8,47) sa teritorije Vojvodine koji su ispunili onlajn bateriju testova: Skala nezadovoljstva telom, Skala depresivnosti, anksioznosti i stresa, Skala zadovoljstva životom, Skala prijatnih i neprijatnih doživljaja i samoprocena telesne mase i visine na osnovu kojih je izračunat indeks telesne mase. **Rezultati**. Rezultati ukazuju na to da je nezadovoljstvo telom kod oba pola značajan moderator povezanosti između indeksa telesne mase i pokazatelja subjektivnog blagostanja. Naime, žene sa višim vrednostima indeksa telesne mase, a koje su manje nezadovoljne telom, značajno manje izveštavaju o emocionalnom distresu i procenjuju da imaju viši nivo prijatnih emocija od žena sa nižim indeksom telesne mase. S druge strane, muškarci sa visokom preokupiranošću telesnom masom i niskim indeksom telesne mase iskazuju značajno viši nivo prijatnih emocija od onih sa višim vrednostima indeksa telesne mase. **Zaključak**. Ovi rezultati ukazuju na potrebu za detaljnijim proučavanjem ovog odnosa kako na kliničkom uzorku tako i na uzorku opšte populacije u Srbiji.

Ključne reči: Preterano gojazni; Gojaznost; Lično zadovoljstvo; Veličina tela; Poremećaji ishrane; Indeks telesne mase; Promocija zdravlja; Psihološki stres; Upitnici; Društveni mediji

Introduction

Being overweight or obese is a widespread health problem in an increasing number of countries worldwide. According to the data from a study conducted by the Ministry of Health in Serbia in 2006, out of 54.4% of adults who are overweight, 36.2% are pre-obese, and 18.3% are obese. The largest percentage of overweight people has been recorded in the Province of Vojvodina and eastern Serbia. Out of 55.7% of adults in Vojvodina who are overweight, 35.2% are pre-obese and 20.5% are obese

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Abbreviations
BMI – body mass index
WHO – World Health Organization

[1]. Obesity has consistently been reported to be significantly related to numerous health issues, among which the most frequent are metabolic and hormonal complications, as well as diseases of organ systems (cardiovascular, respiratory, malignant diseases) [2, 3]. Considering these complications, as well as the data which show that these can be significantly improved by regulating the excess bodyweight, it is justifiable to invest large sums of money into health care systems in order to provide better understanding of the factors of occurrence, maintenance and consequences of excess bodyweight, or in other words to design an effective strategy for the prevention and treatment of obesity.

In addition to biological and social factors, psychological factors are significant determinants of occurrence, maintenance and reduction of obesity [5]. A considerable number of researchers in the field of health psychology believe that studying psychological factors related to obesity can significantly improve the understanding of this problem. The important issues in the context of obesity are related to the subjective well-being of overweight people, which includes the level of their pleasant and unpleasant emotional states and how satisfied they are with their lives. The assumption is that the information about the health risks of obesity, social pressure to be fit, and stigmatization and discrimination of overweight individuals can lead to a lower level of subjective well-being among overweight people. However, unlike the considerably clear results about the relationship between obesity and health parameters, no consistent conclusions have been made concerning how obesity is related to one's mood, satisfaction with life, emotional distress, etc. [6]. A number of systematic reviews and individual studies indicate the correlation between obesity and a lower satisfaction with life, as well as a lower estimation of the quality of life [7, 8]. However, other studies and their reviews imply that there is no such correlation [9–11], or even imply a positive correlation between obesity and a positive affect [12].

The inconsistency of data could be explained by the fact that the samples of the participants in the studies focused on this issue are quite often heterogeneous in age and in health status, the history and the causes of obesity, etc. Another difficulty in reaching a reliable conclusion and generalization of the results of these studies is the fact that the samples having a significant relationship between psychological well-being and obesity were mostly clinical, meaning that most frequently this relationship was examined in people who were receiving obesity treatment at university clinics where these studies were conducted [10, 13]. It is justifiable to assume that this part of the overweight population is different in their level of well-being, perception of the quality of life, etc, from those who do not seek help for their excess weight. Accordingly, a few studies with samples from the general population show that overweight people are not different from non-overweight people in terms of psychological well-being parameters or psychopathological indicators [14].

These inconsistent results imply that obesity is a complex phenomenon due to a large number of factors which contribute to its occurrence, as well as numerous factors which contribute to the regulation and maintenance of that condition. Therefore, the most important question is not whether overweight people suffer in general, but who of them suffer from psychological distress and under what conditions. Therefore, it is necessary to examine the factors which could affect the relationship between the level of obesity and subjective well-being.

Body dissatisfaction is one of the constructs often considered important for this relationship [9, 15]. The results of research conducted on large samples show high percentage of people who report dissatisfaction with their appearance and bodyweight, as well as with their body shape [16]. These findings are often interpreted by taking into consideration the influence of a large number of external and internal factors, such as expectations, social pressure to attain ideal parameters of body shape, etc. [17]. Additionally, the assumption that the people who have excess weight are more preoccupied and dissatisfied with their bodies in comparison to non-overweight people has significant empirical justification [18, 19] although certain studies report the absence of a correlation between the level of bodyweight and dissatisfaction with the body [20].

Another significant and largely consistent result suggests that women with a high body mass index generally report a greater level of body dissatisfaction than men [21]. However, there has recently been a greater interest in studying the correlation of body mass index with body dissatisfaction in men, where, according to some findings, the results suggest a somewhat specific, but also a significantly present level of body dissatisfaction, which is more related to preoccupation with muscles than with weight [22].

On the other hand, studies on the relationship between body dissatisfaction and subjective well-being indicators have not yielded consistent results. Although the results of these studies have not given conclusions yet, a certain number of them indicate the expected positive correlation between body dissatisfaction and lowered indicators of mood and self-esteem [15, 23].

The conclusion is that further research is necessary in order to understand the nature of the relationship between bodyweight and subjective well-being better, especially in non-clinical samples. Inconsistencies among the results of studies describing this relationship justify studies of the potential moderators of this relationship and identify body satisfaction as one of the possible. In addition, a survey of the available literature reveals almost complete absence of studies examining the relation-

ship between bodyweight and subjective well-being, as well as the influence of body dissatisfaction on this relationship in samples from Serbia. Bearing in mind the widespread problem of obesity in Serbia, especially in the Province of Vojvodina, this study was aimed at investigating this relationship in a non-clinical sample from Vojvodina.

The main objective of this study was to examine the moderating effect of body dissatisfaction on the relationship between bodyweight and subjective well-being. Due to the significant discrepancies between the values of body mass index among men and women, this relationship has been examined for each gender separately.

Material and Methods

This study included 731 participants (72.6% female), their mean age being 28.93 (SD = 8.47). The convenience sample was made up of people living in Vojvodina who belong to various online social groups. The sampling was done via the Internet. This particular study was conducted as a part of larger research focused on the possibilities of using Internet in order to reduce weight. The sample included mostly people with vocational and university degrees (56.4%) and university students (23%). In this sample, 22% of participants were married, 38% were in non-marital relationships and 36.4% were single.

Body Mass Index (BMI) is the standard measure of body mass used by the World Health Organization (WHO). According to the criteria of the WHO, the categories of BMI are underweight (BMI < 18.50), normal weight (BMI between 18.50 and 24.99%), overweight (BMI between 25.00 and 29.99) and obese (BMI > 30.00). In this study sample, the highest percentage of men was categorized as having normal weight (51.3%), while 33.5% of men were overweight, 11.2% were obese and 4.1% were underweight. The highes percentage of women were also categorized as being of normal weight (76.9), 10.1% as overweight, 4% as obese and 9% were underweight.

Body Shape Questionaire - the 8 questions version (BSQ-8c) [24] consists of eight questions (e.g. How often have you felt excessively large or rounded), which are used to estimate the level of body dissatisfaction and preoccupation with bodyweight. The answers are given on the six-point Likert scale (range from 1 – never to 6 – always). The reliability of the scale was expressed by the excellent Cronbach's α (alpha) internal consistency estimate (α= .92).

Depression Anxiety Stress Scale-21 (DASS-21) [25] is a 21-item scale designed to measure depression, anxiety and stress indicators experienced by a person throughout the previous week. The scale is divided into three subscales of 7 items, which are answered on a 4-point severity/frequency scale ranging from 0 (did not apply to the subject at all) to 3 (applied to the subject very much, or most of the time). Only the total score on the scale was used for this study as a measure of general emotional distress. The reliability of the DASS-21 scale in this study was excellent (α = .93).

Satisfaction with Life Scale (SWLS) [26] is a 5-item scale (e.g. I am satisfied with my life) designed to measure general Satisfaction with Life. The answers are given in the 7- item Likert scale (ranging from 1 – strongly disagree to 7 – strongly agree). The reliability of the SWLS scale in this study was good (α = .88).

Scale of Positive and Negative Experience (SPANE) [27] is a scale designed to measure positive and negative emotions experienced by the subject during the past four weeks. The scale has 12 items, six items to assess positive feelings and six items to assess negative feelings on the scale from 1 (very rarely or never) to 5 (very often or always). Only the subscale for positive feelings was used in this research, and it demonstrated excellent reliability (α = .92).

Results

Table 1 shows arithmetic means, standard deviations and correlations between the variables used in the research, separately for the male and female part of sample.

As expected, the men had a statistically considerably higher BMI than the women ($t_{(718)} = 10.07$, $p < .01$), while the women reported greater body dissatisfaction ($t_{(729)} = 5.15$, $p < .01$) and greater satisfaction with life ($t_{(729)} = 4.02$, $p < .01$). The relations among BMI, body dissatisfaction and subjective well-being indicators were similar for the men and the women. There was a moderate positive correlation between BMI and body dissatisfaction, while the correlations between BMI and well-being indicators were poor. On the other hand, body dissatisfaction had moderate positive correlations with emotional distress and low negative correlations with the positive affect in both genders. Body dissatisfaction had a low negative correlation with satisfaction with life in the women, while the same correlation in the men was non-significant. Moderate positive correlations between positive affect and body satisfaction as well as moderate negative correlations between distress and both positive well-being indicators were found in both genders.

Tables 2 and 3 show the results of a hierarchical regression analyses which examined the moderating role of body dissatisfaction in the relationship between BMI and three indicators of well-being: emotional distress, positive emotions and satisfaction with life. Due to significant gender differences in BMI and body dissatisfaction, the results are shown separately for men and women.

As shown in **Table 2**, body dissatisfaction in the women is a significant moderator of the relationship between BMI and emotional distress, and BMI and positive emotions.

Moderating effects are shown in **Graph 1** (emotional distress) and **Graph 2** (positive emotions). As shown in **Graph 1**, in the women with high body

Table 1. Descriptive statistics, differences between genders and correlations among study variables
Tabela 1. *Deskriptivna statistika, polne razlike i korelacije između varijabli*

	M	SD	1	2	3	4	5
Women/*Žene*							
1. Body Mass Index/*Indeks telesne mase*	22.02	3.62	–				
2. Body dissatisfaction/*Nezadovoljstvo telom*	2.10	1.19	.39**	–			
3. Emotional distress/*Emocionalni distres*	.64	.51	.10*	.44**	–		
4. Positive emotions/*Prijatne emocije*	3.80	.71	-.08	-.29**	-.62**	–	
5. Life satisfaction/*Zadovoljstvo životom*	4.66	1.33	-.00	-.20**	-.49**	.56**	–
Men/*Muškarci*							
1. Body Mass Index/*Indeks telesne mase*	25.11	3.82	–				
2. Body dissatisfaction/*Nezadovoljstvo telom*	1.61	1.02	.42**	–			
3. Emotional distress/*Emocionalni distres*	.62	.47	.11	.38**	–		
4. Positive emotions/*Prijatne emocije*	3.72	.72	-.11	-.17*	-.60**	–	
5. Life satisfaction/*Zadovoljstvo životom*	4.21	1 .39	-.10	-.13	-.38**	.48**	–

* $p < .05$, ** $p < .01$

dissatisfaction there is no difference in perceived emotional distress, regardless of BMI. However, among the women who are less preoccupied with their weight (i.e. less dissatisfied), those with higher BMI report significantly less emotional distress.

On the other hand, **Graph 2** shows that the women with lower body dissatisfaction who have higher BMI report a significantly higher level of positive emotions than those with lower BMI values.

The results of the moderation analysis for men (**Table 3**) show that body dissatisfaction is a significant moderator of the relationship between BMI and positive emotions.

The moderating effect of body dissatisfaction in the relationship between BMI and positive emotions in the men is shown in **Graph 3**. As shown in **Graph 3**, the men with high preoccupation with bodyweight and low BMI report a significantly higher level of positive emotions than those with higher BMI values.

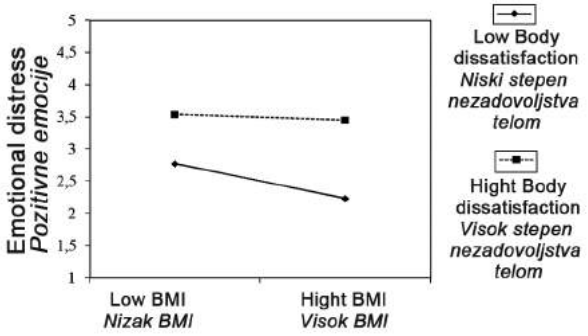
Discussion

This study examined the moderating role of body dissatisfaction in the relation between BMI and indicators of subjective well-being. The study

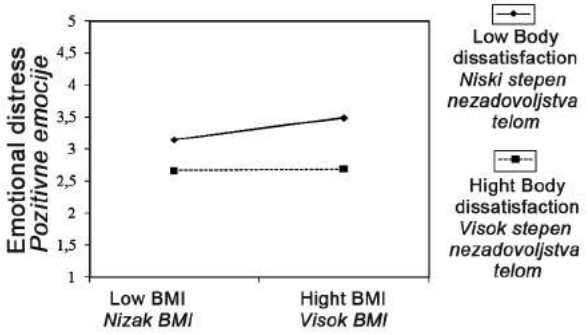
Table 2. Hierarchical regression analysis for women
Tabela 2. *Hijerarhijska regresiona analiza za žene*

Dependent variable/*Zavisna varijabla*	R2	ΔR2	B	SE B	b
Emotional distress/*Emocionalni distres*					
Step 1/*Korak 1*	.19**	.19			
BMI/*Indeks telesne mase*			-.09	.05	-.08
Body dissatisfaction/*Nezadovoljstvo telom*			.46	.04	.46**
Step 2/*Korak 2*	.21**	.01**			
BMI X Body dissatisfaction/*Indeks telesne mase X Nezadovoljstvo telom*			.11	.04	.13**
Positive emotions/*Prijatne emocije*					
Step 1/*Korak 1*	.09*	.09			
BMI/*Indeks telesne mase*			.04	.05	.04
Body dissatisfaction/*Nezadovoljstvo telom*			-.30	.04	-.30**
Step 2/*Korak 2*	.09	.00			
BMI X Body dissatisfaction/*Indeks telesne mase X Nezadovoljstvo telom*			-.08	.04	-.09*
Life satisfaction/*Zadovoljstvo životom*					
Step 1/*Korak 1*	.05*	.05			
BMI/*Indeks telesne mase*			.10	.05	.10*
Body dissatisfaction/*Nezadovoljstvo telom*			-.23	.04	-.24**
Step 2/*Korak 2*	.06	.01			
BMI X Body dissatisfaction/*Indeks telesne mase X Nezadovoljstvo telom*			-.07	.04	-.09

* $p < .05$, ** $p < .01$



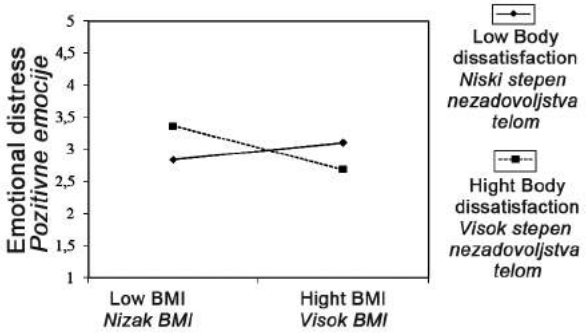
Graph 1. The moderating role of body dissatisfaction in the relationship between BMI and emotional distress in females
Grafikon 1. *Moderatorska uloga nezadovoljstva telom u relaciji između indeksa telesne mase i emocionalnog distresa kod žena*



Graph 2. The moderating role of body dissatisfaction in the relationship between BMI and positive emotions in females
Grafikon 2. *Moderatorska uloga nezadovoljstva telom u relaciji između indeksa telesne mase i pozitivnih emocija kod žena*

was conducted on a convenience sample from the general population of Vojvodina by means of the following: the 8-item Body Shape Questionnaire, the Depression Anxiety Stress Scale-21, the Satisfaction with Life Scale, the Scale of Positive and Negative Experience and self-assessment of bodyweight and body height for calculating BMI.

The obtained results were to a certain extent consistent with the results from previous studies. Higher body dissatisfaction in women, positive relationship between BMI and body dissatisfaction, as well as a poor to moderate correlation between body dissatisfaction and indicators of subjective well-being in both genders were expected and consistent with the previous research [15, 19, 21]. On the other hand, poor and non-significant correlations between BMI and subjective well-being indicators within the context of otherwise inconsistent results of this relationship suggest the necessity of a more detailed examination. The moderating role of body dissatisfaction in the relationship between BMI and subjective well-being was analyzed separately for the men and the women because of the



Graph 3. The moderating role of body dissatisfaction in the relationship between BMI and positive emotions in males
Grafikon 3. *Moderatorska uloga nezadovoljstva telom u relaciji između indeksa telesne mase i pozitivnih emocija kod muškaraca*

significant gender differences in BMI and body dissatisfaction.

The results of the moderation analysis show that body dissatisfaction in the women is a significant moderator in the relationship between BMI and emotional distress, and BMI and positive emotions, but not in the relationship between BMI and satisfaction with life. In other words, the level of distress and positive emotions experienced by the women with high BMI depends on the degree of body dissatisfaction, while their satisfaction with life does not depend on the degree of body dissatisfaction. The results of previous research suggest that the relationship between BMI and satisfaction with life is complex and that it demonstrates a non-linear relation [28]. Therefore, it would be useful to analyze this relation more thoroughly in future studies and also to examine the factors upon which this relation depends.

