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ЗА ЦЕЛОКУПНО ЛЕКАРСТВО Осн.1872

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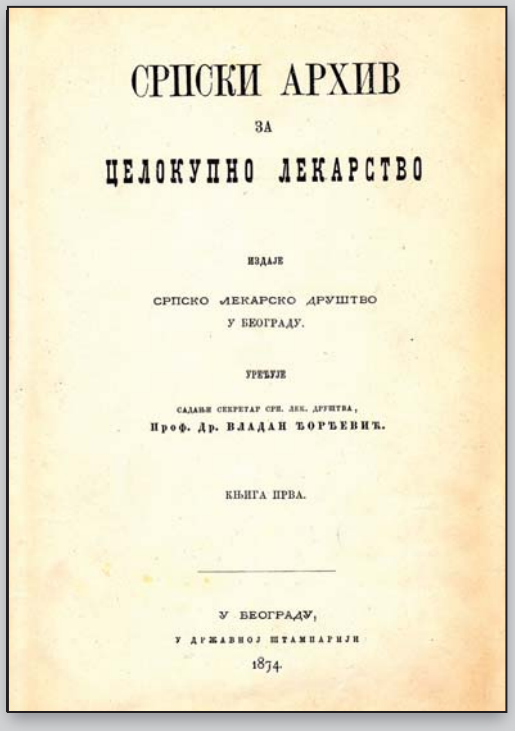

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ЗА

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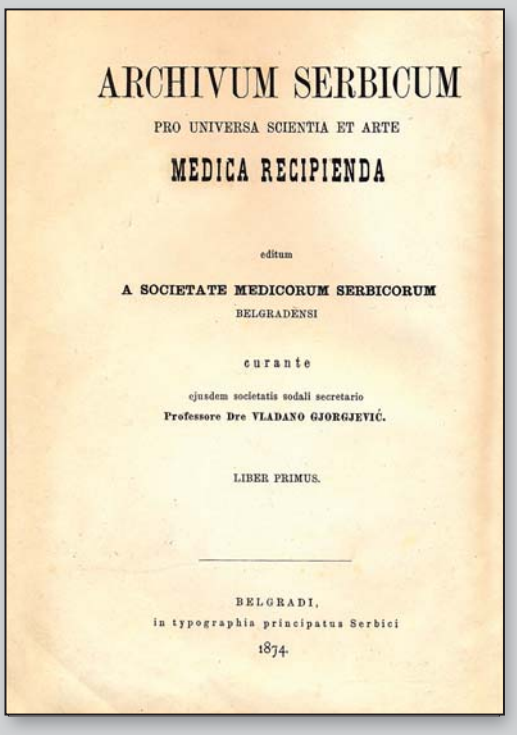

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EDITORIAL • УВОДНИК

ORIGINAL ARTICLES • ОРИГИНАЛНИ РАДОВИ

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EDITORIAL / УВОДНИК

New developments, treatment options and possible complication in complex coronary artery disease, structural and congenital heart disease, and heart failure

Branko Beleslin
Cardiology Clinic, Clinical Centre of Serbia, Belgrade, Serbia

Developments of interventional techniques and devices for the treatment of coronary artery disease, structural heart diseases, including valvular and congenital heart disease, as well as heart failure, have changed the practice of modern cardiology. In this issue of the *Serbian Archives of Medicine* we present five articles on different novel techniques, devices, as well as complications of device implantation for the treatment of chronic total occlusion [1], aortic valve disease [2], patent ductus arteriosus [3], pacemaker systems upgrade [4], and finally critical analysis of the most common complications during the implantation of cardiac rhythm management devices [5].

Recanalization of chronic total occlusion remains one of the most demanding and complex interventions for the treatment of coronary artery disease. However, continuous technological developments including new dedicated guidewires enabling safer and easier recanalization, have made this challenging procedure available not only for elite centers of excellence but also for other high volume interventional laboratories with huge experience in the interventional treatment of coronary artery disease. Recanalization of chronic total occlusions has been introduced in Serbia during Belgrade BASICS interventional meeting more than 10 years ago by Japanese and other distinguished operators. Now, with this proctoring approach and large gained experience in implementation of this procedure, several our centers are successfully performing this procedure [6]. Ivanović et al. [1] presented two cases of a specific retrograde approach for the treatment of chronic total occlusion where after failed anterograde crossing of the occlusion, the occluded coronary artery was crossed from the contralateral coronary artery through collaterals. The rationale of this approach is based on the fact that the distal cup of coronary artery occlusion is thinner and more suitable for guidewire penetration in comparison with the proximal cup of the occlusion. By introduction of the retrograde approach during the last 10 years, the success of the technique improved from just above 50% to more than 90% when performed by experienced operators [7].

Most of the innovations in modern cardiology practice in the last decade come from the developments in the treatment of valvular heart disease, aortic valve stenosis in particular. In fact, transcatheter aortic valve implantation (TAVI) has swiftly moved from being a promising option in inoperable patients to the standard of care in high-risk patients, and at least an alternative treatment option in intermediate-risk patients with symptomatic aortic stenosis [8, 9]. Although it proved to be a safe procedure, unusual and life-threatening complications can occur, as shown in the article by Lazerević et al. [2]. This case report still supports the application of on-site echocardiography imaging during the procedure to search for possible causes of sudden hypotension that may lead to severe hemodynamic compromise in these fragile patients. Simultaneous echocardiography imaging might be particularly important for centers with limited experience in this procedure and technique, as are the centers in our country regarding the experience with TAVI.

On the other hand, the treatment of congenital heart disease in children and adults by interventional techniques in our country is characterized by respectable tradition, experience, and success. Here, Đukić et al. [3] present their experience from the Children's Hospital in Belgrade on the management of patent ductus arteriosus by transcatheter closure of the defect, which is considered standard procedure in most young patients after early infancy. The authors compared two devices and concluded the superiority and safety of the Amplatzer duct occluders

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over spiral shape coils, both early after intervention and in the follow-up (100% closure after one and two years).

In the last decade, we have also witnessed tremendous evolution and efficiency of devices used in patients with heart failure, including primarily cardiac resynchronization therapy (CRT) along with implantable cardioverter defibrillators. Moreover, CRT devices have been used to upgrade older pacemaker systems in cases of adverse effects of chronic right ventricular pacing that may lead to heart failure. Here, Radovanović et al. [4] present a case of a patient in whom the upgrade of the pacemaker was needed due to a newly developed heart failure. The case was further complicated by subclavian vein thrombosis on the side of the previously implanted pacemaker. Therefore, the authors decided to carry out a more complex and less-used intervention in clinical practice (but with a potential long-term benefit to reduce new venous thrombosis) to implant one new left ventricular lead on the right side and then to transfer it subcutaneously by pre-sternal tunneling to the previous left prepectoral pocket.

Finally, the same group of authors from the Pacemaker Center of the Clinical Center of Serbia reported the rate of pneumothorax, one of the most common complications of cardiac rhythm management devices, including antibradycardia pacemakers, implantable cardioverter defibrillators, and CRTs, during one year [5]. Among 999 patients, the rate of pneumothorax was 1.8% (incidence from the literature data is 0.66–5% [10]), and more often found in women, older patients, subclavian vein puncture, and the use of intravenous contrast during the procedure. According to their experience and data, the authors suggested that cephalic vein cut-down is the preferred and safer technique to subclavian or axillary vein puncture with careful use of contrast venography.

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Transcatheter closure of patent ductus arteriosus using Flipper coil and Amplatzer Duct Occluder – Ten-year experience from a single center

Milan Đukić[1,2], Vojislav Parezanović[1,2], Stefan A. Đorđević[1,2], Igor Stefanović[1,2], Vesna Miranović[3], Slobodan Ilić[1,4], Ida Jovanović[1,2]

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SUMMARY

Introduction/Objective Transcatheter closure is a well-established procedure for treatment of patent ductus arteriosus (PDA).

We aimed to make a comparison between transcatheter PDA occlusion with Flipper coil and Amplatzer Duct Occluder (ADO) and to determine the incidence and significance of procedural complications.

Methods Between November 2004 and October 2014, 148 patients were eligible for transcatheter PDA closure at the University Children's Hospital in Belgrade, Serbia. The median age was 5.9 years (the range of 0.9 years to 17.3 years) and the median weight was 21 kg (the range of 8.8 kg to 94 kg). Follow-up evaluations with Doppler echocardiogram were performed at one day, three months, and one and two years after the PDA occlusion.

Results Median narrowest PDA diameter was 1.5 mm (the range of 0.5 mm to 5.6 mm). Flipper coil was used for PDA closure in 84 (59.2%) and ADO in 58 patients (40.8%). There was no significant difference in the rate of immediate complete closure between the coil and the ADO group (86.9% vs. 75.9%, p = 0.089), but a significantly higher rate of complete closure was achieved with ADO at one day (83.3% vs. 98.3%, p = 0.004), three months (85.7% vs. 100%, p = 0.002), and both one and two years after the implantation (91.7% vs. 100%, p = 0.041). In total, 12 complications occurred during the procedure, seven of which with coil and five with ADO occlusion of PDA.

Conclusion Transcatheter closure of PDA using both coils and ADOs is a very safe and effective procedure. ADO proved superior to coil in terms of complete closure rate as early as one day after the procedure.

Keywords: cardiac catheterization; prostheses and implants; child; adult

INTRODUCTION

Ductus arteriosus is a blood vessel connecting the aortic isthmus with the pulmonary artery in utero. If it fails to close after birth, it is called a patent ductus arteriosus (PDA) and is considered a congenital heart disease. PDA accounts for about 5–10% of all congenital heart diseases, and is an especially common and significant problem in preterm infants [1].

Persistent aortopulmonary flow through the PDA leads to pulmonary overcirculation and volume overload of the left heart. The amount of ductal shunting mainly depends on the size and morphology of the PDA and the level of pulmonary vascular resistance. PDAs vary from extremely small and hemodynamically insignificant (the so-called "clinically silent" PDAs) to large ones leading rapidly to pulmonary hypertension (the so-called "window-like" PDAs). Dilation and dysfunction of the left heart, pulmonary hypertension, or rarely even infectious endocarditis may occur as late complications. Therefore, it is advisable to close PDA unless it is too small and hemodynamically insignificant.

Nonsteroidal anti-inflammatory drugs such as indomethacin or ibuprofen can be used for PDA closure in neonates [2, 3]. Surgical ligation is usually reserved for patients with very large PDAs, unfavorable ductal anatomy (mostly Krichenko type B), associated cardiovascular anomalies, and for infants weighing less than 8 kg [4, 5]. However, transcatheter closure of PDA has now become the treatment of choice for patients after early infancy. The most commonly used devices for transcatheter closure of PDA are spiral-shaped coils and plug-shaped Amplatzer Duct Occluders (ADOs). Flipper coils are one of the most frequently used coils. The results of transcatheter PDA closure are excellent with a high complete closure rate, minimal complications, and virtually no mortality.

This study aimed to compare the safety and efficacy of transcatheter PDA occlusion using Flipper coil and ADO and to determine the incidence and significance of procedural complications.

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METHODS

Study population

Between November 2004 and October 2014, 148 patients were eligible for transcatheter closure of PDA at the University Children's Hospital in Belgrade. All of them had echocardiographic evidence of a PDA and met the criteria for transcatheter PDA closure established by manufacturers of the occlusion devices [6, 7]. Two patients had a residual PDA after attempted surgical ligation.

The great majority of patients (134) were asymptomatic. Four patients failed to thrive, six patients complained of fatigue with exertion, and three patients experienced palpitations. In addition, one patient with associated pulmonary hypertension and a small interatrial communication within the oval fossa was mildly cyanozed.

A written informed consent was obtained from all patients and/or their parents prior to the procedure.

Description of the procedure

Catheterizations were carried out under general anesthesia using Axiom Artis angiography system (Siemens, Erlangen, Germany). For transcatheter PDA closure we used Flipper coils (Cook medical, Inc., Bloomington, IN, USA) and Amplatzer Duct Occluders (St. Jude Medical, Inc., MN, USA).

After femoral artery access, left heart catheterization was performed with the measurement of aortic pressures. Then, an aortogram was taken in the lateral and occasionally right anterior oblique projection to determine the morphology of the PDA based on the Krichenko classification [4]. Furthermore, PDA diameters at the aortic and pulmonary end and their lengths were measured on the aortogram.

The decision whether to use Flipper coil or ADO for PDA closure and the choice of the optimal size of the device were based on the morphology and the narrowest diameter of the PDA (Figures 1 and 2) [8]. Coils were used for smaller PDAs with the narrowest diameter smaller than or equal to 2.5 mm, while ADOs were mostly employed for larger PDAs greater than 2 mm in the narrowest diameter (Figure 2).

If Flipper coil was chosen for the occlusion of PDA, a 4-Fr end-hole catheter was passed through the aorta and the PDA to the pulmonary artery. Then, pulmonary artery pressures were obtained and the coil of the appropriate size was introduced through the catheter and carefully placed in the PDA, avoiding protrusion into the aorta or left pulmonary artery. After the assessment of adequate positioning, the coil was finally released (Figure 3).

When ADO was used for PDA closure, aortography was followed by femoral vein puncture and right heart catheterization with pressure measurements in the right heart and the pulmonary artery. If increased pulmonary artery pressure (mean pressure > 25 mmHg) was recorded, flows and resistances in the pulmonary and systemic circulations were calculated. Pulmonary vascular reactivity was assessed as needed, using vasodilating agents (nitric oxide and 100% oxygen) and by temporary test occlusion of the PDA with a sizing balloon [9]. Next, a catheter was introduced through the femoral vein and passed through the pulmonary artery and PDA to the descending aorta and then exchanged over a guidewire for a long sheath of adequate size. Afterwards, ADO of appropriate size was introduced through the long sheath and advanced to the descending aorta. Initially, only the retention disk was opened and then the remainder of the

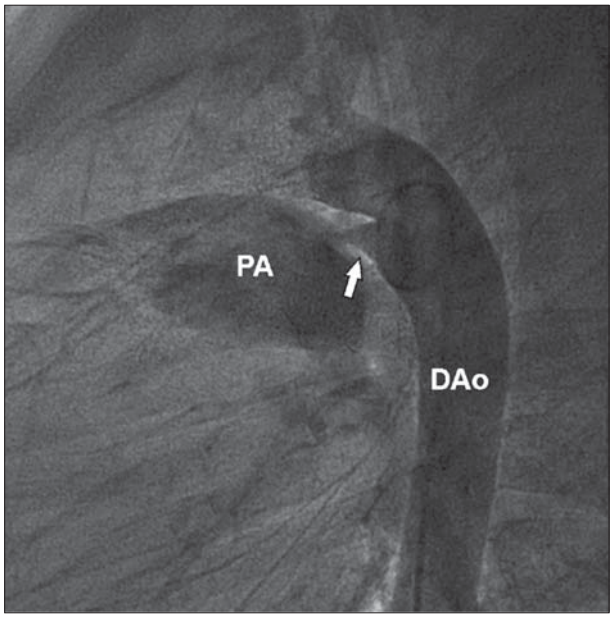

Figure 1. An aortogram in lateral projection showing a smaller patent ductus arteriosus (PDA) type A (arrow); there is a prominent ductal ampulla (the widened aortic end of the PDA); the narrowest PDA diameter is at the pulmonary end; PA – pulmonary artery; DAo – descending aorta

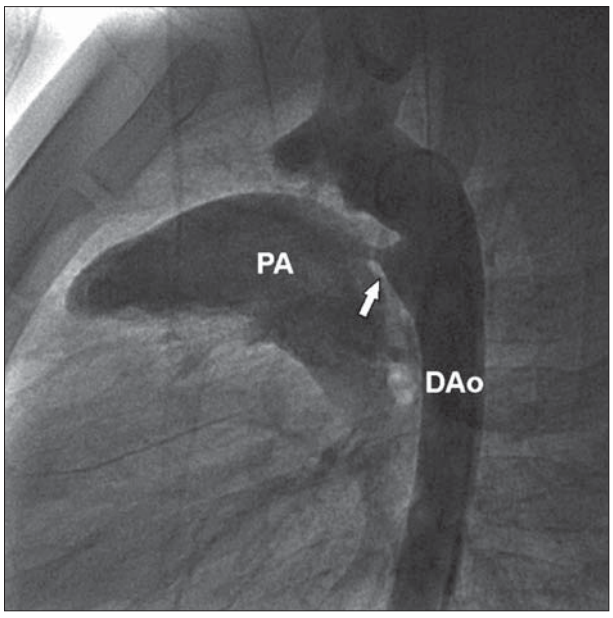

Figure 2. This aortogram in lateral projection shows a larger patent ductus arteriosus (PDA) type A (arrow) with a well-defined ductal ampulla; the PDA is the narrowest at the pulmonary end; there is a marked opacification of the pulmonary artery from the PDA, suggesting a significant aortopulmonary shunt; PA – pulmonary artery; DAo – descending aorta