The results of this study show that the women with higher levels of BMI, who are less preoccupied with bodyweight, meaning that they are less dissatisfied with their bodies, report significantly less emotional distress and estimate that they have a higher level of positive emotions than women with lower values of BMI. This result is somewhat unexpected considering the data from the previous research [15]. However, as stated in the introduction, the largest number of studies examined this relationship among clinical samples, while a smaller number of studies conducted on the general population more frequently show that overweight and obese people do not experience more negative emotions or distress than non-overweight people [29]. It is also possible that the women in our sample who have a higher BMI and are not dissatisfied with their bodies use food more within the context of stress management and/or emotional regulation than people with a lower BMI. This assumption would be consistent with the demonstrated relationship between the mood and eating habits [30]. At the same time, the results indicate that the women who are dissatisfied with their bodies, regardless of their BMI, report a

Table 3. Hierarchical regression analysis for men
Tabela 3. *Hijerarhijska regresiona analiza za muškarce*

Dependent variable/*Zavisna varijabla*	R2	ΔR2	B	SE B	b
Emotional distress/*Emocionalni distre*s					
Step 1/*Korak 1*	.15**	.15			
BMI/*Indeks telesne mase*			-.06	.07	-.06
Body dissatisfaction/*Nezadovoljstvo telom*			.43	.08	.41**
Step 2/*Korak 2*	.16	.01			
BMI X Body dissatisfaction/*Indeks telesne mase X Nezadovoljstvo telom*			.10	.06	.13
Positive emotions/*Prijatne emocije*					
Step 1/*Korak 1*	.03*	.03			
BMI/*Indeks telesne mase*			-.04	.08	-.04
Body dissatisfaction/*Nezadovoljstvo telom*			-.20	.09	-.17*
Step 2/*Korak 2*	.09**	.06**			
BMI X Body dissatisfaction/*Indeks telesne mase X Nezadovoljstvo telom*			-.23	.07	-.30**
Life satisfaction/*Zadovoljstvo životom*					
Step 1/*Korak 1*	.02	.02			
BMI/*Indeks telesne mase*			-.05	.08	-.05
Body dissatisfaction/*Nezadovoljstvo telom*			-.15	.09	-.13
Step 2/*Korak 2*	.02	.00			
BMI X Body dissatisfaction/*Indeks telesne mase X Nezadovoljstvo telom*			.01	.07	.01

* $p < .05$, ** $p < .01$

higher level of emotional distress (i.e. lower values of positive emotions). This result is consistent with the assumption that the level of BMI in and of itself does not necessarily have to be related to the indicators of subjective well-being, but what is really important is one's attitude toward their weight [9].

This is particularly understandable bearing in mind that being overweight or obese does not automatically cause immediate health or psychological problems or issues. Indirectly, this result can partially explain the phenomenon that overweight and obese people do not often have motivation to regulate their weight. Namely, if a person is not dissatisfied with the bodyweight, if s/he is generally emotionally relaxed and in a good mood, it is understandable that it would be more difficult for them to decide to reduce their bodyweight. On the other hand, in order to understand this result better we can use findings which show that body dissatisfaction is determined not only by weight, but also by body shape and other esthetic parameters [16].

In this sense, when interpreting these results, one should not neglect the cultural context of the area where this research was conducted. Since studies investigating this topic within a cross-cultural context [31] stress the importance of knowing specific cultural norms related to food, body perception and how overweight people are viewed, as well as the typical attitudes and eating behaviors in Vojvodina, it would be important to include these factors in future studies. Some of the studies [32] conducted on samples from developing countries suggest another potential explanation for the absence of results indicating that obesity is necessarily accompanied by body dissatisfaction and lower levels of subjective well-being. According to the interpretation proposed by these authors from these developing countries, obesity can represent a sign of prosperity and well-being rather than one of a low quality of life, as is often the case in developed countries. However, the absence of research dealing with this subject in Vojvodina so far makes it difficult to draw reliable conclusions about the effect of cultural context in this area.

The results referring to the male part of the sample suggest that body dissatisfaction has a significant moderating role in the relationship between BMI and positive emotions. This is indicated by the result showing that the men who have higher preoccupation with bodyweight and a low BMI report a significantly higher level of positive emotions than those with higher BMI values. This result could be interpreted from different standpoints. Specifically, a certain number of studies show that body dissatisfaction, i.e. preoccupation with bodyweight, can present a potential risk of developing eating disorders, especially in young people or those who demonstrate a tendency to go frequently on weight-loss diets [33]. However, it is also possible to assume that the men with lower BMI have intentionally reduced their bodyweight or are currently trying to lose weight, and which is accompanied by a positive effect, are still dissatisfied with their body image. On the other hand, the results indicate that there are a certain number of men in the sample who are dissatisfied with their bodies and have higher BMI values who also report a low level of positive emotions. This is inconsistent with

the results indicating that men are more frequently dissatisfied with their bodies when they see themselves as underweight (i.e. when they aspire to gain more muscle mass) than when they believe that they have excess bodyweight [34]. For this group, body dissatisfaction could present a source of motivation to consider preparation for, or reduction of weight, as reported in previous studies [35].

According to all above mentioned, it can be concluded that these relationships are complex and that further research into the relationships among the constructs examined here is necessary for definitive conclusions. Such research should include additional variables (such as history of obesity and dieting, ongoing reduction of weight, health indicators, etc.) and explain these results. It should also include longitudinal studies and studies with representative samples. The results presented so far definitely indicate the importance of studying the relationship between the level of BMI and subjective well-being on samples from Serbia. The continuation of such research could help in an overall understanding and more reliable identification of specific groups of the population so that the methods of monitoring and preventing obesity could be adjusted according to their requirements and motivations. At the same time, the findings of this research can stress the importance of monitoring body dissatisfaction, as well as its relation to bodyweight and subjective well-being in the context of prevention and treatment of obesity. The observation of these results would allow for a clearer recognition of people's specific requirements, objectives and motivations regarding their bodyweight.

In this sense, the results of this study indicate that the programs designed for weight reduction should highlight psychological factors, meaning that in addition to the basic objective of weight reduction, the examination should focus on attitudes toward body image and increase in body satisfaction. Furthermore, these results might inspire researchers and practitioners dealing with obesity prevention to observe the psychological needs or motives besides observing the financial and health risks, and to take into account the result that the level of BMI does not necessarily dictate a certain body dissatisfaction or subjective distress, but rather that this relationship is obviously more complex and requires subtle preventive methods.

Conclusion

The main objective of this study was to examine the moderating effect of body dissatisfaction on the relationship between body mass index and subjective well-being. The results indicate that body dissatisfaction in both genders presents a significant moderator of the relationship between body mass index and indicators of subjective well-being. Women with higher body mass index who are more satisfied with their bodies report a considerably lower level of emotional distress, and a higher level of positive emotions than women with lower body mass index. On the other hand, men who have high preoccupation with bodyweight and lower body mass index report a considerably higher level of positive emotions than those with higher body mass index values. These results suggest the necessity of a more detailed study of this relationship on both clinical and general population samples from Serbia.

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COMPLETE CORRECTION OF ANEMIA WITH RECORMON® (ERYTHROPOIETIN β) IN PATIENTS ON CHRONIC HEMODIALYSIS

KOMPLETNA KOREKCIJA ANEMIJE REKORMONOM® (ERITROPOETIN β) KOD BOLESNIKA NA HRONIČNOM PROGRAMU HEMODIJALIZE

Nada DIMKOVIĆ[1,2], Igor MITIĆ[3,4], Branislav ANDRIĆ[5], Branislav LILIĆ HAVIDŽA[6], Rosa JELAČIĆ[7] and Nataša MILIĆ[8]

Summary

Introduction. Suboptimal correction of anemia is associated with increased prevalence of cardiovascular diseases and increased morbidity and mortality of pre-dialysis and dialysis patients. The aim of the study was to compare the effect of optimal vs. suboptimal correction of anemia in hemodialysis patients with left ventricular hypertrophy. **Material and Methods.** The study included 50 patients, 32 males and 18 females, their mean age being 49.4±11.8 years, from five hemodialysis centers (Clinical Hospital Center Zvezdara, Beograd, Clinical Center Novi Sad, hospitals in Kruševac, Pirot and Zrenjanin). The patients had suboptimal hemoglobin level in spite of therapy (7.8±3.8 g/dl). In addition, the most important inclusion criteria was the left ventricular mass index above 160 g/m^2 and the primary efficacy parameter was a decrease in the left ventricular mass index during 12 month study period. **Results.** During the study, the number of patients who reached their hemoglobin >12 g/dl increased and the target hemoglobin (12-13 g/dl) was achieved in 24 (52%) of patients at the end of the study. At the same time, the left ventricular mass index significantly decreased as compared with the initial values (p=0.014). The left ventricular mass index was not significantly decreased in the patients who did not achieve the target hemoglobin level (207±65 vs. 217±38 g, p=ns) as compared with the patients who achieved the target hemoglobin (179±32 g/m^2 vs. 197±38 g/m^2, p=0.007). The left ventricular ejection fraction did not change significantly during the study period. **Conclusion.** Anemia correction with erythropoietin β resulted in the significantly corrected left ventricular hypertrophy in hemodialysis patients who had had a suboptimal hemoglobin level. Our results have shown that correction of left ventricular hypertrophy is possible with hemoglobin value of 12 g/dl at least.

Key words: Anemia; Erythropoietin; Kidney Failure, Chronic; Renal Dialysis; Hypertrophy, Left Ventricular; Hemoglobins; Treatment Outcome

Sažetak

Uvod. Suboptimalna korekcija anemije udružena je sa povećanom prevalencijom kardiovaskularnih bolesti i povećanim morbiditetom i mortalitetom bolesnika na dijalizi. Cilj ove studije bio je da se uporedi efekat optimalne u odnosu na suboptimalnu korekciju anemije kod bolesnika na hemodijalizi koji imaju hipertrofiju leve komore. **Materijal i metod**e. U ovu multicentričnu studiju u trajanju od 12 meseci uključeno je 50 bolesnika (32 muškaraca, prosečna starost 49,4±11,8 godina) iz pet centara za hemodijalizu (Kliničko bolnički centar Zvezdara, Beograd, Klinički centar Novi Sad, bolnice u Kruševcu, Pirotu i Zrenjaninu). Bolesnici su i pored terapije imali suboptimalne vrednosti hemoglobina (7,8±3,8 g/dl) i indeks mase leve komore preko 160 g/m^2. Primarni parametar efikasnosti bio je smanjenje indeksa mase leve komore tokom studijskog perioda od 12 meseci. **Rezultati.** Tokom trajanja studije povećan je broj bolesnika sa hemoglobinom ≥ 12 g/dl i na kraju ciljne vrednosti hemoglobina (12−13 g/dl) postignute su kod 24 (52%) bolesnika. Vrednosti indeksa mase leve komore značajno su se smanjile u odnosu na početne vrednosti (p = 0,014). Indeks mase leve komore nije značajno smanjen kod bolesnika koji nisu dostigli ciljne vrednosti hemoglobina (207±65 vs. 217±38 g, p = ns) u odnosu na bolesnike koji su postigli ciljne vrednosti hemoglobina (179±32 g/m^2 vs. 197±38 g/m^2, p = 0,007). Ejekciona frakcija leve komore nije se značajno menjala tokom trajanja studije. **Zaključak.** Korekcija anemije primenom eritropoetina β dovela je do značajne korekcije hipertrofije leve komore kod bolesnika koji su prethodno imali suboptimalne vrednosti hemoglobina. Naši rezultati pokazuju da je za ovaj efekat potrebna korekcija hemoglobina do vrednosti od najmanje 12 g/dl.

Ključne reči: Anemija; Eritropoetin; Hronična bubrežna insuficijencija; Hemodijaliza; Hipertrofija leve komore; Hemoglobin; Ishod lečenja

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Abbreviations

CKD – chronic kidney disease
ESA – erythropoiesis-stimulating agents
LVH – left ventricular hypertrophy
Hb – hemoglobin
LVMI – left ventricle mass index
LVEF – left ventricular ejection fraction

Introduction

Anemia is a common finding in patients with chronic kidney disease (CKD). The moment when anemia occurs during the progression of CKD is individual and depends on various factors, but it is usually present when creatinine clearance is decreased under 30 ml/min/1.73 m^2 [1]. Although anemia has multifactorial etiology, it is usually a consequence of erythropoietin deficiency and decreased synthesis by the impaired kidneys. Therefore, the main strategy of renal anemia treatment is administration of erythropoiesis-stimulating agents (ESA) [2, 3].

It has been shown that anemia and its suboptimal correction are associated with the increased prevalence of cardiovascular diseases which is in correlation with the increased morbidity and mortality in pre-dialysis patients, as well as in those who are on renal replacement therapy [4–7]. Statistical analyses show that 50-60% of deaths among the patients on dialysis are related to cardiovascular complications [8, 9]. Anemia is associated with left ventricular hypertrophy (LVH) and coronary artery disease (CAD) [10, 11]. Thus, if the left ventricular mass exceeds 165 g/m^2, the risk of death is 3.7 times higher than in case of the normal left ventricle morphology [9]. Higher heart rate and higher stroke volume due to anemia increase the minute volume which is a significant stimulus for LVH development [12, 13].

Literature data show that treatment of anemia with ESA has resulted in decreased LVH [14, 15]. Besides, correction of anemia has increased ischemic tolerance and coronary reserve [16]. These results suggest the importance of early detection of anemia during the progression of renal disease as well as of the administration of appropriate therapy [9].

In Serbia, ESA therapy has been applied in more than 50% of patients who are on renal replacement therapy. Due to the current National Heath Fund restriction, therapy of renal anemia is suboptimal. Therefore, the aim of this study was to compare the effect of optimal and suboptimal correction of anemia in patients on hemodialysis having left ventricular hyperthrophy.

Material and Methods

The aim of this open, comparative, multicenter phase IV study was the complete correction of anemia with RECORMON® (*erythropoietin β)* in patients on hemodialysis already receiving suboptimal doses of ESA and who had suboptimal correction of hemoglobin. Another inclusion criterion was the presence of LVH.

The study sample consisted of 50 patients, 32 males and 18 females, their mean age being 49±11 years (median 52 years) from five dialysis centers (Clinical Hospital Center /CHC/ Zvezdara, Belgrade, Clinical Center (CC) Novi Sad, hospitals in Kruševac, Pirot and Zrenjanin). Forty six patients ended the study: one patient was excluded due to the deterioration of hypertension, one patient was diagnosed to have hepatic tumor and sudden cardiac death was registered in 2 patients. The most common renal disease was chronic glomerulonephritis (30% of patients) and nephroangiosclerosis (14%). The main inclusion criteria were:

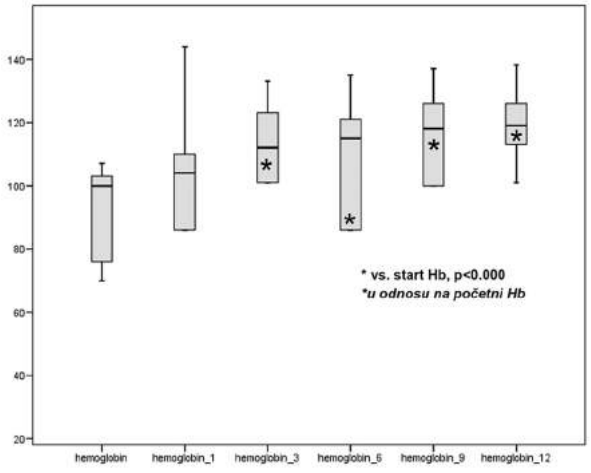
- 18-75 years of age
- Hemodialysis treatment over 6 months
- Previous therapy with erythropoietin β 3 months prior the inclusion in the study
- Steady hemoglobin level with values ≤10.5 g/dl during the last 3 months
- Left ventricle mass index (LVMI) above 160 g/m^2
- Hemodialysis adequacy: Kt/V≥1.2
- No contraindications for anemia correction up to the target values defined in the study

The major exclusion criteria were: pregnancy (diagnosed by detection of human chorionic gonadotropine levels), patients with hypersensitivity to erythropoietin β, administration of other ESA, hemoglobin (Hb) levels above 10.5 g/dl, unregulated hyperparathyroidism (intact parathormone (iPTH) >300 pg/ml), hypertension not regulated with the administered therapy (≥160/100 mmHg), history of myocardial infarction, unstable angina, thromboembolic disease and cerebrovascular insult during the last six months.

The target levels of HE were 12-13 g/dl. Erythropoietin β was administered several times a week until target Hb levels were achieved, followed by the reduction in dosing interval (once a week or once in two weeks) if the investigator assed that the target level of Hb would not be compromised by this dosing schedule.

The major efficacy endpoints were a decrease in LVMI (the primary efficacy endpoint) and maintenance of Hb levels within the targeted range (the secondary efficacy endpoint). The safety profile of drug was closely monitored, and all adverse events were reported, including changes of diastolic and systolic blood pressure. This study went on for 12 months, and the patients had 6 visits in total – at the beginning, after one, three, six, nine and twelve months. All patients signed the informed consent to participate in the study having been given detailed information about the protocol. The study was approved by the local Ethics Committees and the National Regulatory Authority.

Laboratory tests were conducted in the automatic analyzer at the baseline, after 3, 6, 9 and 12 months. Cardiac ultrasound (LVMI, left ventricular ejection fraction /LVEF/) was performed at the beginning of the study, after 6 months and at the end of the study. LVH was defined as interventricular



Graph 1. Hemoglobin values during the study visits (mean±SD)
Grafikon 1. *Vrednosti hemoglobina po vizitama (X ± SD)*

septal diameter (IVSd) > 1.2 cm and/or left ventricular posterior wall diameter (LVPWd) > 1.1 cm. LVMI values higher or equal to 110 g/m^2 for the female patients and 131 g/m^2 for the male patients were considered as LVH according to Framingham trial criteria.

The doses of ESA were defined according to the current guidelines. Iron stores were monitored at 3 to 6 months intervals and iron supplementation was performed if concentration of serum ferritin was under 100 μg/L.