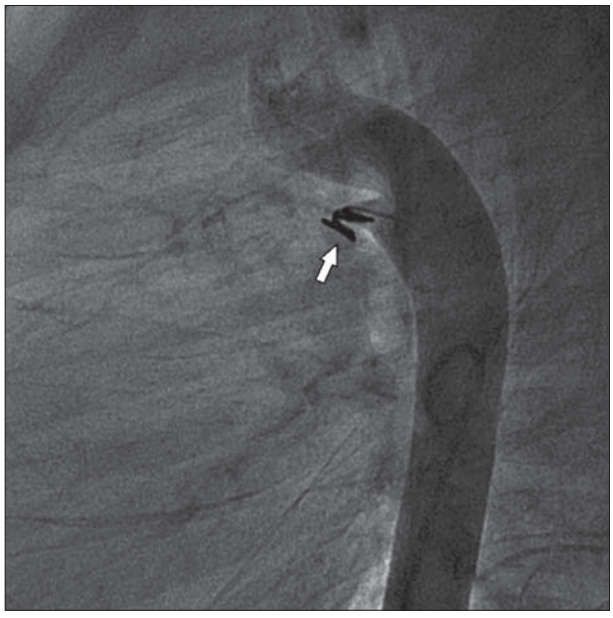

Figure 3. An aortogram of the same patient as in Figure 1 demonstrates complete closure of the patent ductus arteriosus (PDA) after coil placement (arrow)

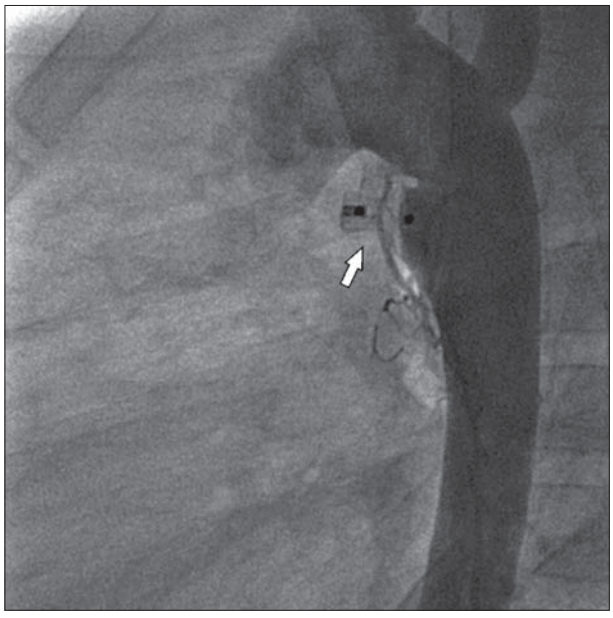

Figure 4. An aortogram of the same patient as in Figure 2 reveals an Amplatzer Duct Occluder (ADO) implanted in the patent ductus arteriosus (PDA) (arrow); there is no residual shunt

device was embedded into the ductal ampulla. After being carefully placed and in stable position, ADO was released from the delivery cable. The mean diameter of the ADO occluder was at least 2 mm larger than the narrowest diameter of the duct. A repeat angiogram was performed 10 minutes after the implantation of occluder in order to assess the position of the device, its relationship to adjacent structures, and the presence of the residual shunt (Figure 4).

Following removal of catheters and vascular introducers, digital compression, and after checking the pulses, the patients were transferred to the ward for close observation. All the patients received antibiotic prophylaxis prior to the procedure. Intravenous heparin was reserved for prolonged procedures or absence of pulses immediately after the catheterization.

Follow-up Doppler echocardiograms were performed at one day (pre-discharge), three months, one and two years after closing the PDA to evaluate the presence of the residual shunt and device protrusion into the aorta or the pulmonary artery.

Statistical analysis

Continuous variables were summarized using descriptive statistics. Parametric data were expressed as mean and standard deviation, while non-parametric data were given as median and range between minimum and maximum values. Mann–Whitney U-test (two-tailed) was applied for comparison of two independent groups of nonparametric data. Independent-samples t-test was used to examine the difference between two groups of data that follow a normal distribution. Fisher's exact test and χ^2 test were used to analyze the difference between categorical variables. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Of 148 patients eligible for transcatheter PDA closure, the procedure was abandoned in four patients. Three of them had extremely small angiographic PDA diameter at the pulmonary end (< 0.5 mm) and one patient had unfavorable morphology and size of the PDA (closure was possible only with ADO, but we assumed it would cause considerable protrusion into the pulmonary artery). Furthermore, spontaneous occlusion of very small PDAs occurred following the placement of the guide wire in two patients.

Thus, a total of 142 patients underwent coil or ADO occlusion for PDA, of which 56 males and 86 females. The median age of the patients was 5.9 years (range of 0.9–17.3 years), weight 21 kg (range of 8.8–94 kg), and body surface area 0.8 m^2 (range of 0.4–2.2 m^2). Median narrowest PDA diameter was 1.5 mm (range of 0.5–5.6 mm). Coil was used for PDA closure in 84 (59.2%) and ADO in 58 (40.8%) patients. Baseline demographic data and PDA characteristics, as well as hemodynamic data for both the coil and the ADO group are given in Table 1. The narrowest diameter of the PDA was significantly larger in the ADO group (p = 0.000). PDA type B was more prevalent in the ADO group (p = 0.042), and type C in the coil group (p = 0.001). Mean pulmonary artery pressures were significantly higher in patients who underwent ADO than coil closure of PDA (p = 0.030). Furthermore, a total of eight patients had mean pulmonary artery pressure > 25 mmHg (two in the coil group, and the rest in the ADO group).

The various sizes of coils and ADOs used during the procedure are shown in Table 2 and Table 3, respectively. One patient needed the placement of two coils. In five patients a larger coil was deployed since the smaller one was not appropriately positioned. In nine patients, ADO was placed after initial unsuccessful coil implantation (five coils were unstable and four coils embolized). In two

Table 1. Comparison of baseline demographic data, PDA characteristics, and hemodynamic parameters between the coil and the ADO group

Type of device	Coil	ADO	p-value
Demographic data			
Age (yrs)	6.1 (1.1–17.3)	4.8 (0.9–17.2)	0.094
Male to female ratio	38 : 46	18 : 40	0.089
Weight (kg)	24 (10–94)	18.8 (8.8–78)	0.075
Body surface area (m^2)	0.9 (0.5–2.2)	0.8 (0.4–2.0)	0.135
PDA characteristics			
Narrowest PDA diameter (mm)	1.1 (0.5–2)	2.3 (1.3–5.6)	0.000
PDA length (mm)	7.5 (3.3–22)	7.8 (5–18)	0.334
PDA type:			
A	35 (41.7%)	26 (44.8%)	0.708
B	1 (1.2%)	5 (8.6%)	0.042
C	24 (28.6%)	4 (6.9%)	0.001
D	13 (15.5%)	14 (24.1%)	0.196
E	11 (13.1%)	9 (15.5%)	0.683
Hemodynamic parameters prior to procedure			
Mean aortic pressure	82.8 ± 15.5	82.3 ± 12.7	0.855
Mean pulmonary artery pressure	17.5 (7–26)	20 (11–46)	0.030
Mean pulmonary-to-systemic arterial pressure ratio	0.22 (0.09–0.44)	0.23 (0.14–0.53)	0.062

PDA – patent ductus arteriosus; ADO – Amplatzer Duct Occluder

Table 2. The size and number of coils deployed

Coil sizes (mm)	Number
8 × 5	2
6.5 × 4	1
5 × 5	8
5 × 4	12
5 × 3	13
3 × 5	4
3 × 4	16
3 × 3	29
Total	85

Table 3. The size and number of ADOs deployed

ADO sizes	Number
5/4	32
6/4	20
8/6	4
10/8	2
Total	58

ADO – Amplatzer Duct Occluder

Table 4. The type and number of procedural complications encountered during coil and ADO closure of PDA

Complications	Coil group		ADO group	
Major complications	Device embolization	4	Device embolization	1
	Device embolization and red blood cell transfusion	1		
Minor complications	Mild device protrusion into the aorta	2	Mild device protrusion into the left pulmonary artery	3
			Arrhythmia requiring medication	1

ADO – Amplatzer Duct Occluder; PDA – patent ductus arteriosus

patients, the PDA was closed with ADO after failed surgical ligation.

Repeat angiogram showed complete occlusion of PDA in 117 (82.4%) patients, while trace residual shunting was found in 25 (17.6%) patients. Residual ductal shunting on angiogram was present in 11 out of 84 (13.1%) patients in the coil group, compared to 14 out of 58 (24.1%) in the ADO group. There was no statistically significant difference in the rate of immediate complete closure of PDA with coil or ADO (86.9% vs. 75.9%, p = 0.089). Follow-up Doppler echocardiography at one day, three months, and both one and two years showed only a trace residual shunt in 15 (10.6%),12 (8.4%), and seven (4.9%) patients, respectively. There was a significant difference in complete closure rate between the coil and the ADO group at one day (83.3% vs. 98.3%, p = 0.004), three months (85.7% vs. 100%, p = 0.002), and both one and two years (91.7% vs. 100%, p = 0.041).

Elevated pulmonary artery pressures returned to normal levels in both patients in the coil group, and in almost all patients in the ADO group, except in one with pulmonary hypertension documented prior to procedure.

In total, 12 complications occurred during the procedure, seven of which with coil and five with ADO closure of the PDA (Table 4).

Coil embolization occurred in five patients. Coils migrated towards the pulmonary artery in four patients, and to the common hepatic artery in one case. All embolized coils were successfully retrieved and replaced with a larger coil (one patient), or ADO (four patients) during the same procedure. One of the patients with coil embolized to the pulmonary artery required a red blood cell transfusion due to the prolonged attempts to retrieve the coil. ADO embolization happened in a three-year-old girl weighing 14 kg. Namely, ADO was released too early during the procedure and it lodged in the abdominal aorta. The embolized device was successfully retrieved, using a snare catheter and long sheaths of a large diameter, and subsequently implanted in the PDA during the same procedure. Coil embolizations were associated with Krichenko type A (2), and C (3) PDAs, and ADO embolized in a patient with PDA type A.

In two patients, coil was not appropriately positioned at the aortic end. In one of them, the last coil loop was placed along the wall of the distal aortic arch, while in the other the distal end of the coil protruded about 3 mm into the aorta. Both complications occurred in the setting of PDA type C. In three patients, ADO protruded into the left pulmonary artery without causing significant flow disturbance (Doppler echocardiographic flow velocity of 1.8 m/s). All these patients were asymptomatic and there was no progression of obstruction or need for additional procedures during follow-up. ADO protrusion was associated with PDA type A (1), B (1), and E (1).

A 3.5-year-old girl developed supraventricular tachycardia during the placement of the long sheath through the right heart. Tachycardia was rapidly terminated by intravenous amiodarone, and an ADO was successfully implanted.

DISCUSSION

In the period from 1939 to the mid-1990s, surgical ligation of PDA was considered the gold standard for managing PDAs. Mavroudis et al. [10] reported that ligation of PDA, performed on 1,108 patients older than 30 days with isolated PDA, was successful in 100% of cases. In addition, mortality was zero and morbidity as low as 4.4% [10].

In the past few decades, numerous new cardiac catheterization procedures for correction of congenital heart diseases have been developed to avoid the disadvantages of surgical procedures. Portsmann was the first to attempt to perform a non-surgical closure of PDA with the so-called "plug" in the 1970s. However, this method was not widely accepted because of the large dimensions of the device and catheter through which it was passed. Later on, Gianturco embolization coil was introduced into the clinical practice and was followed by the Rashkind double-umbrella device. At the beginning, the use of nondetachable Gianturco coils frequently led to device embolization to the pulmonary artery and the aorta. Afterwards, the original Gianturco coil was redesigned into the so-called "detachable" coil, which was attached to a cable, thus allowing full control during the placement and release of the coil with the possibility of easy repositioning and retrieval when necessary. A major advance in transcatheter closure of larger PDAs occurred with the advent of ADO in 1998 [11].

Currently available devices designed for PDA occlusion are very efficient, but have some shortcomings [12, 13, 14]. The limitations of transcatheter closure of PDA include the failure of the procedure, the presence of residual shunt with or without hemolysis, device embolization and other cardiovascular complications, device protrusion into surrounding vasculature, and exposure to radiation. As previously mentioned, coils are used for closure of smaller PDAs with the narrowest diameter being smaller than or equal to 2.5 mm, while ADOs are usually reserved for larger PDAs, greater than 2 mm in diameter. In our study, the median narrowest PDA diameter was 1.1 mm (range of 0.5–2 mm) in the coil group and 2.3 mm (range of 1.3–5.6 mm) in the ADO group, and was significantly larger in the latter group. We achieved a high complete closure rate regardless of the device employed. In total, 25 (17.6%) patients had a trace residual shunt at the end of the procedure and only seven (4.9%) at both one and two years after the procedure. Furthermore, complete closure of PDA at both one and two years was achieved in 91.7% and 100% of cases in the coil and the ADO group, respectively.

Studies analyzing the efficiency of coil occlusion of PDA reported that complete closure rate varied from 63.4 to 96.6% at the end of the procedure, and from 80.5% to 96.2%, at one year [15–19]. When present, the residual ductal shunt was almost invariably hemodynamically insignificant. However, in some patients with residual ductal shunting after coil placement, acute hemolysis occurred because of mechanical destruction of erythrocytes after their contact with the metal structure of the coil. In our study, out of seven patients with residual ductal flow none had hemolytic anemia. According to the literature, the rate of complete closure of the PDA using ADO varied from 56.6% to 100% immediately after the procedure, and from 99.7% to 100% at one year [17–23]. The studies of PDA closure with ADO showed that, if present, there was only a small residual shunt after the procedure comparable to that seen with coil placement.

The mortality rate for transcatheter PDA occlusion is nearly zero (0–0.9%). Procedure-related major and minor complications are rare, ranging 0–9.1% and 0–16.2%, respectively [17–27]. Similarly, our results showed zero mortality rate and the equal occurrence of major and minor complications (4.2%).

The single most common procedural complication is probably device embolization (0–6%), with coils being more prone to embolize than ADOs [17–26, 28]. In most cases, embolized devices could be readily retrieved without consequences. Apart from operator skill, the occurrence of coil embolization appears to be related to the type of PDA. It was found more likely to occur with PDAs of Krichenko type B (window-like) and C (tubular) [23]. By comparison, coil embolizations in our study were associated with PDAs type C and type A (conical). In addition, it is of immense importance to accurately determine the size of the PDA so that the proper device and its size could be chosen for the procedure. Retrospective analysis of all cases where coil embolization occurred showed that underestimation of the size of the PDA caused the selection of the wrong type or size of the device. As mentioned above, in one patient, complete closure of the PDA was achieved with a larger coil after the smaller one embolized. In four patients, after retrieving the embolized coils, the PDA size appeared larger on aortogram than previously estimated. After reassessing the size of the PDA, we successfully implanted ADO in all four patients.

Apart from the device embolization, another concern is the possibility of device protrusion into surrounding vascular structures, i.e., the descending aorta and the pulmonary arteries. A number of studies have reported the problem of device protrusion and impingement on the lumen of the left pulmonary artery and occasionally the descending aorta, with the incidence ranging 0–14% [17–26]. This was more commonly seen in infants and small children and in patients requiring the placement of additional devices for PDA closure. Device protrusion into the left pulmonary artery was observed in three (2.1%) patients in our study group and was hemodynamically insignificant in all cases, which is comparable to the results from other studies. Two patients (1.4%) had a slight coil protrusion into the descending aorta with repeat aortograms showing a stable position of the device without obstruction to flow. Since both were small children in whom the aortic diameter would increase with growth and since PDAs were completely closed, the coils were left in place. Follow-up echocardiograms revealed no progression of aortic obstruction.

CONCLUSION

Transcatheter closure of PDA using both coils and ADOs is a very safe and effective procedure in pediatric patients beyond the early infancy. ADO proved superior to Flipper coil in terms of complete closure rate within a day after implantation. The good estimate of the ductal size and anatomy is crucial for the optimal choice of the device. This, in turn, prevents the occurrence of complications including device embolization and protrusion into surrounding vasculature, and decreases the incidence of residual shunt.

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Транскатетерско затварање отвореног артеријског канала коришћењем *Flipper coil*-а и дукталног затварача *Amplatzer*: десетогодишње искуство једног центра

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САЖЕТАК

Увод/Циљ Транскатетерско затварање је опробана метода лечења отвореног артеријског канала (ОАК).