The following descriptive statistical methods were used in this study: arithmetic mean with standard deviation, median with the interquartile range, minimal and maximal values as well as relative numbers for categorical variables. Differential statistical analysis methods were also used, such as: Student's T test, ANOVA for repeated measures, Friedman test, Chi square test, Fischer's exact test depending on numerical limitations, as well as McNemar's test. Pearson's coefficient of linear correlation was used for correlation analysis. Statistical analysis was performed in SPSS software (SPSS for Windows, release 17.0, SPSS, Chicago, IL).

Results

Correction of Anemia

At the baseline, the patients had suboptimal values of Hb (mean Hb 7.8±3.8 g/dl) with suboptimal dose of erythropoietin β. After increasing ESA doses, the Hb levels increased as compared to the baseline values, and a statistically significant difference was present after the third, sixth, ninth and twelfth month of therapy compared to the baseline values (8.4±4.3 g/dl, 9.1±4.6 g/dl, 9.1±4.6 g/dl, 9.5±4.8 g/dl, 11.7±1.8 g/dl, p=0.000 vs. baseline values, **Graph 1**). **Table 1** shows that during the study the number of patients with Hb levels of ≥12 g/dl gradually increased, and the number of patients with Hb levels of ≤12 g/dl gradually decreased (p=0.0001). At the end of the study, the target Hb levels were achieved in 24 (52%) patients.

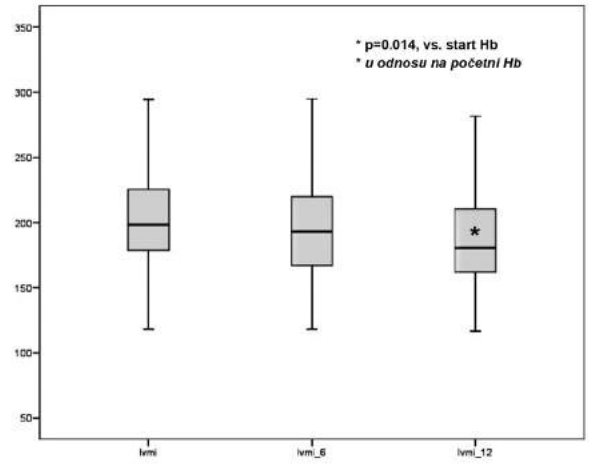
Dosing and Frequency of Administration

Mean erythropoietin β doses were increased in the phase of correction (from the initial to the third visit), and then the doses were stabilized in the maintenance phase (from the third to the twelfth month). There was a statistically significant difference between a weekly dose of drug at the baseline and after one month. During this study, the frequency of drug dosing was variable. During the correction phase, the majority of patients had multiple doses during a week (90% of patients after one month and 82% patients after 3 months), while the patients received the drug mainly once a week or once in two weeks in the maintenance phase. **Table 2** shows the mean weekly dose of erythropoietin β by visits. It is obvious that patients who did not decrease LVMI required the higher doses of erythropoietin β for anemia correction than the patients who decreased LVMI at the end of the study.

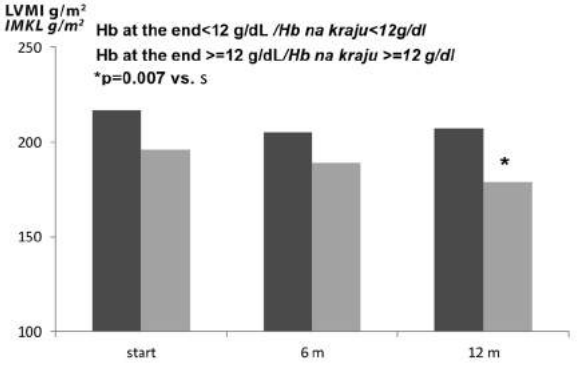
Table 1. Hemoglobin values during the study visits (number, %)
Tabela 1. *Vrednosti hemoglobina po vizitama (broj, %)*

	Hb < 120 g/L	Hb ≥ 120 g/L	p
Beginning/*Start* n= 50	50 (100%)	0 (0%)	
1st month/*1. mesec* n= 50	44 (88%)	6 (12%)	
3rd month/*3. mesec* n= 49	26 (53%)	23 (47%)	
6th month/*6. mesec* n=48	28 (58%)	20 (42%)	<0,0001
9. month/*9. mesec* n=47	19 (40%)	28 (60%)	
12th month/*12. mesec* n=46	22 (48%)	24 (52%)	

Hb - hemoglobin



Graph 2. Left ventricular mass index at the beginning, after 6 and 12 months (median)
Grafikon 2. *Indeks mase leve komore na početku studije, posle 6 i posle 12 meseci (medijana)*



Graph 3. Left ventricular mass index (LVMI) in patients with Hb < 12 g/dl and in patients with Hb >=12 g/dl at the end of the study
Grafikon 3. *Indeks mase leve komore (IMLK) kod bolesnika koji su dostigli vrednost Hb < 12 g/dl i kod bolesnika koji nisu dostigli vrednost Hb > = 12 g/dl*

Left Ventricle Mass Index

LVMI values are shown in **Graph 2**. During this study, LVMI decreased, and at the end of it there was a statistically significant difference between the value of LVMI compared to the baseline values (p=0.014). The baseline values of LVMI were not statistically different between the compared groups. **Graph 3** shows that the patients who did not achieve the target Hb levels did not have a significant decrease of LVMI (207±65 vs. 217±38 g, p=ns) compared to the patients who achieved the target Hb levels (179±32 g/m^2 vs. 197±38 g/m^2, p=0.007). The LVEF values were not significantly different after 6 and 12 months compared to the baseline values.

Adverse Events

During the study all adverse events as well as blood pressure values were recorded. Neither systolic nor diastolic blood pressure was statistically different during the study. Four patients did not finish the study: deterioration of hypertension was recorded in one patient probably due to the drug used, sudden death was registered in two patients, and one patient was diagnosed to have hepatic tumor (neither event was considered to be associated with the study drug).

Discussion

The results of this multi-center study showed that hemoglobin was significantly increased by increasing the dose of erythropoietin β during the study compared to the baseline values. This significant increase was recorded after the third month of therapy, and it continued up to the twelfth month. Although at the end of the study, 52% of patients achieved the target hemoglobin level, a higher percentage of patients (83%) achieved hemoglobin levels >11 g/dl, that being in accordance with the current guidelines (10–12 g/dl) [17], and much higher than the range defined by legislation in Serbia (10–11 g/dl).

Although erythropoietin therapy began in 1989, the optimal hemoglobin was often the subject of clinical studies. Normal Hematocrit trial, CHOIR trial and TREAT trial have shown that the range of normal Hb level for healthy population is not optimal for patients with CKD and patients on dialysis, and the majority of authors agree that hemoglobin

Table 2. Mean doses of erythropoietin β in the patients who decreased their left ventricular mass index (LVMI) and in those who did not decrease it
Tabela 2. *Prosečne doze eritropoetina β kod bolesnika kod kojih je na kraju studije smanjen indeks mase leve komore (IMLK) i kod kojih nije smanjen indeks mase leve komore*

Mean weekly erythropoietin β dose *Prosečna nedeljna doza eritropoetina β*	LVMI/*IMLK*	
	Decreased (N = 24) *Smanjen* (N = 24)	Not decreased *(N = 22) Nije smanjen* (N = 22)
Month 1, IU/*Mesec 1, IJ*	6125±2379	6166±2758
Month 3, IU/*Mesec 3, IJ*	6156±2515	8208±3041
Month 6, IU/*Mesec 6, IJ*	5351±2772	7500±2576
Month 9, IU/*Mesec 9, IJ*	4587±2387	6958±3414
Month 12, IU/*Mesec 12, IJ*	5397±3155	7208±3939

values above 12 g/dl are not recommended due to potential adverse events, primarily cardiovascular ones. However, according to the current guidelines, the Hb levels of 12 g/dl can be recommended if it is assumed that the patient may have benefit, and if cardiovascular and cerebrovascular risk is low [17]. This criterion was taken into consideration when selecting the patients for this study.

The primary efficacy endpoint in this study was a decrease in LVMI values as a consequence of correction of anemia with erythropoietin β. The results show that LVMI was significantly decreased compared to the baseline values after 12 months of therapy with erythropoietin β. More importantly, a decrease in LVMI was recorded in the patients who achieved the target levels of hemoglobin (≥12 g/dl). This finding indicates that the target hemoglobin level set in this study is the level that can lead to regression of identified changes in the cardiac muscle, unlike suboptimal correction of anemia.

It is well known that a coronary disease and left ventricle hypertrophy are the leading comorbidity in dialysis patients. Both are the risk factors for myocardial ischemia and heart failure, which is the strong predictor of death in these patients [21–23]. Several studies have shown that the long-term administration of ESA leads to LVH decrease primarily by normalizing diastolic left ventricular dimension [24–26]. Partial correction of anemia may reduce the load-mediated myocardial ischemia [16, 27]. Other authors agree that ESA therapy leads to regression of LVH, repairs morphology of left ventricle, ejection fraction and cardiovascular status [14, 28–30]. It is shown that Hb is an independent indicator of hospitalization rate as well as of the survival of patients on dialysis [30]. In addition, it is shown that the Hb levels of 12-13 g/dl were associated with a higher risk of death [31]. Since mortality in dialysis patients usually has cardiovascular causes [32], the results of this study are in accordance with other results where the Hb levels >12g/dl have beneficial effect on cardiac muscle leading to regression of LVH [33]. Our authors also showed that therapy with erythropoietin β during 25 months led to partial LVH regression (17%) in 30 hemodialysis patients [34].

During this study, the dosing schedule was variable. As usual, the dose of the drug was significantly increased in the correction phase (first months of the study) and then gradually decreased until the end of the study. The frequency of dosing was changed in line with the increase in hemoglobin: 94% of patients were administered the drug several times a week at the beginning of correction phase, while 50% of patients were administered the drug once a week, or once in two weeks at the end of the study. According to the current guidelines, the drug dosage can be decreased either by absolute dose decrease or by increasing the dosing interval.

It is shown that average doses of erythropoietin β were higher in the patients who did not decrease LVMI values. It is possible that in this group of patients, anemia had additional co-factors (chronic inflammation, hyperparathyroidism, or other) which disable optimal correction of hemoglobin and require an increase in erythropoietin dose. Finally, these patients may have another factor(s) besides anemia that led to LVH (hypertension, uncontrolled hypervolemia).

The left ventricular ejection fraction (LVEF) is a measure of left ventricle function, and the values < 50% with left ventricular fractional shortening of <25% and mid-wall fractional shortening (mwFS) <14% are a sign of systolic dysfunction [35]. Systolic dysfunction is present in approximately 15% of patients who start dialysis [36]. Anemia usually causes a hyperdynamic state in order to maintain an adequate oxygen supply to the peripheral tissues [37]. During this study, the LVEF values were not significantly changed, thus indicating the preserved left ventricular function after the correction of hyperdynamic state.

This study had certain limitations. Its design was predominantly focused on the correction of anemia as an important risk factor for the development of LVH, while other risk factors were not investigated (principal diagnosis including diabetes, previous cardiovascular diseases, hypertension and its duration, dialysis conditions and hydration status, inflammatory status, homocysteine, prescribed therapy, etc.). However, these factors were constant during the study, and did not change significantly which may indicate that the resulting effects in this study were mainly the consequence of the drug administration and correction of anemia.

Conclusion

This national, multicenter study showed that correction of anemia with erythropoietin β in the patients who were on hemodialysis and who had had suboptimal levels of hemoglobin led to the correction of left ventricle hypertrophy, with preserved the left ventricle ejection fraction and with the excellent safety profile of administered therapy. Our experience shows that reversion of left ventricular hypertrophy requires minimal hemoglobin values of 12 g/dl. It is necessary to conduct new clinical studies that will include a larger number of patients and assess whether the results obtained in this study are specific for erythropoietin β or the same results can be obtained when administering other erythropoiesis-stimulating agents.

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ASSESSMENT OF THE ROLE OF PRIMARY HEALTH CARE IN TUBERCULOSIS CONTROL IN SERBIA

PROCENA ULOGE PRIMARNE ZDRAVSTVENE ZAŠTITE U KONTROLI TUBERKULOZE U SRBIJI

Maja STOŠIĆ[1], Nataša LAZAREVIĆ[1], Vesna KURUC[2] and Lidija RISTIĆ[3]

Summary

Introduction. At the onset of the 21st century, tuberculosis is still a public health problem. Due to the implementation of tuberculosis control program in Serbia, there is no fear of an epidemic. Within the reform of the health care system, the service for pulmonary diseases is being restructured, calling for strengthening the role of primary health care. This study was aimed at analyzing the current role of primary health care in tuberculosis control. **Material and Methods.** A cross-sectional study was conducted between the 12th and 30th September, 2010. For evaluating the current role of primary health care in tuberculosis control, four questionnaires were designed based on the "Performance assessment questionnaire regarding TB control for use in PHC", Journal Brasileiro de Pneumologia, print version ISSN 1806-3713 (vol. 35, no 6, Sao Paulo, June 2009). The following methods were used to analyze the results: descriptive statistical analysis, Student's T-test, Fisher's analysis of variance. The reliability of the results was tested with Cronbach's alpha and factor analysis. The level of significance in all the methods bordered 0.05. **Results.** Primary health care does not participate in tuberculosis control in line with the possibilities of the existing legal framework. Although the paper proves that tuberculosis notification rate is higher in the areas less covered by the pneumophysiological service, the role of primary health care does not differ from the areas fully covered. **Conclusion.** There is a need for strategic empowerment of the primary health care system to be actively involved in the diagnostics, treatment and follow up of tuberculosis in Serbia.

Key words: Primary Health Care; Tuberculosis; Serbia; Delivery of Health Care; Questionnaires; Follow-Up Studies

Sažetak

Uvod. Na početku 21. veka tuberkuloza je u svetu i dalje značajan javnozdravstveni problem. Zahvaljujući sprovođenju programa kontrole tuberkuloze u Srbiji, epidemološka situacija je značajno unapređena. U kontekstu reforme sistema zdravstvene zaštite, reorganizuje se služba za plućne bolesti, te je za očuvanje dobre kontrole bolesti neophodno jačati ulogu primarne zdravstvene zaštite. Cilj rada je ispitivanje aktuelne uloge primarne zdravstvene zaštite u kontroli tuberkuloze. **Materijal i metode.** Sprovedena je studija preseka u periodu 12–30.9.2010. godine. Za procenu sadašnje uloge primarne zdravstvene zaštite u kontroli tuberkuloze razvijena su 4 upitnika po uzoru na *Performance assessment questionairre regarding TB control for use in PHC, Journal Brasileiro de Pneumologia, print version ISSN 1806-3713 (vol. 35, no 6, Sao Paulo, June 2009)* koji je prilagođen za potrebe istraživanja. U analizi rezultata istraživanja korišćene su metode deskriptivne statističke analize, Studentov t-test i Fišerova analiza varijanse. Pouzdanost upitnika je proveravana Kronbahovim koeficijentom, a primenjena je i faktorska analiza. Nivo značajnosti u svim primenjenim metodama bio je na granici od 0,05. **Rezultati.** Primarna zdravstvena zaštita ne učestvuje u kontroli tuberkuloze u skladu sa mogućnostima datim u postojećoj zakonskoj regulativi. Ovim radom je dokazano da je stopa prijavljivanja tuberkuloze veća u okruzima koji imaju slabiju pokrivenost pneumoftiziološkom službom, ali da se uloga primarne zdravstvene zaštite u kontroli tuberkuloze ne razlikuje među okruzima. **Zaključak.** Postoji potreba da se strateški planira osnaživanje primarne zdravstvene zaštite za veće učešće u dijagnostici, lečenju i praćenju tuberkuloze u Srbiji.

Ključne reči: Primarna zdravstvena nega; Tuberkuloza, Srbija; Pružanje zdravstvene zaštite; Upitnici; Studije praćenja

Introduction

At the onset of the 21st century, tuberculosis is still a considerable global public health problem. According to data from 2009, 9.4 million people (139/100.000) suffer from different types of tuberculosis (TB), while 1.3 million people (28/100.000 inhabitants) die of tuberculosis [1].

The most significant progress in tuberculosis control in the past decades has been made due to the development and widespread implementation of the World Health Organization (WHO) strategies, which represent a combination of technical and organizational components that enable the functioning of the diagnostic network, and which are easily applicable in the population.

WHO STOP TB Strategy represents a framework for the implementation of the National Tuberculosis Control Program in Serbia from 2010 to 2015. Within the components of the STOP TB Strategy, primary health care (PHC) has been recognized as a factor that can contribute significantly to improve disease control [2].

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Abbreviations

WHO – World Health Organization
TB – tuberculosis
PHC – primary health care
AIDS – acquired immune deficiency syndrome
HIV – human immunodeficiency virus

The result of the implementation of the National TB Program in Serbia, with the financial support of the Global Fund for *acquired immune deficiency syndrome* (AIDS), tuberculosis and malaria, has been a considerable decrease in the TB notification rate, from 32/100 000 in 2005 to 23/100 000 in 2009. The total number of multi-drug resistant TB patients was 20 in 2009, while 2 extremely drug resistant TB patients were registered. In the same year, 11 TB/*human immunodeficiency virus* (HIV) co-infected patients were notified. The highest TB rate in Serbia districts in 2009 was in Kolubara (53/100 000) and Mačva (46/100 000) district [3].

Primary health care is the basic health care which relies on practical, scientifically acclaimed and socially acceptable methods and technologies, widely accessible to individuals and families in the community, in which they participate to a great extent, and at a price that the society and the state are able to afford so that the principle of self-determination is preserved at all levels of development [4].

The principles contained within the Declaration from Alma-Ata still represent the basis of an efficient PHC and remain in focus in health care of TB patients:

– universal access to PHC and an efficient coverage of all populations needs;
– equity of health, as part of the society orientation on social justice;
– community participation in the development and implementation of health plans and activities;
– multi-sector access to PHC [5].