Циљ рада је био да упоредимо транскатетерско затварање ОАК коришћењем *Flipper coil*-а и дукталног затварача *Amplatzer* (ДЗА) и да утврдимо учесталост и значај насталих компликација.

Методе У периоду од новембра 2004. до октобра 2014. године код 148 болесника је урађено транскатетерско затварање отвореног артеријског канала. Просечан узраст је био 5,9 (0,9–17,3) година, а телесна маса 21 (8,8–94) *kg*. Контролни ехокардиографски прегледи су урађени један дан, три месеца, једну и две године после интервенције.

Резултати Просечан најужи пречник ОАК је био 1,5 (0,5–5,6) *mm*. *Flipper coil* је коришћен код 84 (59,2%), а ДЗА код 58 (40,8%) болесника. Непосредно после интервенције није постојала значајна разлика у учесталости потпуног затварања ОАК између *coil* и ДЗА групе (86,9% тј. 75,9%, $p = 0,089$), али је она била значајно већа у ДЗА групи један дан (83,3% тј. 98,3%, $p = 0,004$), три месеца (85,7% тј. 100%, $p = 0,002$) и једну и две године после интервенције (91,7% тј. 100%, $p = 0,041$).

Укупно се десило 12 компликација у току интервенције, од чега седам при употреби *Flipper coil*-а, а пет при примени ДЗА.

Закључак Транскатетерско затварање је безбедна и ефикасна процедура, било да се користи *coil* или ДЗА. Учесталост потпуног затварања ОАК значајно је већа у ДЗА групи у односу на *coil* групу, већ у року од једног дана од интервенције.

Кључне речи: катетеризација срца; вештачке протезе и имплантати; деца; одрасли

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Pneumothorax as a complication of cardiac rhythm management devices implantation

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SUMMARY

Introduction/Objective Pneumothorax is one of the most common complications of cardiac rhythm management (CRM) devices implantation.

We aimed to assess the incidence of pneumothorax after implantation of these devices and to determine risk factors for this complication.

Methods A retrospective, observational study included patients in whom CRM devices were implanted, pacing system was upgraded, or lead revision was performed during 2012 at the Pacemaker Center, Clinical Center of Serbia. We determined the connection between different variables, including sex, age, type of implanted device, prior history of chronic obstructive pulmonary disease, operator experience, venous access, the use of intravenous contrast during procedure, and the development of pneumothorax as the procedure-related complication, using multiple logistic regression.

Results A total of 999 patients were included in this study. The patients' mean age was 68.1 ± 9.2 years; 665 (66.6%) patients were male. The incidence of pneumothorax was 1.8% and an invasive treatment of this complication was required in 13 (72.2%) patients. Pneumothorax was more frequent in women (B = -2.136, p = 0.015), in patients with age > 75 years (B = 4.315, p = 0.001), venous access with subclavian vein puncture (B = 2.672, p = 0.045), and use of intravenous contrast during procedure (B = 3.155, p = 0.007).

Conclusion Pneumothorax is a relatively rare complication of CRM device implantation, and for reducing its incidence, cephalic vein cut-down should be preferred to subclavian or axillary vein puncture as venous access, axillary vein puncture should not be avoided when cephalic vein cannot be found or used, and in the case of difficult vein puncture, contrast venography should be done immediately, before risky punctures.

Keywords: pacemaker; pneumothorax; complication; risk factor

INTRODUCTION

The term 'cardiac rhythm management (CRM) devices' refers to antibradycardia pacemakers, implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) devices with or without defibrillation function [1]. Nowadays, implantation of these devices is a routine and safe procedure associated with infrequent complications, which are rarely life-threatening [2, 3]. However, implantation related complications often require reintervention, prolong hospitalization and increase treatment cost [1]. Pneumothorax, lead dislodgement, infection, and pocket hematoma are the most common complications of CRM devices implantation [1, 2]. The incidence of iatrogenic pneumothorax varies 1–5% according to literature, and depends on many factors [4]. The exact definition of this complication, its clinical recognition, and data collection are important, but also patients' characteristics, the surgical technique, and operator experience have an impact on its incidence [3, 4].

This study aimed to assess the incidence of pneumothorax after implantation of antibradycardia pacemakers, ICDs and CRT devices, after pacing system upgrade procedures and lead revisions. We aimed to determine the procedure-, patient-, and operator-related risk factors for this complication.

METHODS

This has been a retrospective, observational, single centre study. We included patients in whom a CRM device was implanted, pacing system was upgraded, or lead revision was performed at the Pacemaker Center, Clinical Center of Serbia, in 2012. We excluded replacements and implantations of implantable loop recorders.

Data were collected from the registry that has existed in our center since 2010. It contains the data on all patients who underwent surgery at our center. It holds data on patient general characteristics, medical history, risk factors, on procedure details, including data on procedure-related complications, and on the physician who performed the operation. The registry is updated once a week.

In the study we determined the connection between different variables and the development

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of pneumothorax as a procedure-related complication. We examined many variables including sex, age, type of implanted device, prior history of chronic obstructive pulmonary disease (COPD), operator experience, venous access, and use of intravenous contrast during the procedure. The diagnosis of COPD had to be set by a pulmonologist, confirmed by spirometry. We believe that an experienced operator should have over 200 interventions in the last three years and/or over 400 interventions in his career. There are three methods used for venous access at our center – subclavian vein puncture, axillary vein puncture, and cephalic vein cut-down. Routine post-procedural chest X-ray was not performed at our center in 2012. If a patient complained of shortness of breath, chest pain or the doctor noticed decreased or absent breath sounds over the affected lung, chest X- ray would be done. The diagnosis of pneumothorax was confirmed by thoracic surgeon, who made a decision on how this complication would be treated. Sometimes, specific treatment was not necessary, but occasionally thoracic surgeon had to perform aspiration of free air and/or place a chest tube to evacuate the air.

For statistical analysis we used descriptive and analytic statistic methods. From descriptive methods, mean and standard deviation were used for continuous variables and absolute and relative numbers for categorical variables. Multiple binary logistic regression analysis was used to identify the characteristics associated with a higher rate of pneumothorax. All p-values less than 0.05 were considered significant. All data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp, Armonk, NY, USA) statistical software.

RESULTS

A total of 1,141 procedures were performed at our center in 2012. This study comprised 999 patients. We excluded 129 patients in whom a CRM device was replaced and 13 patients in whom an ILR was implanted. Patient, operator, and procedure characteristics are presented in Table 1. The majority of patients were males (66.6%) and the mean age at implantation was 68.1 ± 9.2 years. Most patients received a dual-chamber pacemaker (46.8%) and most procedures were performed by experienced operators (77.6%).

Table 1. Patient, operator, and procedure characteristics

Parameter		n	%	Ptx (n)
Male		665	66.6	10
Age		68.1 ± 9.2		73.4 ± 7.3
Chronic obstructive pulmonary disease		65	6.5	0
Device type	VVI	266	26.6	4
	DDD	468	46.8	10
	ICD-VR	80	8.0	1
	ICD-DR	16	1.6	1
	CRT-P	123	12.3	1
	CRT-D	22	2.2	1
	Lead revision	24	2.4	0
Operator experience	Experienced	775	77.6	13
	Not experienced	224	22.4	5
Intravenous contrast		49	4.9	3

ICD – implantable cardioverter-defibrillator; CRT – cardiac resynchronization therapy; Ptx – pneumothorax

In total, 618 atrial leads were implanted, dominantly by subclavian vein puncture, and 995 leads in the right ventricle, mainly by cephalic vein cut-down (Table 2). Venous access for all 146 leads for coronary sinus was with vein puncture, subclavian or axillary. In some patients, double cut-down of the cephalic vein was used to implant atrial and ventricle lead, and in some multiple punctures of the subclavian vein were required. The diagnosis of COPD was reached in 65 (6.5%) patients before implantation. During the procedure, for easier visualization of the axillary and subclavian vein, intravenous contrast injection in the peripheral arm vein was used in 49 (4.9%) patients.

In our study population, the incidence of pneumothorax was 1.8%. If we know that the total number of vein punctures, subclavian or axillary, is 957, than we can conclude that 1.9% of all punctures led to pneumothorax, as a procedure-related complication. Invasive treatment of pneumothorax was required in 13 (72.2%) patients, aspiration of free air was made in nine (50%) patients, and four (22.2%) patients were treated with a chest tube. There were no fatalities due to detected pneumothorax. In multiple logistic regression analysis we identified age > 75 years, female sex, venous access with subclavian vein puncture, and the use of intravenous contrast during procedure as risk factors for the occurrence of pneumothorax during the implantation of CRM devices (Table 3).

Table 2. Venous access technique in regard to the lead type

	VVI	DDD	ICD -VR	ICD -DR	CRT -P	CRT -D	Upgrade	LR	Total (%)	Venous access technique	n (%)	Ptx n
AL	0	465	0	14	111	20	3 VVI → DDD + 2 ICDVR → DR	3	618 (35.1)	Cephalic vein cut-down	202 (32.7)	0
										Subclavian vein puncture	362 (58.6)	7
										Axillary vein puncture	54 (8.7)	1
RVL	266	468	80	16	123	22	0	20	995 (56.6)	Cephalic vein cut-down	600 (60.3)	0
										Subclavian vein puncture	364 (36.6)	9
										Axillary vein puncture	31 (3.1)	0
CSL	0	0	0	0	123	22	0	1	146 (8.3)	Cephalic vein cut-down	0 (0.0)	0
										Subclavian vein puncture	137 (93.8)	1
										Axillary vein puncture	9 (6.2)	0

AL – atrial lead; RVL – right ventricle lead; CSL – coronary sinus lead; ICD – implantable cardioverter-defibrillator; CRT – cardiac resynchronization therapy; LR – lead revision; Ptx – pneumothorax

Table 3. Correlation between the patient, operator, and procedure characteristics with the occurrence of pneumothorax (dependent variable)

Predictor	B	p
Sex	-2.136	0.015
Age	4.315	0.001
VVI	16.479	0.998
DDD	19.712	0.998
ICD-VR	21.169	0.996
ICD-DR	21.614	0.998
CRT-P	18.136	0.997
CRT-D	23.464	0.998
COPD	-17.147	0.997
Operator experience	-0.485	0.650
Subclavian vein puncture	2.672	0.045
Axillary vein puncture	-0.646	0.606
Intravenous contrast	3.155	0.007

B – regression coefficient; ICD – implantable cardioverter-defibrillator; CRT – cardiac resynchronization therapy; COPD – chronic obstructive pulmonary disease

DISCUSSION

The incidence of pneumothorax as a procedure-related complication after CRM devices implantation in our sample was 1.8%. Previous studies have found an incidence varying 0.7–5.2% [3]. It is difficult to compare our results with findings of other studies, because many factors have an impact on this variation in the incidence of pneumothorax. When we examine the results of a study, it is important to analyze the study design, characteristics of study population, to consider differences in the surgical technique and clinical recognition of pneumothorax. In our observational retrospective one-year survey, population is large and widely selected. Our position is that the cephalic vein cut-down is preferred to subclavian vein puncture as venous access. Some operators in our center choose to implant two leads using cephalic vein, when diameter of the vein is sufficient. The puncturing of the axillary vein is routinely done at our center. We have not performed routine post-procedural chest X-ray, but our patients have been continuously monitored and every symptom that can indicate that pneumothorax has occurred, such as chest pain or respiratory distress, is followed by chest X-ray and then pulmonary examination. In a large, nationwide study performed in Denmark, based on the data in the Danish pacemaker register, the incidence of pneumothorax was 0.66% [4]. In this study, only patients with pneumothorax treated with a chest tube were abstracted. Also, patients with implanted ICDs were not investigated. In a study from 2006, Pakarinen et al. [1] found that the incidence of pneumothorax after CRM devices implantation was 1.9%. In this study, pre-discharge chest X-ray was routinely done and axillary vein puncture was preferred as venous access. The same incidence of pneumothorax was seen in a Dutch multicenter study from 2007 [5]. Bond et al. [2] enrolled 1,286 patients and found a pneumothorax rate of 3.7%. In this study, post-procedural chest X-ray was performed for all patients, the favored method of venous access was via the subclavian vein, procedures were done by 16 different operators with very differing levels of experience, and pneumothorax was managed conservatively in even more then 55% of patients [2].

This study confirms that patients older than 75 years have a higher risk of developing pneumothorax as a procedure-related complication. This finding is in accordance with previous studies [6]. In the Pacemaker Selection in the Elderly study, age of more than 75 years was associated with higher risk of pneumothorax, and in the Danish study, this complication was statistically more frequent in patient older than 80 years [4, 7].

In our study, pneumothorax was significantly more frequent in women. Some previous studies showed similar results. Peterson et al. [8] concluded that sex was an independent factor associated with adverse events, including pneumothorax, in patients receiving an ICD. Nowak et al. [9], in a study that included more than 17,000 patients, showed that women had significantly more frequent pneumothorax after a pacemaker implantation, regardless of the age and the implanted pacing system [9]. The same conclusion was made in the Danish study [4]. There are many possible explanations for this finding, from differences in anatomy, smaller body size, to hormonal differences and higher prevalence of comorbidities and risk factors in women.

We found that subclavian vein puncture is a procedure-related risk factor for the development of pneumothorax during the implantation of CRM devices. This finding is confirmed in many previous studies [3, 4, 10]. There are many advantages of puncturing the subclavian vein. Extensive skin and muscle dissection is not needed, the access to the subclavian vein is easy for an experienced operator and this vein can be used repeatedly [3, 11]. The most important drawbacks of this approach are increased incidence of intraoperative complications such as pneumothorax or bleeding, and chronic complications like lead damage (insulation damage or lead fracture) and venous thrombosis [3]. On the other hand, cephalic vein cut-down rarely leads to procedure-related complications, but for this approach, the operator should have better surgical technique; also, sometimes, the cephalic vein cannot be located or used [3]. The third method used for venous access is axillary vein puncture. This approach is not used often due to fear of pneumothorax, but for an experienced operator, who knows the regional anatomy well, this should be the method of choice [11, 12, 13]. Considering these facts, cephalic vein cut-down is preferred to subclavian or axillary vein puncture as the venous access in most medical centers, but whenever the cephalic vein cannot be found, or it is too small and thin, puncturing of the subclavian or the axillary vein must be done. In our center, cephalic vein cut-down is preferable to subclavian vein puncture as well, and the puncturing of the subclavian and the axillary vein is performed routinely by cardiologists and surgeons.

It is expected that the risk of pneumothorax is higher after the implantation of dual-chamber devices compared to single-chamber ones due to the higher probability of vein puncture; also pneumothorax is expected to be more common after implanting resynchronization pacemakers

than after implanting antibradycardia ones because during the implantation of a CRT device at least one vein puncture is needed [14, 15]. However, in our study, we did not find significant relations between the type of an implanted device and pneumothorax.

Although we expected that the incidence of pneumothorax will be higher in patients with COPD, our results are somewhat surprising [16]. Not only that we did not find a significant connection between COPD and pneumothorax, but none of our patients with COPD developed pneumothorax as a procedure-related complication. In the Danish study, COPD was a patient-related risk factor for this complication [4]. A possible explanation for our result is that the access via the cephalic vein was used in most patients with COPD, that intravenous contrast was routinely used, before the puncturing of the subclavian or the axillary vein in this subpopulation, and that our operators are quite experienced.

In our study, the incidence of pneumothorax was not lower in implantations performed by experienced doctors. This is not a surprising result, since trainees at our center work under the strict supervision of their mentors. Pakarinen et al. [1] found that pneumothorax was much more common in pacemaker implantations performed by trainees, but in the Danish study significant relations between pneumothorax and the experience of operators was not found [4].

At our center, when the cephalic vein cannot be located or used and the puncturing of the subclavian or the axillary vein is difficult, intravenous contrast injection in the peripheral arm vein is used. Contrast venography did not lead to a reduction in the frequency of pneumothorax in our study. On the contrary, we found that the use of intravenous contrast during the procedure is a risk factor for the development of pneumothorax. Possible explanation for this finding is the fact that operators at our center choose to give intravenous contrast after multiple unsuccessful punctures, when high risk of pneumothorax already exists. In other studies, the role of contrast venography in the reduction of incidence of pneumothorax was not tested.

CONCLUSION

Our observational retrospective one-year single-center survey shows that pneumothorax is a relatively rare complication of CRM devices implantation that often requires an intervention by a thoracic surgeon. We identified the following four variables as risk factors for this complication: age of more than 75 years, female sex, venous access with subclavian vein puncture, and the use of intravenous contrast during the procedure. According to these findings, for reducing the incidence of pneumothorax as a procedure-related complication, cephalic vein cut-down should be preferred to subclavian or axillary vein puncture as venous access; in cases of difficult vein puncture, contrast venography should be done immediately, before risky punctures; axillary vein puncture should not be avoided; and trainees should work under the strict supervision of their mentors.