Role and tasks of primary health care in tuberculosis control

– implementation of anti TB preventive measures,
– passive TB detection based on symptoms,
– community nursing visits to patients and their families,
– involvement in direct supervision of TB treatment and detection of adverse effects of anti-tuberculosis therapy,
– referral of vulnerable groups to TB specialist examinations (cooperation of health institutions with the Red Cross of Serbia, civil society organizations, social welfare centers, etc.) [6].

The aim of this study was to assess the current role of PHC in TB control and to identify strategic activities in order to strengthen its role in TB control in Serbia.

Hypotheses:

There was a statistically significant association between higher TB notification rate and reduced coverage of municipal TB services.

There is no difference in the PHC role in tuberculosis control in Serbia in districts with a low coverage in municipal TB services when compared to those districts where this is not the case.

Material and methods

A cross sectional study was performed from the 12th to 30th of September, 2010. For the assessment of the current role of the PHC in TB control, four questionnaires were developed based on the "Performance assessment questionnaire regarding TB control for use in PHC", published in Journal Brasileiro de Pneumologia, in June 2009. The questionnaire was adapted for the study in terms of the overall current national legislation as well as legislation regarding PHC and TB [7–9].

The questionnaires were composed of the questions related to the organization of primary level of health care (availability and coverage of services in general practice and TB services), health activities performed in the field of TB, collaboration with health services in TB issues and compliance of health services with health needs related to TB.

The following health institutions were involved: Municipality Institutes for Pulmonary Diseases and Tuberculosis in Belgrade and Nis, all primary health centers in Belgrade and Niš, TB services in all districts in Serbia, all primary health centers in Mačva, Kolubara and Braničevo district.

The districts of Mačva, Kolubara and Braničevo were selected because of the highest TB rate in Serbia in 2009 and the weakest coverage of municipal TB services according to the data from 2009.

The results of each questionnaire (mean, variance and relative numbers) were analyzed by methods of descriptive statistical analysis. The data were described and analyzed by the type of questionnaire. Student's t-test was applied to analyze the two groups and Fisher analysis of variance (ANOVA) was used for the analysis of more than two groups. In two of the four questionnaires, the reliability analysis was performed. In the remaining two questionnaires, the number of questions was not enough for the reliability analysis. The factor analysis (step by step method) was performed in order to reduce the number of questions and to check the validity of questionnaires. The level of significance in all applied methods was 0.05.

Results

Questionnaire for TB Services in all Districts in Serbia

The questionnaire was filled in19 (70%) out of the 27 districts. The average age of TB specialists in Serbia was 50. A statistically significant difference was found among the districts in the number of remote places, more than 20 kilometers away from the TB outpatient services ($\chi^2 = 8.000$; $p < 0.01$). In Mačva, Braničevo and Kolubara district, a large number of places are far from the ambulatory service (8-13).

There was no statistically significant difference in the role of the PHC in TB control ($\chi^2 = 1.314$; $p > 0.05$) among the districts. PHC practitioners prescribed anti-TB drugs in 55% of cases, they were involved in treatment of comorbidities in 33.3% of cases and in early

TB detection in 14.1% of cases. TB was treated only by TB specialists. According to the respondents, the cooperation with other departments in terms of TB control in all districts was assessed as good. The compliance of health services with health care needs was evaluated as good in 73% of cases ($p<0.05$), but there was a statistically significant difference among the districts.

The Cronbach's alpha reliability analysis was applied to the questions number 3, 5, 6, 8, 10, 12, the age of TB specialists and the number of TB specialists in the district. The question 7 and 11 were not covered by the analysis since they were answered in the same way, neither were the question 6.1 and 10.1 due to a low number of answers. Cronbach's alpha was 0.453 for the whole model.

The validity of the questionnaire was analyzed by factor analysis. The same questions were analyzed as in the case of reliability analysis. Five components of factors explained 87% of the total variability of the questionnaire. The first component included the question 3 and 5, the second included the question 8, 9 and 10 (the question 10 correlated to 8 and 9 negatively). The question 6 and the number of TB specialists were covered by the third component, the fourth component covered the question 12 and the age of TB specialists, and the fifth group was on the border of factor load.

Questionnaire for Municipality Institutes for Pulmonary Diseases and Tuberculosis in Belgrade and Niš

There was a statistically significant difference in the number of employees at the Institute in Belgrade and Niš ($\chi^2 = 9.091$, $p <0.01$). No statistically significant difference was found in the age structure of employees among the institutions and in relation to the average for Serbia ($t = 0.3$, $p>0.05$), nor in the health service they perform.

There was a statistically significant difference in the assessment of the cooperation of the Institute in Belgrade with the primary health centers in Belgrade, in relation to the cooperation with the Institute of Niš with the primary health centers in Niš. The primary health centers in Belgrade do not transfer the authority for prescribing anti-TB drugs from the chosen general practitioner to the TB specialists working at the Institute. According to the Institute in Belgrade, it affects treatment monitoring and might cause treatment defaults. There was no statistically significant difference in the assessment of compliance of health services with the health needs.

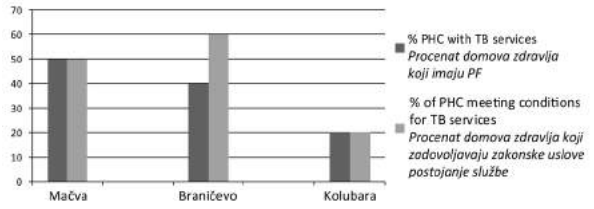
Questionnaire for Primary Health Centers in Belgrade and Niš

The questionnaire was filled in 14 out of 17 Primary Health Centers (82%), 13 in Belgrade and one in Niš. There was a statistically significant difference between the preventive activities provided by primary health centers in Belgrade in relation to Niš ($\chi^2 = 9.308$; $p <0.01$). primary health centers in Belgrade did not differ among themselves ($\chi^2= 7,167$; $p> 0.05$), early TB detection being performed in all of them. The cooperation with the Institutes was good except in case of primary health centers in Mladenovac and Grocka ($\chi^2 = 6.231$; $p <0.05$).

Questionnaire for Primary Health Centers in Mačva, Kolubara and Braničevo district

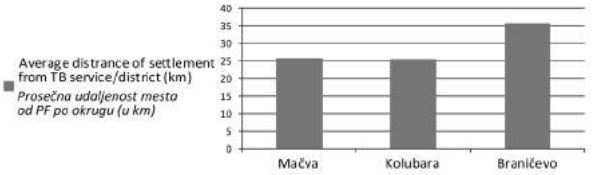
The questionnaire was filled in 18 (86%) out of 21 primary health centers. The variance analysis determined no statistically significant difference among districts in the number of settlements ($F = 0.853$; $p> 0.05$). The average number of out-patient departments per area was highest in Mačva (11, 1) and lowest in Kolubara district (4, 8), but this difference was not statistically significant ($F = 0.157$, $p>0.05$).

Graph 1 shows that the percentage of primary health centers with TB service in relation to the percentage of primary health centers meeting the legal requirements for the existence of the service is lowest in Branicevo, being 20%. However, the difference among districts was not statistically significant ($\chi^2 = 0.889$; $p> 0.05$). The number of settlements more than 20 km away from a TB service is largest in Kolubara district. The difference between districts was statistically significant ($\chi^2 = 3.556$; $p<0.05$). The average distance of the settlement from the nearest outpatient department was largest in Braničevo (35.6 km), as shown in **Graph 2.**



Graph 1. Percentage of PHC with TB services in relation to the percentage of PHC meeting legal conditions for the existence of TB services in Mačva, Braničevo and Kolubara district

Grafikon 1*. Procenat domova zdravlja koji imaju pneumoftiziološku službu u odnosu na procenat domova zdravlja koji zadovoljavaju zakonske uslove za postojanje službe u Mačvanskom, Braničevskom i Kolubarskom okrugu*



Graph 2. The average distance of settlement from the TB service by district (in km) in Mačva, Kolubara and Braničevo

Grafikon 2. *Prosečna udaljenost mesta od pneumoftiziološke ambulante po okrugu (u km) u Mačvanskom, Kolubarskom i Braničevskom okrugu*

In all districts, 64.7% of the health activities in the field of TB were performed by TB specialists. In 35.3% of cases, general practitioners, pediatricians, doctors of other specialties, such as infectious disease specialist, performed these tasks. No significant differences among districts was identified ($\chi^2 = 1.471$; $p > 0.05$).

Health activities in the field of TB were performed by 64% of primary health centers on average in all districts (80% in Braničevo, 75% in Kolubara and 50% in Mačva) in early TB detection (82%), in prescribing anti-B drugs (55%), in TB treatment (45,5%), whereas side effects of anti-TB drugs were not dealt with in any of these centers. The cooperation with other services related to TB control in all districts was assessed as good. The compliance of health services with the health needs was estimated as good in 58.8%. There were no statistically significant differences among districts ($p \leq 0.05$).

The questionnaire reliability analysis showed that the question 2, 3 and 7 should be removed since Cronbach's alpha was low. If these questions were removed, Cronbach's alpha would be 0.394. If the question 11 was removed, Cronbach's alpha would be 0.567. The best question was 4, since its removal led to the decrease in Cronbach's alpha to 0.160. For the question 2, 3 and 7 separately, Cronbach's alpha could not be interpreted.

Factor analysis was applied to assess the validity of the questionnaire and reduction of the number of questions. The questions 8.1, 11.1 and 12 were not covered by the analysis due to insufficient availability and the same answers. The results of the analysis shoved 4 components of factors that explain 80% of the variability of the questionnaire. The first component included the questions 2, 3, 7 (the question 7 was negatively related to the question 2 and 3). The second component covered the questions 4, 13 and 8, the questions 5 and 11 were in the third component and the questions 9 and 6 were in the fourth one. If the factor analysis was applied without the question 2, 3 and 7, the percentage of variability would change (81.2%) compared to the analysis including these questions.

There was a statistically significant correlation between a higher TB notification rate and a reduced coverage of municipal TB services, as proven by Spearman correlation coefficient ($\rho = 0.445$; $p < 0.05$).

All PHC institutions perform anti-TB preventive measures, passive TB detection based on symptoms, community nursing "patronage" visits to the TB patients, while not a single institution in any of the districts performed direct supervision of treatment and detection of adverse effects of anti-TB drugs.

Discussion

The obtained results have shown that the average age of TB specialists in Serbia is 50 years. According to a subjective estimate of the interviewed health workers, health services in these districts satisfy the needs, with the exception of Mačva, Braničevo and Kolubara districts, where there is the lowest coverage and accessibility to municipal TB services and where the TB notification rate is highest in Serbia. The situation should entail greater involvement of general practitioners in TB control, which is not the case according to the results.

All PHC institutions perform anti-TB preventive measures, passive TB detection based on the symptoms and community nursing visits during treatment, while not a single one is involved in direct supervision of TB treatment and detection of adverse effects of anti-TB therapy, which was not to be expected in districts less covered with TB services.

Health services in PHC are performed by 157 primary health centers in Serbia, with the network of health (fist aid) stations and outpatient departments [9]; however, 84 of them perform specialized consultative health activities in the field of TB. Until several years ago, the vertical structure of specialized TB services excluded the cooperation with the general practitioners.

Within the reform of PHC system in Serbia, health institutions and services were decentralized and their status was transformed, so local municipalities took over the founding of the majority of PHC institutions [10]. General hospitals and primary health centers became organizationally independent health institutions. Former milestones of TB control in Serbia, the so-called 'anti-tuberculosis dispensaries' used to be organizationally separate units; however, they are now affiliated to the specialized consultative services at the PHC level (according to legal conditions) or to pulmonary departments in hospitals.

In order to achieve a more efficient user-oriented PHC, the 2008 healthcare reforms introduced the concept of 'chosen general practitioner', who would be responsible for the overall patient's health, including TB. According to the patients needs, the chosen doctor refers the patient to all consultative specialized examinations, including TB, thus disenabling the direct access to TB services. Prescribing drugs has become the exclusive right of the chosen doctor, and when necessary, the doctor can transfer the right to prescribe anti-TB drugs to a TB specialist [11]. It can be concluded that the situation in Serbia related to anti-TB drug prescribing varies in each district.

Regulations on specialization of health workers and associates (Official Gazette of RS No. 10/13) from the 7th of February, 2013 excluded the specialization in pneumophysiology. After the natural staff outflow, the specialized consultative services in the field of TB will be provided by specialists of internal medicine at the primary (according to legal conditions) and secondary level, and pulmonary specialists at the tertiary level of health care.

The main limitation of this study is that it was not conducted on a representative sample.

Other limitations include the subjective evaluation of health workers, on which the study was

based, as well as the existence of responses to certain questions from the questionnaire whose adequate interpretation and comparison was not possible due to open-ended questions.

Conclusion

Primary health care performs anti-tuberculosis preventive measures, passive tuberculosis detection based on symptoms and community nursing visits, while for other interventions defined as primary health care tasks, the patients are referred to specialized tuberculosis service. This study has confirmed the hypotheses and proved that the tuberculosis notification rate is higher in the districts where the coverage of municipal tuberculosis services is reduced, as well as that the role of primary health care in tuberculosis control does not differ from districts where the coverage in tuberculosis services is better.

Therefore, the first medium-term task of tuberculosis program in Serbia should be strengthening of primary health care in order to perform the roles as defined by the existing regulatory framework.

In the long term, further decrease in tuberculosis rate will reduce the need for specialized tuberculosis services and need for strengthening primary health care for diagnostics, treatment and follow up of tuberculosis through continuous medical education.

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SPONTANEOUS CORONARY ARTERY DISSECTION

SPONTANE DISEKCIJE KORONARNIH ARTERIJA

Živojin JONJEV

Summary
Spontaneous coronary artery dissection is a rare, but very important clinical phenomenon usually described as an uncommon cause of an acute coronary artery syndrome. It typically affects young healthy people, predominantly female, and is usually diagnosed postmortem. The overall incidence of spontaneous coronary artery dissection in coronary angiograms ranges from 0.1 to 1.1%. However, routine coronary angiography in acute coronary syndromes has demonstrated that the true incidence of this phenomenon is underestimated. The pathophysiology is unclear, and clinical presentation usually demonstrates great variability. However, three types of spontaneous coronary artery dissection have been recognized: atherosclerotic, puerperal, and idiopathic. The appropriate treatment of spontaneous coronary artery dissection is difficult, and there is no clinical consensus on the appropriate management of these patients. Reports from the literature suggest that stable patients with limited dissections demonstrate spontaneous healing with medical management alone. Recent evidence has shown an improved prognosis after urgent restoration of the coronary flow by percutaneous intervention or coronary artery bypass surgery. Reports of uncontrolled escalating coronary dissections, extension of intramural hematoma, and acute coronary thrombosis after stenting mark this method as controversial. Thus, the decision making process for the appropriate management should respect evidence based medicine and have an individual approach to each patient alone. Clinical perspectives of the spontaneous coronary artery dissection are analyzed in this review article, based on personal experience and recently published literature.
Key words: Acute Coronary Syndrome; Coronary Vessel Anomalies; Aneyrism, Disecting; Coronary Artery Bypass; Coronary Angiography

Sažetak
Spontane disekcije koronarnih arterija su redak, ali veoma važan klinički fenomen, koji se u literaturi najčešće opisuje kao „akutni koronarni sindrom nepoznatog porekla“. Spontane disekcije koronarnih arterija najčešće se javljaju kod zdravih osoba mlađeg životnog doba, a dijagnoza se najčešće potvrđuje *post mortem*. Ukupna incidencija spontanih disekcija koronarnih arterija fluktuira između 0,1 i 1,1%. Međutim, rutinske koronarne angiografije kod akutnih koronarnih sindroma ukazuju da je prava incidencija ovog kliničkog fenomena značajno potcenjena. I pored velike varijabilnosti u etiologiji i kliničkoj slici, spontane disekcije koronarnih arterija je moguće klasifikovati u tri grupe: aterosklerotske, trudničke/postpartalne i idiopatske. Značaj spontanih disekcija koronarnih arterija je u kliničkoj praksi nepravedno potcenjen, i trenutno ne postoji ekspertski konsenzus o terapijskom algoritmu spontanih disekcija koronarnih arterija. Klinički stabilni pacijenti sa morfološki ograničenim disekcijama pokazuju visok stepen spontanog restituisanja koronanog protoka uz adekvatnu medikamentnu terapiju. Kod pacijenata gde dominira hemodinamička i ritmička nestabilnost predlaže se što hitnija perkutana koronarna angioplastika i/ili kardiohirurška revaskularizacija miokarda. Komplikacije tokom koronarne angioplastike, u smislu eskalirajućih koronarnih disekcija sa ekstenzivnim intramuralnim hematomom i koronarnom trombozom kao posledicom, ukazuju da je ovaj oblik lečenja spontanih disekcija koronarnih arterija kontroverzan. S obzirom na to, tokom donošenja odluke o modalitetima lečenja spontanih disekcija koronarnih arterija neophodan je individualni pristup svakom pacijentu ponaosob, baziran na jasno definisanim naučnim dokazima. U ovom preglednom članku analizirana je etiologija, patofiziologija, savremena dijagnostika i terapija spontanih disekcija koronarnih arterija oslonjena na sopstveno kliničko iskustvo i pregled aktuelne literature.
Ključne reči: Akutni koronarni sindrom; Anomalije koronarnih krvnih sudova; Disekcija aneurizme; Bajpas koronarnih arterija; Koronarna angiografija

Introduction

Spontaneous coronary artery dissection (SCAD) is defined as a non-traumatic and non-iatrogenic separation of the arterial walls, which leads to acute coronary ischemia and sudden cardiac death [1]. It typically affects young healthy people, and is usually diagnosed postmortem [2]. According to lit-

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Abbreviations

SCAD – spontaneous coronary artery dissection
IVUS – intravascular ultrasound
CT – computerized tomography
PCI – percutaneous coronary intervention

erature data, the overall incidence of SCAD in coronary angiograms ranges from 0.1 to 1.1% [3]. However, routine coronary angiography in acute coronary syndromes has demonstrated that the true incidence of this phenomenon is underestimated [4].