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Пнеумоторакс као компликација уградње уређаја за регулисање срчаног ритма

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САЖЕТАК

Увод/Циљ Пнеумоторакс је једна од најчешћих компликација уградње уређаја за регулисање срчаног ритма.
Циљ рада је био да се утврди учесталост пнеумоторакса после уградње ових апарата и да се одреде фактори ризика за његов настанак.

Методе У ретроспективну, опсервациону студију укључени су болесници којима су током 2012. године уграђени ови уређаји, учињена надоградња пејсмејкер система или ревизија електроде. Користећи мултиплу логистичку регресиону анализу, испитали смо повезаност настанка пнеумоторакса и различитих варијабли: пол, старост, тип уграђеног апарата, присуство хроничне опструктивне болести плућа, искуство имплантера, венски приступ и интраоперативно коришћење интравенског контраста.

Резултати У студију је укључено 999 болесника, старости 68,1 ± 9,2, од којих је 665 (66,6%) било мушког пола. Учесталост пнеумоторакса је била 1,8%, а инвазивно лечење је било неопходно код 13 (72,2%) болесника. Пнеумоторакс је био чешћи код жена ($B = -2,136$, $p = 0,015$), болесника старијих од 75 година ($B = 4,315$, $p = 0,001$), када је као венски приступ коришћена пункција поткључне вене ($B = 2,672$, $p = 0,045$) и када је коришћено контрастно средство ($B = 3,155$, $p = 0,007$).

Закључак Пнеумоторакс је релативно ретка компликација уградње уређаја за регулисање срчаног ритма. За смањење његове учесталости треба као венски приступ препарисати цефаличну вену пре него пунктирати поткључну или пазушну вену. У случају отежане пункције контрастну венографију треба одмах урадити, пре ризичних пункција.

Кључне речи: пејсмејкер; пнеумоторакс; компликација; фактор ризика

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Minithoracotomy as the primary alternative for left ventricular lead implantation during cardiac resynchronization therapy – Can the cardiac surgeon reduce the number of nonresponders

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SUMMARY

Introduction/Objective Numerous anomalies of the cardiac venous system prevent the optimal endovascular implantation of the left ventricular (LV) lead in more than 15% of patients with indication for cardiac resynchronization therapy (CRT). The endovenous approach in these patients can be one of the potential reasons for the large number of nonresponders reported in the literature.
The purpose of this study was to analyze the results of an alternative myoepicardial approach to the stimulation of the left ventricle in CRT.

Methods From June 2014 to December 2015 at the Department of Cardiac Surgery of the Clinical Centre of Serbia, 15 myoepicardial LV leads for CRT were implanted. Coronary sinus venography revealed thrombosis of the coronary sinus in nine patients, and unfavorable anatomy of the coronary venous system in six patients. In all patients, limited left thoracotomy was used as an approach to the lateral wall of the heart.

Results There were no major surgical complications and no lethal hospital outcomes. In a six-month follow-up period we registered a significant increase in the length of the six-minute walk test (for an average of 57.9 m), reduction of the QRS complex width (to 26.25 ms), increase in left ventricular ejection fraction (12.2%), and reduction of mitral regurgitation for 1+. Based on all the parameters, it was concluded that all patients responded favorably to the applied CRT.

Conclusion Closer cooperation between cardiologists and cardiac surgeons in identifying patients who would benefit the most from a myoepicardial approach for LV stimulation is necessary in order to attempt to reduce the nonresponder rate.

Keywords: CRT; minithoracotomy; surgically placed LV leads

INTRODUCTION

Cardiac resynchronization therapy (CRT) restores the synchronicity of the atrioventricular, interventricular, and intraventricular contractions [1]. Comprehensive trials have shown that CRT improves symptoms of congestive heart failure, improves ejection fraction and survival, increases exercise tolerance, and decreases hospital readmission [2]. Today, widely used is the less invasive transvenous approach of placing the left ventricular (LV) lead via the coronary sinus (CS) [3, 4]. However, 30–40% of patients fail to show improvement in clinical symptoms or cardiac function, and are considered nonresponders to this method [5].

Favorable response to CRT depends mostly on positioning the LV pacing lead coincident with the lattermost activated areas of the left ventricle so as to achieve the maximum hemodynamic effect. Therefore, the optimal LV lead placement is one of the most important aspects of CRT implantation [6]. Restrictions to achieve the maximum response are related to unfavorable coronary sinus anatomy, non-optimal position of the LV pacing lead, high-myocardial scar burden, and unintended stimulation of the left phrenic nerve [7]. Several studies showed that not all CS tributaries give the same response to CRT, leading to the group of lateral or posterolateral wall of the left ventricle to be the most suitable. Limited availability of suitable tributaries due to thrombosis of CS or the unfavorable coronary venous anatomy are among crucial factors that lead to the lack of the optimal hemodynamic effect of CRT [8, 9].

As an alternative to endovenous placement of LV lead in these patients, a surgical approach via mini-thoracotomy, video-assisted thoracoscopy, or with robotic assistance, should be considered [10].

The purpose of this study was to analyze the results of a myoepicardial approach to the stimulation of the left ventricle in CRT.

METHODS

Patient selection

Patient selection criteria were standard indications for CRT implantation [11]: severe

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congestive heart failure rated as New York Heart Association (NYHA) class III or IV despite the optimized pharmacologic heart failure treatment; dilated ischemic or non-ischemic cardiomyopathy with left ventricular systolic dysfunction defined as left ventricle ejection fraction (LVEF) ≤ 35% and left ventricular end-diastolic diameter of ≥ 60 mm; and LBBB as reflected on the surface electrocardiogram by a QRS duration of ≥ 120 ms in spontaneous rhythm. The indiciation for the surgical approach was the failure of transvenous approach to LV lead implantation, as well as limited availability of suitable CS tributaries.

Operative course

Left-sided operative approach was used in all the patients. Right atrium and right ventricle leads were placed in standard pacing sites. The device pocket was made in the upper left pre-pectoral area. The thrombosis of CS and unfavorable CS anatomy were the main criteria for the failure of the transvenous approach for the LV lead implantation.

Immediately after the failed transvenous approach, the LV lead connector was temporarily protected with a cap and the operating site was secured, while the patient was transferred to the operating theatre of the Cardiac surgery department, located on the same level, for the myoepicardial LV lead implantation. The surgery was done under general endotracheal anesthesia with single right-lung ventilation, using a double lumen endotracheal tube, while standard invasive hemodynamics monitoring was performed. Left antero-lateral minithoracotomy through the fourth intercostal space was used to access the left ventricle wall. Next, the pericardium was partially opened for 2–3 cm anterior to the phrenic nerve while ensuring sufficient distance. The pericardium was then fixed with traction sutures to the skin, rotating the heart to the right and creating the optimal exposure to the LV lateral wall. The LV lead was then placed between the left anterior descendent branch of the left coronary artery and the obtuse margin branch of the circumflex artery. We used the 5-0 or 6-0 polyprolene to secure the steroid eluting epicardial lead to avoid the trauma of the heart.

After completing the threshold measurements, the connector of the lead was brought through the third intercostal space and tunneled submuscularly to the previously made device pocket and the device itself. Minithoractomy was then closed by a standard wound closure and a small pleural drain was inserted.

CRT response criteria and follow-up

We recorded QRS complex width, LVEF, six-minute walk test, mitral regurgitation grade, and NYHA class prior to the intervention and six months after. Also, all the patients were observed for complications during their hospital stay.

The patients who had significant enhancement of one or more observed hemodynamic parameters (NYHA class reduction by one grade or more, LVEF + > 5%) after six months, were designated as responders to the CRT therapy [11].

RESULTS

The study involved 15 patients with myoepicardial LV leads for CRT implanted at the Department of Cardiac Surgery of the Clinical Centre of Serbia between June 2014 and December 2015. The venography revealed the thrombosis of CS in nine patients and unfavorable CS anatomy (non-accessible lateral or posterolateral group) in six patients. The hemodynamic characteristics of our patients before the surgery and after six months are shown in Table 1. There were 10 patients in NYHA class III and five were in NYHA class IV before the surgery, while after six months there were no patients in NYHA class IV, six were in NYHA I, eight in NYHA II, and just one patient was in NYHA III. The QRS complex width has decreased by the mean of 26.5 ms after the surgery. Also, at six months follow-up an increase in LVEF was recorded by the mean of 12.2%.