Epidemiology and Classification

The first description of SCAD was published in 1931 and it was based on the autopsy findings of a 42-year old woman, who had passed away suddenly after a severe chest pain [5]. In the next 50 years around 150 cases of SCAD were reported in the scientific literature. The introduction of selective coronary angiography in the diagnosis of heart disease confirmed previously expressed doubt that the majority of SCAD with sudden cardiac death was undiagnosed [6]. SCAD is most common in women from 35 to 40 years of age, with very variable clinical presentations, which depend on the size of the ischemic region and the importance of the affected coronary territory [7]. The most commonly affected artery is the anterior descending artery from the left coronary artery system; however, multivessel SCAD is also seen in the clinical practice **(Figures 1 and 2)**. The pathophysiology is unclear, and clinical presentation usually demonstrates great variability. However, SCAD patients can be classified into three groups: atherosclerotic, pregnancy/postpartum and idiopathic [2].

SCAD patients with coronary atherosclerosis are more frequently seen in the practice than in the medical reports which has been confirmed scientifically by intravascular ultrasound (IVUS) used to visualize atherosclerotic plaque rupture and consequent coronary dissection. Moreover, IVUS has proved the existence of small SCAD in cases with poorly expressed coronary atherosclerosis, without clinical presentation at all [8]. These SCADs are usually treated by drugs only and are later described as significant atherosclerotic stenosis after control coronarography [1].

A significant number of scientific reports describe SCAD in pregnancy or in the early postpartum period. The earliest clinical manifestation of SCAD is described in the 9th week of gestation and no later than three months postpartum [2, 5, 8–11]. At this time, the most appropriate explanation for the development of SCAD in pregnancy is hormonal hypothesis. According to this hypothesis, the influence of estrogen and progesterone is responsible for changes in the medial layers of the wall of coronary arteries in terms of the proliferation of smooth muscle cells, collagen synthesis, and redistribution of proteins and mucopolysaccharides. In addition to these histological changes there are transient changes in the cardiovascular system during pregnancy which are characterized by an increase in volume of the circulating blood (up to 50%), and increased stroke heart volume and cardiac output. These changes increase intraluminal stretching (shearing stress) of the coronary artery wall, followed with intimal cracks and consequent initiation of SCAD [2].

The third group of patients with SCAD is the most controversial one, with very heterogeneous predisposing factors (e.g.: smoking, hypertension, Marfan syndrome, polyarteritis nodosa, lupus erythematosus, cocaine, cyclosporin, oral contraceptives, etc.) [12, 13]. They are mostly younger or middle aged people in who SCAD usually occurs at some stage of physical exertion (e.g. running, weightlifting) that increases coronary shearing stress and cardiovascular hemodynamics. This observation supports the hypothesis that increased shearing stress in addition to transient changes in the cardiovascular system could be taken as an independent risk factor for the presence of SCAD with or without coronary atherosclerosis [2, 14].

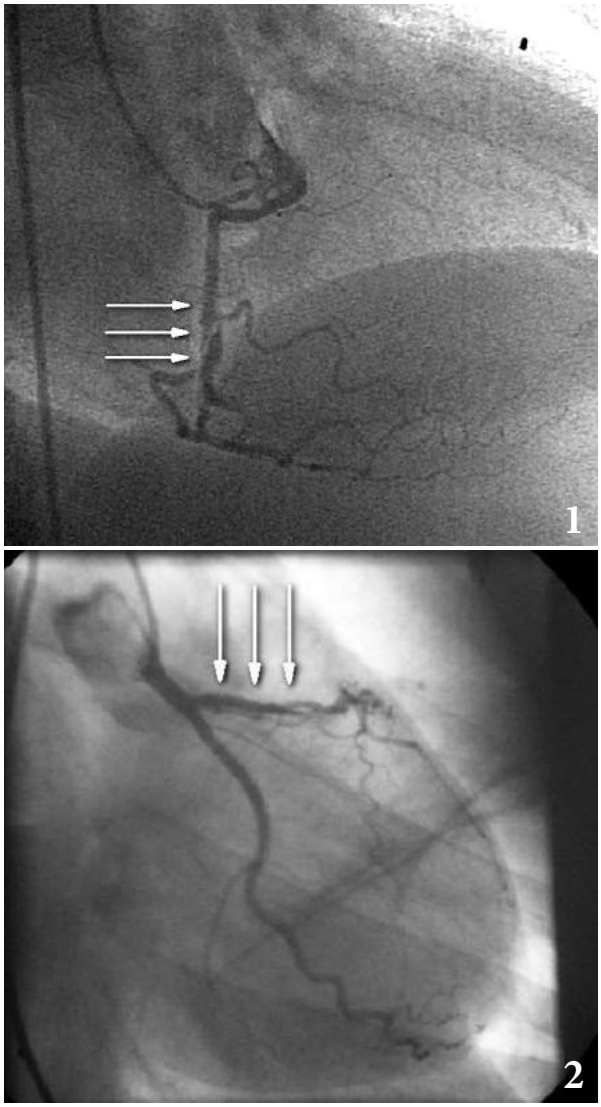
Pathogenesis and Pathophysiology

In most cases SCAD is the result of intimal rupture and formation of intramural hemorrhage. Expansion of intramural hematoma creates the false lumen, which leads to the compression of the true lumen of the coronary artery resulting in myocardial ischemia and/or myocardial infarction. Histological analysis has shown that SCAD usually happens between the intima and media of the artery, i.e. at the internal elastic membrane (Latin: lamina elastica interna). This pathohistological finding is unique since the dissecting layer in other forms of coronary dissection is located in the outer part of media i.e. at the external elastic membrane (Latin: lamina elastica externa) [9].

On the other hand, intimal disruption is not infrequently found in the area with the histological confirmation of localized inflammatory processes (focal vasculitis). This finding is the basis for the inflammatory hypothesis about the origin of SCAD [2, 6]. According to this hypothesis, the release of lytic enzymes from eosinophilic leukocytes leads to the weakening of the artery wall and creating of "high risk zones" prone to rupture and dissection. However, a detailed histological analysis has shown the presence of very inhomogeneous postmortem findings which makes inflammatory hypothesis in the development of SCAD unlikely.

Clinical Picture and Diagnosis

From the clinical point of view the mechanism of SCAD is mostly irrelevant, and the variety in clinical presentation usually makes the diagnosis of SCAD a real challenge. It could be highly symptomatic, leading to a congestive heart failure and death or totally asymptomatic, depending upon the coronary artery involved and the extent of dissection. Therefore, SCAD is a part of the differential diagnosis in the patients presenting with acute coronary syndromes



Figures 1 and 2. Selective angiography of the right and left coronary artery shows SCAD of the right coronary artery just before bifurcation (1), as well as SCAD of the left anterior descending artery and its major branches (2). ***Slike 1 i 2****. Selektivne koronarografije desne i leve koronarne arterije koje prezentuju spontanu disekciju glavnog stabla desne koronarne arterije neposredno pre račve (1); i spontanu disekciju prednje descendentne arterije i njenih pobočnih grana (2)*

without the presence of traditionally accepted risk factors for the development of atherosclerosis [15, 16]. Clinical presentation and treatment outcomes depend on the importance of irrigation areas of the dissected vessel, and the extensiveness of the dissection [9, 17].

Diagnosing of SCAD begins as in any other case of acute coronary events. Younger people known to have used oral contraceptives, vasoactive agents, energy drinks and recreational drugs (nicotine, cocaine, caffeine, etc.) can arouse suspicion of SCAD [3, 10, 18]. In such cases, the method to confirm the working diagnosis of SCAD is computerized tomography (CT) angiography, IVUS and selective coronary angiography. Since IVUS is not available in most hospitals, the detailed interpretation of CT angiography and selective coronary angiography should be given more attention. It should be kept in mind that SCAD demonstrates morphological changes over time. Thus, in such cases it is sometimes very difficult to make angiographic difference between SCAD and classical atherosclerotic stenosis, particularly in cases of delayed angiography [2, 19].

Treatment

SCAD treatment is very difficult and presents a clinical challenge. There is evidence of successful SCAD healing by drug only, percutaneous coronary intervention (PCI) and surgical operation (*coronary artery bypass graft surgery* CABG) [5, 17, 20–23]. However, the absence of literature data on the overall outcomes makes it difficult to select the appropriate method of treatment; therefore, management of such cases is highly controversial. Currently, there is no clinical consensus on universal treatment of SCAD, so the adequate method of treatment must be chosen by analyzing each patient individually.

Reports from the literature suggest that stable patients with limited dissections demonstrate spontaneous healing with drugs only [3]. In the acute phase of dissection with angina pectoris associated with hemodynamic instability, coronary artery stenting or bypass surgery is usually proposed [2, 3, 9, 24]. However, uncontrolled escalating coronary dissections, extension of intramural hematoma, and acute coronary thrombosis have been reported after stenting. Procedural success of PCI is lower than expected with postprocedural myocardial infarction around 9%, followed with periprocedural mortality rate of 3.8-4.5%. In some cases, these complications were responsible for heart failure and requirement of left ventricle assist devices even in case of single vessel disease [2, 25–27].

Surgical management of SCAD is still considered the most reliable one, with favorable short and long term results especially in unstable patients. However, such results depend not only on the extensiveness of acute coronary syndrome, but also on the selection of surgical techniques [9, 24, 28–30]. The results of the retrospective studies show higher survival rate (postoperative mortality <1%), low incidence of perioperative myocardial infarction (<3%) and favorable long term results especially after unsuccessful PCI. This information confirms the need for being critical when selecting the method of treatment and taking into account the individual approach to the treatment of each patient [1, 9, 12].

Conclusion

Spontaneous coronary artery dissection is a medical emergency leading to acute coronary syndrome and sometimes fatal outcome. Since this clinical entity was neglected in the literature, there is a lack of standardi-

zation in the diagnosis and treatment of spontaneous coronary artery dissection. Clinical results indicate that the prompt restitution of coronary flow based on urgent coronary angiography leads to an acceptable risk and a better outcome prognosis. In this regard, the urgent surgical revascularization has yielded more reliable long-term results especially in unstable patients.

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PROFESSIONAL ARTICLES
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COMPARISON OF T-SCORE VALUES OBTAINED BY ULTRASOUND OSTEODENSITOMETRY OF CALCANEUS AND BY DUAL-ENERGY X-RAY ABSORPTIOMETRY SCAN

KOMPARACIJA VREDNOSTI T-SKORA DOBIJENIH ULTRAZVUČNOM OSTEODENZITOMETRIJOM PETNE KOSTI I METODOM DVOSTRUKE APSORPCIOMETRIJE X-ZRAKA

Aleksandra HADŽIAVDIĆ[1], Nataša VAJIĆ[2] and Nikola GAVRIĆ[3]

Summary

Introduction. Osteoporosis is the most frequent metabolic disease of bones. Early detection of pathological loss of bone mineral density represents the first step in prevention, treatment and rehabilitation of osteoporosis. This study was aimed at establishing the correlation of T-score values obtained by ultrasound osteodensitometry of calcaneus with dual-energy x-ray absorptiometry scan. **Material and Methods.** The study was conducted on the sample of 569 female patients from September 13, 2010 to March 10, 2011. Measurement was made with ultrasound osteodensitometry of ACHILLES make. Quantitative ultrasound method revealed that 77 female patients had a lower value of T-score (osteopenia with risk factors or osteoporosis) and they were referred to T-score measurement with dual-energy x-ray absorptiometry scan. Dual-energy x-ray absorptiometry scanning was performed using LUNAR DPX scanner and 49 female patients were examined. **Results.** It was concluded that there was no statistically significant difference between T-score values obtained by quantitative ultrasound and dual-energy x-ray absorptiometry scanning. **Conclusion.** According to this study, it is necessary to provide a greater number of scanners for ultrasound osteodensitometry of calcaneus in order to secure prevention and to refer the patients to further diagnosing on time.

Key words: Osteoporosis; Bone Diseases, Metabolic; Bone Density; Calcaneus; Absorptiometry, Photon; Risk Factors; Questionnaires; Female; Bone and Bones + ultrasonography

Sažetak

Uvod. Osteoporoza je najčešća metabolička bolest kostiju. Rano otkrivanje patološkog gubitka mineralne gustine kosti predstavlja prvi korak u prevenciji, lečenju i rehabilitaciji osteoporoze. Cilj rada je utvrđivanje korelacije vrednosti T-skora dobijenih ultrazvučnom osteodenzitometrijom petne kosti i metodom dvostruke apsorpcioneometrije X-zraka. **Materijal i metode.** Ispitivanje je sprovedeno u periodu od 6 meseci na ultrazvučnom osteodenzitometru ACHILLES. Korišćeni su upitnici o postojanju faktora rizika za osteoporozu. Od 569 ispitanih pacijentkinja, izdvojen je uzorak od 77 (13,5%) pacijentkinja kod kojih je nađena osteopenija sa postojanjem faktora rizika ili osteoporoza, te su upućene na merenje metodom dvostruke apsorpciometrije X-zraka. Daljem testiranju na skeneru LUNAR DPX pristupilo je njih 49 (63,6%). **Rezultati.** Ispitivanja su pokazala da ne postoji statistički značajna razlika između vrednosti T-skora merenim ovim dvema metodama. **Zaključak.** Na osnovu dobijenih rezultata smatramo da je potrebno obezbediti veći broj aparata za ultrazvučnu osteodenzitometriju petne kosti. Tako se omogućava prevencija i pravovremeno upućivanje pacijentkinja na dalju dijagnostiku ukoliko je to potrebno.

Ključne reči: Osteoporoza, Metaboličke bolesti kostiju; Gustina kosti; Petna kost; DEXA; Faktori rizika; Upitnici; Žena; Kost i kosti + ultrasonografija

Introduction

According to the definition obtained at the Consensus Development Conference from 1993 "osteoporosis is a progressive, system and metabolic condition of bones in which the bones become brittle thereby increasing bone fragility which, as a result, has an increased risk of bone fractures" [1].

Osteoporosis is the most frequent bone disease. The severity of the problem is aggravated by its frequency among the world population. About 75 million people in Europe, United States of America and Japan are affected. Women over 45 years of age spend more

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The study was conducted from September 13,2010 to March 10, 2011 on a sample of 569 patients between 25 and 86 years of age. The patients were classified into groups as shown in the graph.

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Abbreviations

WHO – World Health Organization
QUS – quantitative ultrasound
BMD – bone mineral density measurement
DEXA – dual-energy x-ray absorptiometry
BMI – body mass index
OP – osteoporosis
P – osteopenia

days in hospital because of osteoporosis than because of many other diseases including diabetes, acute myocardial infarction and a breast cancer. In the world, less than 1/3 of patients are diagnosed to have this disease and only 1/7 of the patients are medically treated.

According to the estimation made by Bureau of Statistics from 2013, there are 320, 957 women over 50 in the Republic of Srpska. According to data obtained from the World Health Organization (WHO), 30% of the total number of women have osteoporosis [2] so the expected number of persons with osteoporosis in the Republic of Srpska is about 96,287.

It has been estimated that about 375,000 women in Serbia suffer from osteoporosis. Only 30% of that number are medically treated. Early detection of pathological loss of bone mineral density represents the first step in prevention, treatment and rehabilitation of osteoporosis.

Anamnesis, a detailed clinical examination with the distinction between high and low risk factors as well as the quantitative ultrasound (QUS) make it possible to recognize the persons at an increased risk for osteoporosis and to refer them to the bone mineral density measurement (BMD) with double exposition with x-rays by dual-energy x-ray absorptiometry (DEXA) method.

The results of bone density measurement may be expressed as a deviation, number of standard deviations from the medium bone density in young healthy people and is expressed as T-score. This value shows how much the real bone density is different from the standard bone density of the young, healthy people that serves as the basic value. The values of T-score mark:

– normal bone density – if the T-score values are between +1.0 and -1.0 SD from normal values,

– osteopenia – if the T-score value is between -1.0 and -2.5 SD from normal values,

– osteoporosis – if the T-score value is -2.5 SD or less than normal values,

– major osteoporosis – if the T-score value is -2.5 SD from normal value and if there is a bone fracture, at the same time.

The aforementioned criteria have been recommended by the WHO [3]. Anamnesis, risk factor analysis, a detailed clinical examination and QUS enable timely detection of patients at increased risk for osteoporosis and thereby reduction of unnecessary expenses of diagnostics and treatment of possible complications [4].

This study was aimed at establishing the correlation of T-score values obtained by ultrasound osteodensitometry of heel bone and by DEXA measurement.

Material and Methods

The research was conducted at the General Hospital "Saint Apostle Luke" in Doboj and at Special Hospital for Rehabilitation after Cardiovascular Diseases Banja Vrucica, Teslic in the period from September 13, 2010 to March 10, 2011 and mineral density on heel bone was examined by ultrasound osteodensitometry in 569 women. Measurement was done in the form of epidemiological research on osteoporosis representation in women from the region of Doboj. Research was conducted by ACHILLES ultrasound osteodensitometry at the General Hospital "Saint Apostle Luke" Doboj. The authors used questionnaires on risk factors for osteoporosis containing various questions such as body weight and height, body mass index (BMI) (which was calculated as per standard formula), menarche, menopause, family anamnesis for osteoporosis, data on earlier fractures, existence of chronic diseases and the use of drugs indicated as risk factors for osteoporosis, as

Table 1. Results of QUS measurement and patients who had undergone DEXA measurement
Tabela 1. *Rezultati QUS* merenja i pacijentkinje koje su uradile merenje metodom dvostruke apsorpciometrije X-zraka*

Results of QUS measurements/*Rezultati QUS merenja*	Frequency/*Učestalost*		Percent/*Procenat*	
Total/*Ukupno*	569		100%	
Normal finding/*Uredan nalaz*	492		86,5%	
Referred to DEXA/*Upućeno na DEXA*	77	19 Osteopenia+RF 58 Osteoporosis	13,5 %	24,7% Osteopenia+RF 75,3% Osteoporosis
Underwent DEXA measurements/*Uradile DEXA merenje*	Frequency/*Učestalost*		Percent/*Procenat*	
YES/*Da*	49	17 Osteopenia+RF 32 Osteoporosis	63,6 %	34,7% Osteopenia+RF 65,3% Osteoporosis
NO/*Ne*	28		36,4%	

*QUS - utrazvučna osteodenzitometrija; *DEXA - dvostruka ekspozicija x zracima

well as coffee and cigarettes consumption, nutrition and physical activity.

Of the interviewed patients, a sample of 77 (13.5%) was made of those who were diagnosed to have osteopenia with risk factor or osteoporosis.

Out of 77 patients, 49 (63.6%) were tested by DEXA method. The examination was done on the lumbar discs and hip with LUNAR DPX at the Special Hospital for Rehabilitation after Cardiovascular Diseases, Banja Vrucica, Teslic.

Based on results obtained by measuring the bone mineral density, all patients who were diagnosed to have osteopenia with the presence of risk factors or osteoporosis were divided into two groups.

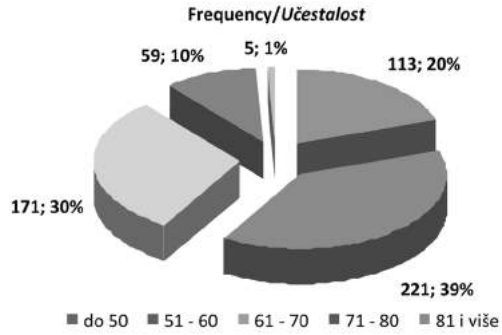
The first group consisted of patients with osteopenia with the presence of risk factors and the second group consisted of patients with osteoporosis (according to the criteria for osteoporosis defined by the WHO/International Osteoporosis Foundation), whereas the examinees with normal medical findings were excluded from further testing.

The study results have been represented by frequencies, arithmetic average, standard deviation, range of maximum and minimal value. X^2 test was used to determine the statistical significance and contingency coefficient (C) and Pearson's correlation coefficient (R) were used to assess the intensity of correlation.

Results

The study was conducted from September 13, 2010 to March 10, 2011 and included a sample of 569 patients between 25 and 86 years of age. The patients were classified into age groups, as illustrated in the **Graph 1.**

The value of T-score was above -1 SD in 492 (86.5%) patients, that being a normal finding; whereas in 77 (13.5%) patients a lower value of T-score was found, in 19 of them (24.7%) the value of T-score was in the range of osteopenia with the presence of risk factor, whereas 58 (75.3%) of patients were diagnosed to have osteoporosis by QUS testing. All patients with such medical findings were recommended to undergo further diagnostics by DEXA method. Of 77 patients referred to DEXA testing, 49 (63.6%) did the testing, whereas 28 (36.4%) patients (2 with osteopenia and 26 with osteoporosis) did not undergo further testing **(Table 1).**



Graph 1. The age structure of respondents
Grafikon 1. *Starosna struktura ispitanica*

T-score values, which were above -2.5 SD with the presence of risk factor, were in the range of osteopenia (P) in 17 (34.7%) patients, and in 32 (65.3%) patients, T-score value which was obtained by ultrasound osteodensitometry indicated osteoporosis (OP) **(Table 2).**

After DEXA testing, T-score values were within the limits of osteopenia (P) in 26 (53.1%) examinees, osteoporosis (OP) was diagnosed in 21 (42.9%) patients and 2 (4.1%) patients had normal medical findings **(Table 3).**

A contingency table was created for the sample of examinees diagnosed to have osteopenia after QUS testing, with the presence of risk factor (19) or osteoporosis (58) including also those who were not

Table 2. Distribution of osteopenia (P) and osteoporosis (OP) in QUS measurements
Tabela 2*. Distribucija osteopenije (P) i osteoporoze (OP) merenja ultrazvučnom osteodenzitometrijom*

	Frequency/*Učestalost*	Percent *Procenat*	Cumulative/*Kumulativno*	Percent/*Procenat*
P	17	34.7	34.7	
OP	32	65.3	100.0	
Total/*Ukupno*	49	100.0		

Table 3. Distribution of osteopenia (P) and osteoporosis (OP) on DEXA measurements
Tabela 3. *Distribucija osteopenije (P) i osteoporoze (OP) na merenju metodom dvostruke apsorpciometrije X-zraka*

	Frequency/*Učestalost*	Percent/*Procenat*	Cumulative Percent/*Kumulativno procenat*
P	26	53.1	53.1
OP	21	42.9	95.9
normal finding *nalaz uredan*	2	4.1	100.0
Total/*Ukupno*	49	100.0	

*DEXA - dvostruka ekspozicija x zracima

tested by DEXA method (28 of them) and χ^2 test was calculated.

The calculated value of χ^2 test was 7.55 with the number of degrees of freedom df=3 for the significance level of 0.05. The limiting value Xg^2 equaled 7.81 for level of significance and number of degrees of freedom. Since χ^2 was $<Xg^2$ (7.55 < 7.81) and p was >0.05, the hypothesis was accepted that there was no statistically significant difference between T-score testing with QUS and DEXA method, even if the fact that 36.4% of patients did not undergo DEXA test is taken into consideration.

However, it should be said that the above mentioned value of χ^2 test was on the significance borderline (p=0.056).

Accordingly, the contingency coefficient (C) was somewhat larger C=0.299; so, there was a moderate contingency between two measurements as well as a moderate positive correlation between the two.

Discussion

Osteoporosis is a medical condition characteristic for women. In addition to postmenopausal osteoporosis, our earlier research from 2009 showed that a large number of women had low values of T-score in premenopausal period as a result of the presence of a great number of risk factors that being the reason why our research was not limited to the women in menopause only [5].

In order to avoid side effects, osteoporosis fractures, osteoporosis must be diagnosed on time. An early diagnosis and timely beginning of medical treatment are of extreme importance especially in persons having one or several factors for disease.

Ultrasound osteodensitometry (quantitative ultrasound QUS) is one of screening tests. It has been developed intensively over years and it is based on measurement of decreased intensity of ultrasound wave when going through the bone tissue (when measured on the heel bone) or on measurement of change of speed of ultrasound wave along the bone (tibia) [1]. Ultrasound screening of the heel, i.e. the examination made by ultrasound densitometry is a relatively fast (few seconds) and comfortable (it is not necessary to take off clothes) and it is done on the heel bone. Ultrasound densitometry measures the peripheral bone density and this method may point out to a higher risk of fracture. In cases of extremely evident osteoporosis assessed by ultrasound densitometry followed by a fracture, it is necessary to do DEXA verification as well [6].

The study, which was performed in the period of 6 months, from September 13, 2010 to March 10, 2011, included 569 patients between 25 and 86 years of age.

All patients filled in the questionnaire on the presence of risk factor for osteoporosis. The questionnaire contained questions about the patients' age, menarche, menopause, body height, weight, (whereby BMI was calculated), presence of earlier fractures, family anamnesis for osteoporosis, presence of diseases associated with osteoporosis, administration of drugs that may cause decrease of bone density and data on smoking, coffee consuming, nutrition and physical activity. Bone density was measured in all patients with ACHILLES ultrasound osteodensitometer.

Out of the total number of patients, 492 (86.5%) had T-score value above -1 SD, that being a normal finding, whereas T-score value was lower in 77 (13.5%) patients, and the obtained value of T-score was within the range of osteopenia with the presence of risk factor in 19 patients (24.7%), whereas 58 (75.3%) patients were diagnosed to have osteoporosis by QUS measurement. All patients with such diagnosis were recommended to undergo further diagnostics with DEXA method. Criteria for patients' referral to DEXA measurement were set in accordance with the Guidelines for prevention, diagnostics and osteoporosis treatment drafted by the Association for Osteoporosis of Republic of Srpska in May 2009 [7].

Out of 77 patients referred to DEXA measurement, 49 (63.6%) were examined. Further diagnostics was not recommended to 28 patients (36.4%), 2 (2.6%) of them having osteopenia and 26 (33.8%) having osteoporosis. It is considered that every third woman having osteoporosis does not take a proper care of her bones [8]. Our research has confirmed such an attitude of women towards osteoporosis diagnostics as well.

A distinction must be made between decreased bone density retaining the adequate architecture of bone tissue and abnormal geometry and density of the tissue. According to the definition made by Harold Frost, the former is called osteopenia, and the latter is osteoporosis. In other words, Frost claims that the difference between osteoporosis and osteopenia is not only a quantitative one but a qualitative one as well. According to the definition made by the WHO/International Osteoporosis Foundation, osteopenia is defined by T-score values ranging from -1.0 to -2.5 SD [9].

It has been understood that parameters of ultrasound testing may serve for the evaluation of bone density and quality and they are independent predictors of risk of bone fracture.

Diagnosis of osteoporosis depends on the analysis of specific locations (spine, hip) and ultrasound osteodensitometry is of great significance in primary osteoporosis diagnostics. It has been recommended that all patients at risk should be referred to ultrasound osteodensitometry of heel bone in order to detect a risk of bone fracture and osteoporosis on time and then for further treatment and DEXA measurement in accordance with the WHO guidelines [10].

In 17 (34.7%) patients who underwent DEXA measurement, the T-score value was within the osteopenia range, being above -2.5 SD with the presence of risk factors. The T-score value obtained by ultrasound osteodensitometry indicated osteoporosis in 32 (65.3%) patients.

After DEXA measurement, the T-score value was within osteopenia range in 26 (53.1%) patients and osteoporosis was diagnosed in 21 (42.9%) patients, whereas 2 patients (4.1%) had normal findings.

Experience gained so far on the use of quantitative ultrasound is contradictory.

El Desoukimi has concluded that by applying the current methods of determining T-score value, quantitative ultrasound cannot be used as a screening method and that it is necessary to make some modifications of T-score values [11].

Pfister et al. made similar conclusions by comparing T-score values obtained by quantitative ultrasound of the heel bone and by DEXA measurement in the patients with hip fracture. They found that the sensitivity and specificity of quantitative ultrasound as a technology was 58% and 80%, respectively,

In the detection of osteopenia and osteoporosis of the hip, quantitative ultrasound of the heel failed to diagnose 37% of patients with abnormal values of the T-score obtained by DEXA measurement [12]. Van den Bergh et al. agree that there is no consensus on osteoporosis diagnostics by quantitative ultrasound of a heel bone. They have proved that quantitative ultrasound may assess a risk of fracture in women aged 65 or older. Currently, there are significant differences between ultrasound devices and there is no standardization. It is necessary to develop the quality standards and intercrossed calibration for quantitative ultrasound devices in order to compare the results obtained by different devices. Standardization is necessary for DEXA osteodensitometers [13]. Gojković stresses that nowadays there is a huge number of devices of various manufacturers used for DEXA measurement. Various devices used for BMD measurement as well as results are such that it is impossible to compare findings obtained with different devices without previous existence of intercrossed calibration in spite of applying the same technology [14].

Van den Bergh has confirmed the results obtained by El-Desoukimi and Pfister that although a quantitative ultrasound of a heel bone is a promising method for the evaluation of osteoporosis fractures, its routine application in clinical practice is still not applicable [13]. On the other hand, research conducted by Lappa et al. has shown that ultrasound parameters are well correlated with BMD of hip and biochemical markers of bone structure in elderly women. Ultrasound measurement may be used as a screening test of the bone status in women of the third age or those living in rural areas where DEXA and biochemical laboratories are less likely to be available [15].

Quantitative ultrasound with the method of self-calculation of osteoporosis risk (OST) is a significant one in detecting population at high risk for osteoporosis which may be an alternative method for osteoporosis diagnostics, especially in regions in which DEXA measurement is not available, as stressed in the paper by Zha et al. [16].

QUS method is also significant for monitoring women over 65 years of age who were found to have normal values of T-score or osteopenia with QUS method thus preventing progression towards osteoporosis, which, according to Goulay et al., developed in women with mild osteopenia (T-score values -1.49 to -1 SD) after 15 years, in women with moderate osteopenia (T-score values -1.99 to -1.5 SD) after 5 years, and in women with severe osteopenia (T-score values -2.49 to -2 SD) after a year [17].

On the other hand, Doshi et al. believe that besides T-score values, clinical risk factors must be taken into consideration when assessing the progression of osteopenia towards osteoporosis [18].

Our study results show that there is no statistically significant difference between T-score measurement by QUS and DEXA method, even if we take into consideration the fact that 36.4% of the patients did not undergo DEXA measurement. However, it is essential that the aforementioned value of the X^2 - test was on the significance level (p=0,056).

Along with clinical examination and blood tests, DEXA represents the "gold standard" when making diagnosis of osteoporosis. However, the classification of patients based only on T-score filters almost half of the patients with clinical diagnosis of osteoporosis [14].

Osteoporosis diagnosis has been improved significantly by complementing BMD findings with vertebral fracture assessment (VFA), micro-architecture estimation (TBS) and fracture risk assessment tool (FRAX) which can be installed on the existing DEXA devices and it is possible to calculate a ten-year risk for fracture and identify patients with osteoporosis and high fracture risk [14]. However, these techniques are still not available to us. Quantitative ultrasound is a safe, easy–to-handle, x-ray free, mobile and economic auxiliary tool for diagnostics.

In comparison with "gold standard" DEXA measurement, quantitative ultrasound used by Schnabel has proved to have the same capability to filter the patients in menopause with proximal femur fracture from the healthy ones. Schnabel believes that quantitative ultrasound may be a useful and valuable technique in clinical practice which has been confirmed by our research as well [19].

Conclusion

This study has shown that there is no statistically significant difference between T-score values obtained by quantitative ultrasound and those obtained by dual-energy x-ray absorptiometry measurement.

Dual-energy x-ray absorptiometry, along with clinical examination and blood tests, represents the "gold standard" in diagnosing osteoporosis.

Osteoporosis diagnosis has been improved significantly by complementing bone mineral density measurement findings with vertebral fracture assessment, micro-architecture estimation and fracture risk assessment tool which can be installed on

the existing dual-energy x-ray absorptiometry devices and it is possible to calculate a ten-year risk for fracture and identify patients with osteoporosis and high fracture risk. However, these techniques are still unavailable in this area.

In line with standards set by European Union, 11 dual-energy x-ray absorptiometry devices should be provided per 1 million of population. Republic of Srpska has the population of 1.326.991. There are 10 dual-energy x-ray absorptiometry devices in Republic of Srpska and only 3 dual-energy x-ray absorptiometry devices are available to the patients through the Health Insurance Fund.

Based on the study results, we think that it is necessary to provide more devices for ultrasound osteodensitometry of the heel bone which are mobile, fast and enable examination of a larger number of patients especially in rural areas. This is the way to ensure prevention and refer the patients to further diagnostics on time, if it is necessary. This is quite indicative because of the large number of patients with osteopenia, before the menopause period.

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CASE REPORTS
PRIKAZI SLUČAJEVA

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Case report
Prikaz slučaja
UDK 618.31-07
DOI: 10.2298/MPNS1510347K

EARLY PRIMARY ABDOMINAL PREGNANCY IMPLANTED IN THE VESICOUTERINE POUCH – A CASE REPORT

RANA PRIMARNA ABDOMINALNA TRUDNOĆA IMPLANTIRANA U VEZIKOUTERUSNOM ŠPAGU − PRIKAZ SLUČAJA

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Summary

Introduction. An abdominal pregnancy is a rare form of ectopic pregnancy and potentially life-threatening condition. It is difficult to make an early diagnosis of abdominal pregnancy. **Case Report**. We present a case of early primary abdominal pregnancy, diagnosed at 6th gestational week, located in the vesicouterine pouch and treated laparoscopically. Despite the rapidly decreasing serum β-human chorionic gonadotropin levels, the presence of the intraperitoneal blood allowed neither expectant management nor medical treatment, although the patient was hemodinamically stable at that moment. The absence of significant bleeding during the surgery and histopathological finding of placental villi with necrosis confirmed that, in this case, the abdominal pregnancy was already the subject of spontaneous involution. **Conclusion.** High index of suspicion and carefully interpreted clinical and ultrasound findings are crucial for timely diagnosis of early abdominal pregnancy before the occurrence of massive and potentially fatal intraperitoneal bleeding.

Key words: Pregnancy, Abdominal; Pregnancy, Ectopic; Laparoscopy; Early Diagnosis; Douglas' Pouch; Ultrasonography; Pregnancy Complications

Sažetak

Uvod. Abdominalna trudnoća je retka forma ektopične trudnoće i stanje koje potencijalno ugrožava i život. Rana dijagnoza abdominalne trudnoće se teško postavlja. **Prikaz slučaja.** Prikazujemo slučaj rane primarne abdominalne trudnoće, dijagnostifikovane u šestoj nedelji gestacije, koja se nalazila u vezikouterinom špagu i bila tretirana laparoskopski. Uprkos brzom padu serumskog β-humanog horionskog gonadotropina, prisustvo krvi u peritonealnoj duplji nije dopuštalo ni ekspektativni pristup niti medikamentni tretman, mada je pacijentkinja bila hemodinamički stabilna u datom trenutku. Odsustvo signifikantnog krvarenja tokom intervencije i patohistološki nalaz placentnih čupica sa nekrozom potvrdili su da je, u ovom slučaju, abdominalna trudnoća već bila subjekat spontane involucije. **Zaključak.** Za blagovremeno postavljanje dijagnoze rane abdominalne trudnoće, pre nego što nastupi masivno i potencijalno fatalno intraperitonealno krvarenje, od suštinskog je značaja da se ima na umu ova mogućnost i pažljivo interpretira klinički i ultrazvučni nalaz.

Ključne reči: Abdominalna trudnoća; Ektopična trudnoća; Laparoskopija; Rana dijagnoza; Duglasov špag; Ultrasonografija; Komplikacije trudnoće

Introduction

The primary abdominal pregnancy is defined as an ectopic pregnancy developing on the serosal surface within the peritoneal cavity excluding tubal, ovarian, intraligamentous pregnancies and secondary implantation of primary tubal implantation [1]. Original Studdiford's diagnostic criteria are: 1. normal tubes and ovaries with no evidence of recent or remote injury; 2. no evidence for uteroperitoneal fistula; 3. the pregnancy related solely to the peritoneal surface and young enough to eliminate the possibility of secondary implantation following a primary nidation in the tube; 4. no evidence of secondary implantation following initial primary tubal nidation [1, 2].

Abdominal pregnancies are very rare, accounting for only 1.3% of all ectopic pregnancies [3]. It is estimated that the primary abdominal pregnancy occurs in 10.9 per 100,000 pregnancies and in 9.2 per 1,000 ectopic pregnancies [4]. The maternal mortality rate is 5.1 per 1000 pregnancies; 7.7 times higher than in tubal ectopic pregnancies and 90 times higher than in an intrauterine pregnancy [1,4]. Here we present the case of early primary abdominal pregnancy located in the vesicouterine pouch and partly on the peritoneal surface of the bladder.

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Abbreviations
β-HCG – β-human chorionic gonadotropin
IUD – intrauterine device

Case Report

A 35-year old gravida 0, para 0 with a 3-year long history of unexplained infertility presented to our Department for treatment. The patient had no history of pelvic inflammatory disease, use of intrauterine devices or gynecological surgery other than diagnostic laparoscopy performed two years before, which demonstrated patent Fallopian tubes and no pathological findings. She was otherwise healthy. Menarche occurred in her thirteenth year and menstrual cycles were regular. Her last menstrual period was 38 days before and in that cycle she did not receive any infertility treatment. On admission, the patient suffered from constant lower abdominal pain, she was pale, but hemodynamically stable. The examination of her cardiac and respiratory systems was unremarkable. Her abdomen was soft, but with mild suprapubic tenderness. The speculum examination indicated the presence of a single cervix, without pathological findings and no bleeding from cervical channel. The bimanual pelvic examination revealed the slightly enlarged soft uterus and tender palpable mass, about 4 cm in diameter in front of the uterus. There were no palpable pathological findings on adnexal regions. The transvaginal ultrasound examination [Toshiba Nemio XG, 6 MHz] showed an empty uterus with 5 mm endometrial strip. A cystic mass, 3 cm in diameter, filled with dense content, was seen in front of the uterus on the left side **(Figure 1)**. Color Doppler examination revealed only scarce vascularisation on the periphery of described mass. Both ovaries appeared normal on ultrasound examination,

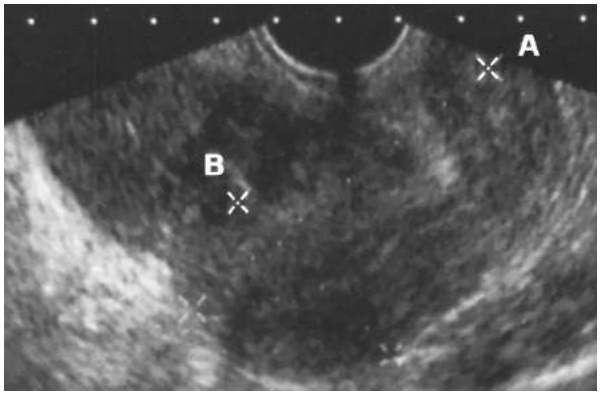

Figure 1. Ultrasound image of an early primary abdominal pregnancy in vesicouterine pouch in 6th gestational week: hemorrhagic mass in front of the uterus. The uterine cavity is empty.
Slika 1. *Ultrazvučni prikaz rane primarne abdominalne trudnoće u vezikouterusnom špagu u šestoj nedelji gestacije: hemoragična masa ispred uterusa; kavum uterusa je prazan.*

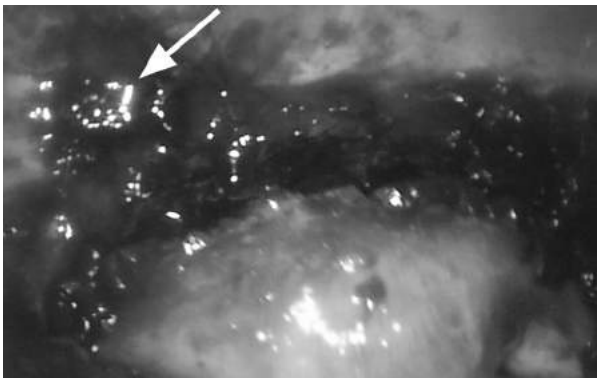

Figure 2. Laparoscopic finding of the early abdominal pregnancy in 6th gestational week, primary implanted in the vesicouterine pouch. The arrow shows the place of the implantation. This photograph shows the moment when the evacuation of ectopic gravidity has been already started and there is no significant bleeding.
Slika 2. *Laparoskopski nalaz rane abdominalne trudnoće u šestoj nedelji gestacije, primarno implantirane u vezikouterusnom špagu. Strelica označava mesto implantacije. Ova fotografija prikazuje momenat kada je već započeta evakuacija ektopične trudnoće i ne postoji nikakvo značajno krvarenje.*

with corpus luteum on the right ovary. Intraperitoneal pooling of fluid in pouch of Douglas was also seen. Her laboratory results were as follows: white blood cells (WBC) $9{,}54 \times 10^9$/l, neutrophil granulocytes (Ne) $5{,}25 \times 10^9$/l, red blood cells (RBC) $3{,}44 \times 10^{12}$/l, hemoglobin (Hb) 105 g/l, hematocrit (Ht) 0,322; platelets (PLT) 396×10^9/l. Serum electrolytes, coagulation profile and liver function tests were all within physiological limits. A day before the admission, her serum β-human chorionic gonadotropin (β-HCG) level [Abbott test; Architect-Total-β-HCG] was 98 mIU/ml and the next day quantitative β-HCG level decreased to 60.54 mIU/ml. Ectopic gravidity was suspected and diagnostic laparoscopy was performed after the written informed consent had been obtained.

Surgery was conducted under general anesthesia. which was induced by means of propofol as an induction agent, fentanyl as an analgesic and rocuronium as a muscle relaxant. Anesthesia was maintained with 1 – 1.5% end-tidal sevoflurane in 50%:50% O_2/N_2O mixture at 6 l/min flow. The lungs were ventilated to maintain end-tidal carbon dioxide concentration 30 – 35 mm Hg. Laparoscopy revealed that there were about 200 ml liquid and coagulated blood in the abdomen. The omentum was in slight adhesions with the anterior abdominal wall and adhesiolysis was immediately undertaken. The uterus was slightly enlarged. On the left side in the vesicouterine pouch and partly on the vesical peritoneum, there was a round hemorrhagic mass, about 3 cm in diameter, with grayish ruptured capsula, filled with almost black coagulated blood **(Figure 2)**. Behind that formation, there were dark

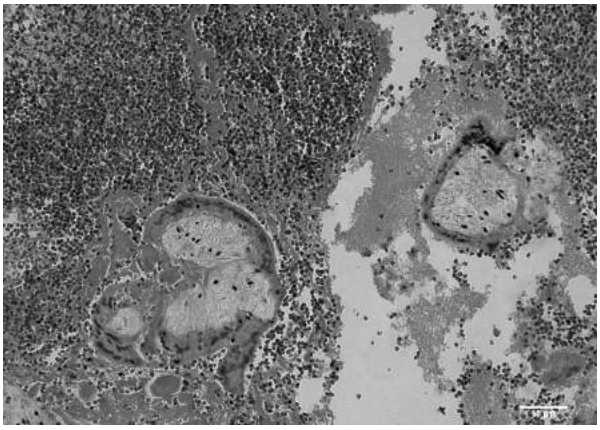

Figure 3. Chorionic villi in necrosis (Haematoxylin-Eosin X200).
Slika 3. *Horionske resice u nekrozi (hematoksilin-eozin X 200)*

(fresh and hemolysed) liquid blood and coagulums, which were also found in the pouch of Douglas. Both ovaries and Fallopian tubes appeared macroscopically normal in size and shape, without any pathological findings. There was no bleeding from the fimbriae bilaterally. A corpus luteum was located on the right ovary. The content of the described mass was carefully removed by forceps and hydrodissection and sent to histopathological examination. There was no significant bleeding during the intervention. The uterine wall was intact, without signs of uteroperitoneal fistula. Biopsy was taken from the vesical peritoneum and the abdomen was closed with drainage placed in the pouch of Douglas. Postoperative course was uneventful. Serum β-HCG levels decreased to 29 mIU/ml after two days and to 16 mIU/ml four days after the surgery. The histopathology report showed chorionic villi with the signs of necrosis in the content aspirated from the described hemorrhagic mass and necrosis and bleeding in the samples from the peritoneal surface of the bladder **(Figure 3).**

Pelvic examination after the surgery revealed a normal finding.

Discussion

An abdominal pregnancy is a very rare, but potentially life threatening condition and very difficult to diagnose in early stages, moreover it is commonly misdiagnosed. It is also difficult to differentiate between primary and secondary peritoneal implantation. Therefore, the original Studdiford's criteria were modified by Friedrich and Rankin in 1968: 1. the presence of pregnancy less than 12 weeks of histologic gestational age whose trophoblastic attachments are related solely to a peritoneal surface; 2. grossly normal tubes and ovaries; and 3. the absence of uteroperitoneal fistula [5, 6]. The case reported hereby fulfills the original as well the modified criteria.

The most frequent locations for early abdominal pregnancies are pouches surrounding uterus (24.3%), primarily located in the pouch of Douglas (87%) [1]. Early abdominal pregnancies are located on the serosal surface of the uterus and tubes in 23.9%, and multiple organs are included in 12.8%. The serosal surface of the bladder (as in the case reported here) is a rare location: in the cited review of 225 reported cases of early abdominal pregnancies from 1965 to 2009, there were only 3 cases located on the serosal surface of the bladder [1]. The other reported locations are: omental [7], bowel [8], hepatic[9], splenic [10,11], retroperitoneal [12-18], (even in close association of major vessels) [19], at intra-abdominal surface of the diaphragm [20], even after hysterectomy [21].

An ectopic abdominal pregnancy could be a result of the primary peritoneal implantation, or the secondary one, following the primary tubal or ovarian pregnancy that subsequently implants somewhere in the abdomen [1, 22]. There are several attempts trying to explain the occurrence of primary abdominal pregnancies. If there was a delayed ovulation, retrograde menstrual flow could reverse the fertilized ovum through the Fallopian tubes into the abdomen [23]. There is also a possibility that fertilization may occur in the pouch of Douglas and intraperitoneal fluid flow may carry the zygote to some other intraperitoneal location [22]. A retroperitoneal ectopic pregnancy is explained by spontaneous migration of the embryo from the uterus to the retroperitoneal space, possibly through the fistula after bilateral salpyngectomy [12] or along the lymphatic channels. The theory of spontaneous migration of the embryo from the uterus to the retroperitoneal space along lymphatic channels was based on findings of trophoblast surrounded by the lymphatic tissue [16]. The contrast-enhanced computed tomography was used to demonstrate the route of embryo migration in a retroperitoneal ectopic pregnancy providing further evidence in support of the proposed embryo migration mechanism via the lymphatic vessels [17].

There is still a possibility of iatrogenic direct placement during the embryo transfer in cases of retroperitoneal pregnancies after *in vitro* fertilization (IVF) [14]. An abdominal pregnancy after total hysterectomy could be explained by a fistulous tract from the vaginal apex to the peritonel cavity or by the prolapse of the Fallopian tube into the vagina, which enable passage for spermatozoa [21]. Intrauterine device (IUD) *in situ* was found in 4.2% of all etopic pregnances [24] and in 8% of abdominal pregnancies, so it is speculated that IUD could be a factor contributing to the development of abdominal pregnancy [1].

Maternal morbidity and mortality associated with abdominal pregnancies could be reduced by early diagnosis. Transvaginal ultrasound examination is the main tool in diagnostics of early abdominal pregnancy. The proposed criteria are: 1) the absence of an intrauterine gestational sac; 2) the absence of tubal

dilatation or a complex adnexal mass; 3) a gestational sac surrounded by loops of bowel and separated from the uterus; and 4) a wide mobility of the gestational sac [25]. In fact, sonographic appearance of early abdominal pregnancy depends of its location. It is usually fixed deep within the pelvis [26] and not mobile as pregnancy in the non-communicating horn of a unicornuate uterus (cornual pregnancy) [27]. If the early abdominal ectopic pregnancy is located in the vesicouterine pouch, as it was in the case reported here, transvaginal ultrasound examination detects a gestational sac or complex cystic mass in front of the uterus, but separated from the uterus with no communication between the gestational sac and endometrial cavity. In such a location, the loops of bowel around it are not necessarily found **(Figure 1).** The absence of communication between the gestational sac and the endometrial cavity differentiates the abdominal pregnancy from the pregnancy in non-communicating horn of a unicornuate uterus (cornual pregnancy) and interstitial ectopic pregnancy [27]. The absence of myometrial layer around the abdominal pregnancy differentiates it from the interstitial pregnancy, which could be demonstrated on ultrasound examination **(Figure 1)**. If the early abdominal pregnancy is located outside the pelvis, transvaginal ultrasound examination is helpless, and other diagnostic tools, such as magnetic resonance imaging and other imaging techniques, must be applied.

Management of early abdominal pregnancy could be surgical, medical, combination of surgical and medical management, and surgery with additional postoperative selective transcatheter arterial embolization for hemostatic failure [1, 28]. Surgical management of early abdominal pregnancies involves laparotomy for the patients with significant intra-abdominal bleeding and laparoscopy for hemodynamically stable patients. It is difficult to diagnose an early abdominal pregnancy and the majority of the cases are presented with intra – abdominal bleeding, so surgical management is more frequent (87.8%) than medical [1]. The patients with the early abdominal pregnancy diagnosed before bleeding are candidates for primary medical treatment with systemic methotrexate [29], laparoscopical embryo methotrexate injection [11] or intracardiac potassium chloride injection (KCl) (in cases with fetal cardiac activity). There is also the combination of these treatments: ultrasound guided feticide and systemic methotrexate, followed by laparotomy for removal of the fetus and placenta [30, 31] or without laparotomy [32, 33]. In later reports there is a tendency to treat an ectopic pregnancy medically after the initial laparoscopic diagnosis. Surgical treatment is used for cases that do not respond to medical treatment [1]. An early abdominal pregnancy, if diagnosed on time - before the occurrence of significant intra-abdominal hemorrhage, could be safely removed by laparoscopy [26, 34, 35]. There are also reports of successful laparoscopic treatment of abdominal pregnancies in second trimester [34]. Immediate surgery is indicated for pregnancies prior to 23 to 24 weeks because of the high incidence of maternal morbidity and a poor prognosis for the fetus. If the patient is stable, more conservative approach could be applied after 24 weeks with better chances for fetus to survive [23]. There are many reports of abdominal pregnancies with viable fetuses and normal-course pregnancies advanced to term [36], but the risk for mother is still very high.

The suspicion is crucial for the timely diagnosis of an abdominal ectopic pregnancy. Rising HCG levels without identification of uterine or ectopic (tubal) pregnancy should raise suspicion of an abdominal ectopic pregnancy. In the case reported here, the diagnosis of ectopic pregnancy was made when the patient was still hemodinamically stable, so we opted for laparoscopic treatment during which the definitive diagnosis of abdominal pregnancy was confirmed. According to the macroscopically normal Fallopian tubes, the absence of extensive pelvic adhesions and the presence of the corpus luteum on the right ovary, it seemed likely that after the fertilization, which could have occurred in the pouch of Douglas, the zygote was carried by intraperitoneal fluid and implanted into the vesicouterine pouch. The possibility of postoperative uterine fistula was excluded in this case: there were no uterine or tubal surgeries in the patent's medical history. The full content of early abdominal pregnancy was removed during laparoscopy without significant bleeding. Decreasing serum β-HCG levels (which were slightly elevated at the beginning) can explain the absence of significant bleeding: in this case, the pregnancy was the subject of spontaneous involution. This statement was confirmed by histopathological report: the presence of the necrosis of chorionic villi and necrosis and bleeding in the samples from the peritoneal surface of the bladder. Nevertheless, the presence of the intraperitoneal blood allowed neither expectant management nor medical treatment in this case, although the patient was hemodinamically stable. We speculate that spontaneous resolution is probably a destiny for the most of early primary abdominal pregnancies. It is crucial to establish the adequate vascularisation for the pregnancy to survive. If it fails, the majority of early primary abdominal pregnancies may undergo spontaneous involution, staying asymptomatic and undiscovered. The wide use of transvaginal ultrasound, determination of serum β-HCG levels and laparoscopy enable diagnosis of early abdominal pregnancy before the intra-abdominal bleeding occurs.

The possibility of gestational trophoblast disease in ectopic pregnancy is small [37], with prevalence of 0.16:1000 deliveries [38]. In the case reported here, there were no clinical suspicions of gestational trophoblast disease, which was also excluded by histopathological findings.

Conclusion

A primary abdominal pregnancy is a very rare and potentially life-threatening condition. A high index

of suspicion, combined with carefully interpreted clinical and ultrasound findings, are crucial for timely diagnosis, before the occurrence of severe intra-abdominal bleeding. We have presented the case of early primary abdominal pregnancy, diagnosed in the sixth gestational week, located in the vesicouterine pouch and treated laparoscopically. Despite the rapidly decreasing serum β-human chorionic gonadotropin levels, the presence of the intraperitoneal blood allowed neither expectant management nor medical treatment in this case, although the patient was hemodinamically stable at that moment. The absence of significant bleeding during the surgery and histopathological finding of placental villi with necrosis confirmed that this abdominal pregnancy was already the subject of spontaneous involution.

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HISTORY OF MEDICINE
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DEVELOPMENT AND ACHIEVEMENTS OF ASSISTED REPRODUCTIVE TECHNOLOGY

RAZVOJ I DOSTIGNUĆA ASISTIRANE REPRODUKTIVNE TEHNOLOGIJE

Artur BJELICA[1,2] and Svetlana NIKOLIĆ[3]

Summary
History of marital infertility is as long as the history of human civilization. Becoming aware about the importance of procreation, as well as the problems with which people may confront, has been the subject of interest since the moment of the first human community creation. Historically, each stage of social development, hence the development of science, has carried within itself certain findings more or less acceptable from today's point of view. The development of human awareness and acquisition of findings based on empirical evidence have contributed to understanding and solution of the problem which was considered to be a result of force majeure until that moment and therefore could not be influenced. This paper deals with the previously mentioned issues through the review of historical development of assisted reproductive technology and its importance. The authors' intention was to present the developmental road of assisted reproductive technology through history succinctly with a special emphasis on the moments which have been of the crucial importance and which have marked certain stages of its development.
Key words: History of Medicine; Reproductive Techniques, Assistive; Infertility; Fertilization in Vitro; Famous Persons

Sažetak
Istorijat bračne neplodnosti dug je koliko i ljudska civilizacija. Sticanje svesti o značaju produžetka vrste i problemima sa kojima se čovek na tom putu može suočiti bili su predmet interesovanja od momenta nastanka prvih ljudskih zajednica. Istorijski gledano, svaka etapa društvenog razvitka, a samim tim i nauke, nosila je sa sobom određena saznanja, sa današnje tačke gledišta, manje ili više prihvatljiva. Razvoj ljudske svesti i sticanje saznanja zasnovanih na empirijskim dokazima doprineli su i shvatanju i rešavanju problema za koje se do tada smatralo da su rezultat dejstva viših sila i da je stoga na njih nemoguće delovati. Ovaj rad se bavi upravo spomenutim pitanjima kroz razmatranje istorijskog razvoja asistirane reproduktivne tehnologije i njenog značaja. Namera autora bila je da na sažet način prikažu razvojni put asistirane reproduktivne tehnologije sa posebnim osvrtom na momente koji su bili od krucijalnog značaja i koji su obeležili pojedine epohe u njenom razvoju.
Ključne reči: Istorija medicine; Asistirane reproduktivne tehnike; Infertilitet; In Vitro fertilizacija; Poznate osobe

Introduction

Marital infertility has been the subject of interest since the moment the man became aware of the importance of reproduction and procreation. Numerous historical writings, which will be discussed further in the text, testify unambiguously that the issues considering birth have attracted attention of numerous scientists throughout the human history. Some of these scientists were frequently misunderstood and cast off because of their visionary ideas especially in the Middle Ages, when the church hindered the development of scientific thought to a large extent. On the other hand, when reviewing the development of this idea through history, the findings emerge about its course and foundation and who were the giants that enabled its development and progress. At the same time this would represent the incentive for further development [1].

If we take into consideration the facts that even the Ancient Egyptians knew about sterility and that it could occur both in men and in women as well as the fact that the medicine used then was slightly modified through centuries [1], it is quite clear that the road leading to the possibility of the latest methods of assisted reproductive technologies, i.e. medically assisted reproduction, has been very long.

History of Assisted Reproduction

The statement that the issue of assisted reproductive technologies is not a modern discovery is testi-

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Abbreviations

IVF – in vitro fertilization
USA – the United States of America
HMG – human menopausal gonadotropin
GnRH – gonadotropin-releasing hormone
DNA – deoxyribonucleic acid
ICSI – intracytoplasmatic sperm injection
PGD – preimplantation genetic diagnosis

fied by the reports of Professor Walter Heap from the Cambridge University going as far as 1890, who made the first known attempt of an embryo transfer in rabbits. In 1930, Aldous Huxley described the techniques of in vitro fertilization (IVF) in his science fiction novel "Brave New World" [2].

In 1934, Gregory Pincus managed to isolate the egg cells and the sperm of rabbits, and to implant the created embryo into a surrogate rabbit. In 1959, Min Chueh Chang, a young Chinese scientist, who dealt with this issue, came to irrefutable evidence about the possibilities of IVF resulting in births of children alive [2]. The first human IVF was performed in 1973 in Melbourne, as reported by Professors Carl Wood and John Leeton. Sadly, this attempt turned out to be unsuccessful [3]. Three years later, Patric Steptoe and Robert Edwards submitted a report on the ectopic pregnancies after IVF [4]. After the birth of the first babies conceived via IVF, Louise Brown (July 25, 1978), Cortney Cross (October 16,1978) and Allister McDonald (January 14,1979), IVF became the procedure widely applied and according to the available data, 5 million babies have been born so far using this method [2]. Assisted reproductive technologies were further developed in the following years, bringing the possibility for many couples confronted with the problem of sterility to realize their dreams of parenthood.

The following moments are important in the development of assisted reproduction methods: in 1987, Alex Lopata, in Melbourne, gave a description of ovarian cycles stimulated by clomiphene citrate [5], while in 1979, Paz with his colleagues in France, started monitoring the follicular growth using ultrasonography and concluded that the ultrasound findings correlated with the laparoscopy findings. Further research suggested that ultrasound monitoring of the follicular diameter represented a more trustworthy indicator of follicular maturation in relation to the level of estradiol in the serum [6]. In 1980, the first baby conceived as the result of IVF technology was born in Australia, the forth one in the world, and the team was headed by Alan Trounson [5].

The first clinic for assisted reproduction in the United States of America (USA) was opened in Virginia in 1980 [6]. The laboratorial examination of semen, cervical mucus, as well as of the interaction between semen and cervical mucus began. Alan Handyside began to study techniques to identify genetic anomalies of embryo in Great Britain [7]. A year later, first babies conceived via IVF were born in the USA, the first one was Elizabeth Jordan Carr after the ovarian stimulation using the human menopausal gonadotropin (HMG) (Howard and Jones), while the other baby, who was also from the US, Samantha Still, was born in England in the same year [6]. Clomiphene citrate and HMG were introduced to IVF by Alan Trounson and John Leeton in Australia [8]. Richard Fleming was the first one who indicated the possibility of using gonadotropin-releasing hormone (GnRH) in ovarian stimulation [9].

The first twins, Taylor and Freddy Axton, were conceived via IVF and born in Great Britain in 1982. In the same year, the first babies conceived via IVF were born in France, Amandine in February and Alexis in October [6]. In Switzerland, the first baby was born after the assisted reproduction in Goteborg [10]. In 1982, the first twins after the transfer of frozen embryo were born in Austria, and the uterine insemination was used for the first time [6]. In Germany the first "test-tube baby" was born on the 16thof April 1982, and Zlatan Jovanovic was the first baby born in Australia after IVF treatment [11].

Danish gynecologists, Susan Lenz and Jorgen Lauristen, were the first ones to indicate the importance and demonstrate the use of ultrasound during the oocyte aspiration [12]. In Australia, the team headed by Alan Trounson succeeded in applying assisted reproductive technology with bilateral oophorectomy of women, with the use of oocyte donor [13], as well as by implanting a donor embryo in the case of a patient with primer ovarian dysfunction [13]. Monash's team in Australia reported on the first successful pregnancy with the transfer of frozen embryo [14]. In the same year, the procedure of immature oocyte in vitro maturation was introduced [2].

Glaicher et al. gave the first evidence about the early culdocentesis aimed at aspiring egg cells using transabdominal ultrasound [15]. Robert Casper et al. were the first to describe the use of low HCG dosages in the process of ovarian stimulation [16]. On January 6, 1984, the first quadruplets conceived via IVF were born at Women's Royal Hospital in Melbourne, Australia, and on March 28, 1984, the first baby, Zoe Lyeland, was born with the use of frozen embryo also in Melbourne, which represents an important moment in the application of assisted reproductive technologies [6]. In 1985, the first pregnancy with the application of percutaneous epididymal sperm aspiration (PESA) was described [17]. A Nordic group headed by Monash Wikland in Sweden described the possibility of transvaginal oocyte scanning during their application. In this manner, visualization and access to smaller follicles as well as their traces were made easier than by the previously used transabdominal approach. The procedure would be conducted under local anesthesia and the patient would leave the clinic an hour after the intervention [18].

In 1986, Lupron*(GnRH agonist) was used for the first time to prevent the early ovulation. Monash's team were the first to report on the pregnancy achieved after the surgical sperm retrieval

from the patient with bilateral obstruction ductus deferens [6]. Wilfred Feichtinger and Peter Kemeter used transvaginal ultrasound guided needle to aspire the grown follicle [19]. Daniel Navot et al. suggested the possibility of artificial endometrium induction in the absence of ovaries [20]. Paul Devroey et al. were successful in trans-laparoscopy zygote intrafallopian transfer (ZIFT) [21]. Christopher Chan from Australia reported on the first pregnancy successfully carried out with the use of oocyte which had undergone cryopreservation (slow freezing with dimethyl sulfoxide/fast thawing) [22]. In 1987, fast cryopreservation was discussed as a very efficient method for the first time [23]. Lewis-King et al. introduced the method called SUZI (sub-zonal-injection) which was a huge improvement in the field of assisted reproduction, and it has retrieved hope to many couples after the countless trials to become parents [24]. Lynda Wilton and Alan Trounson developed the early embryo biopsy technique to perform genetic analysis [25]. In 1989, embryo biopsy was introduced for the first time before the implantation to determine the gender using the method of deoxyribonucleic acid (DNA) amplification [26]. Laser was introduced to the assisted reproduction technology in the same year [27]. In Toronto, Y. Gonen and her associates were the first to apply ultrasonography to assess the quality of endometrium [28]. A breakthrough in treating the male sterility was made in 1993 when Sherman Spielberg et al. reported on the successful sperm extraction from men with non-obstructive azoospermia and the application of intracytoplasmatic sperm injection (ICSI) method [29]. It should be mentioned that in case of congenital bilateral absence of vas deferens (CBAVD) this anomaly could be transmitted on offspring as a cause of male sterility [30]. In 1994, the Australian team headed by Alan Trounson succeeded in in vitro oocyte maturation in women diagnosed to have *polycystic ovary* (PCO) syndrome [31]. A Canadian embryologist, Andrea Jurisicova, was the first to conclude that embryo pre-implantation fragmentation led to the programmed cell death [32]. In 1998, Sun, Jurisicova and Casper, described the procedure of sperm DNA fragmentation detection and its correlation with IVF. They have concluded that spermatozoids with DNA fragmentation have considerably lowered fragmentation ability [33]). The first baby was born after IVF treatment in Nigeria in 1998, and in the same year a success in controlled ovarian hyper-stimulation was recorded with the use of recombined follicle-stimulating hormone and GnRH antagonist (Genirelix), and the report was published by Joseph Itskovic-Eldor [34]. G. Palermo et al. succeeded in obtaining the sperm by testicular extraction from the men with non-mosaic Klinefelter syndrome diagnosis, which resulted in successful pregnancy by applying ICSI method [35]. The first octuplets conceived after the application of ovulary induction were born in December of 1998 in Huston, Texas. A year later the first case of preimplantation genetic diagnosis (PGD) of Sickle-cell disease was recorded [36]. The application of ultrasound-guided transvaginal catheters applied to transfer the embryo largely contributed to the success of IVF treatment (2001) [37]. Kili De Boer and her associates reported on the first baby born alive in 2002 after the blastocysts biopsy applied to make PGD [38]. Comparative genomic hybridization and polar body were used for the first time in the same year to make preimplantation aneuploidy diagnosis [39]. Tea Ki Yoon with her associates reported on the success of applying verification in the process of stimulated IVF protocol in 2003 [40]. Jack Donnez reported on the baby born alive to the patient who had undergone orthotopic transplantation of previously cryopreserved ovarian tissue [41]. In the same year, the Britain's National Health System made a decision about financing the program of pre-implantation genetic diagnosis and human leukocyte antigen (HLA) standardization [42]. David Garner et al. conducted the first randomized study aimed at determining the extent to which the transfer of one blastocyst would increase the rate of successful pregnancy and reduce the possibility of multiple pregnancies at the same time [43]. A Korean group of scientist produced the first cloned blastocyst, and reported on the first baby born alive with preimplantation retinoblastoma diagnosis in the same year [44]. In 2005, Adriana Iliescu, from Backrest, gave birth in her 66th year as a result of IVF treatment after changing the egg cells and sperm donation. In the same year, a patient gave birth after the ovarian cortex transplant, done to treat the ovarian dysfunction resulting from chemotherapy [45]. Mohamed Bedaiwy et al. reported on the successful cryopreservation of intact human ovary with vascular pedicle in 2006 [46]. The first successful pregnancy after the application of PGD procedure on aneuploidy from naturally generated ovarian cycle was reported by the Reproductive Center in Toronto in the same year [46]. The concept of the so called "mild" treatment within IVF was developed in 2007 to reduce the expenses and multiple pregnancies rate [48]. Pascal Patrizio introduced a multi-gradient technology of ovaries cryopreservation aimed at preserving its natural architect [49].

In 2008, Son Weon Young and her associates recommended a span of 38 hours between the HCG injections and oocyte aspiration, pointing out that this time period considerably influenced the level of in vivo and in vitro oocyte maturation [50]. Very intensive research in the generic expression and identification field of viable and non-viable IVF blastocysts began in the same year [51]. In 2009, the second octuplets were born (6 boys and 2 girls) in the US. The interesting fact is that in this case 12 transfers of frozen embryos were performed, and the license was taken away from Michael Kamrava, who had performed this intervention [2]. In the same year, Cetrorelix-acetate (luteinizing hormone - releasing hormone antagonist) was approved by the Food and Drug Administration for clinical use in the framework of IVF protocol, and Simon Fishel, from Nottingham, reported on the successful application of multiple genomic hybridization

[52]. In 2010, Bathory Devy, an Indian woman aged 66, gave birth to two boys and a girl conceived via IVF after 44 years of marriage [2]. The year of 2011 was marked by the introduction of continuous early embryo monitoring within an hour with Embryoscope, which was introduced by Unisense Fertilitech, the USA. In December of the same year, the first twins were born with the application of this method [2]. In the following year, 2010, the number of babies conceived by assisted reproductive technologies and born alive reached 5 million.

The following year, 2013, was marked with the use of Kisspeptin (low risk IVF treatment) with the purpose of ovarian stimulation which reduced the risk from hyper-stimulation syndrome. The British also started with the application of this method, their team leader was Professor Dilly in the Royal Hospital in London [2]. In the same year, Alison Campbell form Manchester introduced a new method called time-lapse imaging for early discovery of a damaged embryo without the need for the use of embryo biopsy or the previously mentioned PGD [2].

Professor Robert Edwards, one of the pioneers for IVF technology and a winner of the Noble Price for medicine in 2010, died in April 2013 [2].

Many achievements are to be expected in the field of assisted reproductive which would be made even more efficient and safer.

Conclusion

The review of literature on the development of assisted reproduction has explicitly shown that this process is exceptionally long and complex, which has required hard labor, interdisciplinary approaches and cooperation of many experts from different fields. In support of this fact there are numerous data presented which have unambiguously indicated the time-consuming research, the application of methods whose results have been more or less satisfactory; however, they have initiated further studies and the procurement of better and more efficient solutions.

The data given in this paper represent the most important moments in the development of assisted reproductive technologies, from its very beginning up to the modern achievements. The importance of the development of reproductive technologies can be best illustrated by the information that this method has helped more than five million babies to be conceived and brought to this world and this number is very likely to increase. Many couples were given a chance with this method to accomplish themselves as parents, which classifies the assisted reproduction into one of the most valuable achievements of medicine.

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Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

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Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

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Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *Sveska sa suplementom*

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∗ *Sažetak u Časopisu*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije:

∗ *Jedan ili više autora*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Urednik(ci) kao autor*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *Poglavlje u knjizi*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders;1974. p. 457-72.

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∗ *Disertacije i teze*

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Elektronski materijal

∗ *Članak u Časopisu u elektronskoj formi*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monografije u elektronskoj formi*

CDI, clinical dermatology illustrated [monograph on CDROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *Kompjuterski dokument (file)*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computeried Educational Systems; 1993.

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– Svaki prilog numerisati arapskim brojevima, prema redosledu njihovog pojavljivanja u tekstu.

– Naslov, tekst u tabelama, grafikonima, shemama i legendama navesti na srpskom i na engleskom jeziku.

– Objasniti sve nestandardne skraćenice u fusnotama koristeći sledeće simbole: *, †, ‡, §, ||, ¶, **, ††, ‡‡.

– U legendama mikrofotografija navesti korišćenu vrstu bojenja i uvećanje na mikroskopu. Mikrofotografije treba da sadrže merne skale.

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Prijem rukopisa vrši se u elektronskoj formi na stranici: **aseestant.ceon.rs/index.php/medpreg/**. Da biste prijavili rad morate se prethodno registrovati. Ako ste već registrovani korisnik, možete odmah da se prijavite i započnete proces prijave priloga u pet koraka.

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Ukoliko autor i svi koautori nisu uplatili članarinu za Medicinski pregled, rad neće biti štampan. Radovi koji nisu napisani u skladu sa pravilima Medicinskog pregleda, neće biti razmatrani. Recenzija će biti obavljena najkasnije u roku od 6 nedelja od prijema rada. Uredništvo zadržava pravo da i pored pozitivne recenzije donese odluku o štampanju rada u skladu sa politikom Medicinskog pregleda. Za sva dodatna obaveštenja obratiti se tehničkom sekretaru:

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INFORMATION FOR AUTHORS

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– It must contain the proof given by the author that the paper represents an original work, that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine)

The manuscript:

Use Microsoft Word for Windows to type the text. The text must be typed in font Times New Roman, page format A4, space 1.5 (for tables as well), borders of 2.5 cm and font size 12pt. The manuscript should contain the following elements:

1. The title page. The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary. The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– original and professional papers should have the introduction (with the objective of the paper), material and methods, results and conclusion

– case reports should have the introduction, case report and conclusion

– review papers should have the introduction, subtitles corresponding to those in the paper and conclusion. It is to be followed by up to 10 Key Words from the list of Medical Subject Headings, MeSH of the American National Medical Library.

3. The summary in Serbian language. The summary in Serbian should be the translation of the summary in English, it should be structured in the same way as the English summary, containing up to 250 words, without any abbreviations.

4. The text of the paper. The text of original studies must contain the following: introduction (with the clearly defined objective of the study), material and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

– The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

– The text should be written in the spirit of Serbian language, without unnecessary abbreviations, whose first mentioning must be explained by the full term they stand for. Abbreviations should not be used in the title, summary and conclusion. Only commonly accepted abbreviations (such as DNA, MRI, NMR, HIV…) should be used. The list of abbreviations used in the text, together with the explanation of their meaning, is to be submitted at the last page of the manuscript.

– All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C). and pressure in mmHg.

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Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Material and methods should contain data on design of the study (prospective/retrospective, eligibili-

ty and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

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Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the problem mentioned in the introduction. Conclusions must be based solely on the author's own results, corroborating them. Avoid generalised and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

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Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organisation as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

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

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *Acomputer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

6. Attachments (tables, graphs, schemes and photographs). The maximum number of attachments allowed is six!

– Tables, graphs, schemes and photographs are to be submitted at the end of the manuscript, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English language.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, ||, ¶, **, † †, ‡ ‡ .

– State the type of colour used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

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