In addition, the value of the six-minute walk test increased by the mean of 57.9 m. The grade of mitral regurgitation decreased by the mean of 1.13. During the hospital stay, we did not record any major surgical complications or lethal outcomes.

Table 1. Hemodynamic parameters before the surgery and after a six-month follow-up

Characteristics	Baseline	After six months
NYHA class (n)		
I	-	6
II	-	8
III	10	1
IV	5	-
QRS complex (ms) ($\bar{x}$ ± SD)	165.3 ± 10.5	138.8 ± 15.6
LVEF (%) ($\bar{x}$ ± SD)	25.1±5.8	37.3 ± 7.3
MR (grade) ($\bar{x}$ ± SD)	2.38 ± 0.9	1.25 ± 0.5
Six-minute walk test (m) ($\bar{x}$ ± SD)	273.4 ± 22	331.3 ± 17

LVEF – left ventricle ejection fraction; MR – mitral regurgitation; NYHA – New York Heart Association

DISCUSSION

To maximize the hemodynamic effect of CRT and the number of responders to it, the LV lead must be placed near the lattermost activated areas of the heart [9]. The lateral and the posterolateral groups of CS tributaries have proven to be the most suitable ones and have the largest number of responders to CRT via transvenous approach [8, 12]. In the InSync study, the optimal LV lead position was achieved in only 71% of patients [13, 14]. Also, in the Easytrack pre-CE Mark clinical trial [15], only 50% of the implanted LV leads were in the lateral group, while 36% were in the anterior group, which, according to Nägele et al. [8], should be avoided. Ailawadi et al. [16] showed even greater percentage of transvenous approach failure, due to the fact that their center accepts only implantation in

these CS tributary groups. The percentage of optimal LV lead position went up to 80% in a MUSTIC trial, which is similar to the results in one of our previous studies [17, 18]. The overall success rate of the transvenous approach ranges 88–92% [12, 17].

The surgical approach gives an alternative solution to the patients who cannot have the LV lead placed or the suitable tributaries group could not be reached by the transvenous approach. Shaw et al. [10] pointed out in their research that the major determinant for transvenous procedure failure is the inability to place the LV lead in an adequate location in the coronary venous system. The thrombosis of CS or the unsuitable CS anatomy that leads to inability to implant the LV lead in the optimal CS tributaries were the main reasons for the surgical approach in our study. In addition to this, the coronary sinus perforation and dissection, cardiac tamponade, ventricular arrhythmia, as well as the LV lead dislodgement, could also be the indications for the shift to the surgical approach [10]. The MIRACLE study showed that 8% of their patients had a failed transvenous approach due to technical failure, 6% due to CS perforation, and another 6% due to LV lead dislodgement [4].

In our study, we showed a significant improvement of all observed hemodynamic parameters of each patient, which showed that all of them responded to CRT. Similar results were presented by Puglisi et al. [19]. Mair et al. [20], as well as Puglisi et al. [19], also compared successful transvenous LV lead implantation in the optimal sites to the surgical approach. They showed similar results between these two groups in response to CRT. Mair et al. [20] even showed better long-term results in the thoracotomy group and emphasized the more stable threshold capture in the thoracotomy group.

During the postoperative follow up, we had no major surgical complications and no lethal outcomes, which is in concordance with the studies mentioned above. The result of mortality outcome appears favorable with no obvious excess occurrence during the follow up.

However, Ailawadi et al. [21] reported a higher tendency for developing kidney failure in the thoracotomy group. They also reported a higher number of urinary tract infections, which may be the result of a longer hospital stay that can be prolonged due to intubation and general anesthesia. We did not observe any of these complications in our study.

The thoracotomy approach gives a lower percentage of lead dislodgement due to a less traumatic fixation mechanism and steroid eluting lead tips vs. screw-in leads used in the transvenous approach. Procedure duration is similar, even favorably shorter in the thoracotomy approach. The absence of X-ray exposure is a great benefit for the patient as well as for his physician. Also, X-ray exposure during the prolonged transvenous approach may present an indication to conversion to thoracotomy. This approach gives a surgeon a clear and vast possibility to place the LV lead closest to the desired site on the LV wall.

Video-assisted thoracic surgery and robotic surgery provide another advantage to surgical approach, reducing the invasive nature of the thoracotomic procedure. Several studies have shown that they are an equal alternative regarding the hemodynamic effect [22, 23]. They have also shown no mortality or an increase in hospital stay or procedure duration. Jansen et al. [24] showed conversion to thoracotomy in less than 0.1% of patients due to adhesions of previous operations or bleeding.

CONCLUSION

The surgical approach showed a high percentage of responders to CRT and a high hemodynamic effect. In addition, low mortality and complications of this procedure emphasize that it cannot be used only in patients with transvenous approach failure due to technical issues or complications. This approach gives a clear advantage for LV lead placement in patients with non-accessible optimal CS tributaries. Closer cooperation between cardiologists and cardiac surgeons in identifying patients who would benefit the most from a myoepicardial approach for LV stimulation is necessary, in order to attempt to reduce the nonresponder rate.

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Миниторакотомија као примарна алтернатива за уградњу електрода за леву комору код срчане ресинхронизационе терапије – може ли кардиохирург смањити број нонреспондера

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САЖЕТАК

Увод/Циљ Бројне аномалије срчаног венског система спречавају оптималну ендоваскуларну имплантацију електрода за леву комору код више од 15% болесника са индикацијом за срчану ресинхронизациону терапију (CPT). Ендовенски приступ код ових болесника може бити један од могућих разлога великог броја нонреспондера пријављених у литератури. Циљ ове студије је да анализира резултате алтернативног миоепикардиалног приступа стимулације леве коморе у CPT.

Методе Од јуна 2014. до децембра 2015. године уграђено је петнаест миоепикардиалних електрода за CPT. Венографијом коронарног синуса откривена је тромбоза коронарног синуса код девет и неповољна анатомија коронарног венског система код шест болесника. Код свих болесника лева миниторакотомија је коришћена као хируршки приступ бочном зида срца.

Резултати Није било већих хируршких компликација ни интрахоспиталних смртних исхода. У периоду праћења од шест месеци регистровали смо значајно повећање у дужини теста хода од шест минута (у просеку 57,9 *m*), смањење *QRS* комплекса ширине (до 26,25 *msec*), повећање ејекционе фракције леве коморе (12,2%) и смањење митралне инсуфицијенције за 1+. На основу свих параметара закључено је да су сви болесници одговорили позитивно на примењену CPT.

Закључак Ближа сарадња између кардиолога и кардиохирурга у идентификацији група болесника је неопходна у покушају смањивања броја нонреспондера у CPT и групе болесника која би имала највише користи од овог приступа.

Кључне речи: CPT; миниторакотомија; хируршко постављање миоепикардијалних електрода

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Association of alpha-1 antitrypsin level and lung function in patients with chronic obstructive pulmonary disease

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SUMMARY

Introduction/Objective Alpha-1 antitrypsin deficiency is a well established inherited risk factor for chronic obstructive pulmonary disease (COPD); however, alpha-1 antitrypsin level may result in different lung function reduction.

The aim of our study was to evaluate possible associations of alpha-1 antitrypsin level and lung function in COPD patients with different alpha-1 antitrypsin phenotypes.

Methods Serum alpha-1 antitrypsin concentration from patients (n = 1,167) with COPD, defined according to the GOLD criteria, were analyzed by nephelometry, and alpha-1 antitrypsin phenotype was determined by means of isoelectric-focusing.

Results In COPD patients without alpha-1 antitrypsin deficiency (MM), a significant negative association of lung function (FEV_1) with serum alpha-1 antitrypsin ($r = -0.511$; $p < 0.05$) and C-reactive protein (CRP) concentrations ($r = -0.583$; $p < 0.05$) was detected; moreover, the level of alpha-1 antitrypsin positively correlated with CRP concentration ($r = 0.667$; $p < 0.05$).

Conclusions In patients without alpha-1 antitrypsin deficiency, detected negative association of alpha-1 antitrypsin level with FEV_1 and positive association with the CRP level defined the importance of alpha-1 antitrypsin for lung function in COPD patients.

Keywords: chronic obstructive pulmonary disease; alpha-1 antitrypsin; lung function

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent and costly disease characterized by a progressive airflow limitation, related to an abnormal inflammatory response of the lung to long-term tobacco smoke exposure or inhalation of toxic gases [1]. Lung inflammation is further amplified by oxidative stress and proteolytic damage by proteinases [2, 3]. There is increasing data of systemic inflammation in patients with COPD [4–7]. Thus, the changes of inflammatory markers can be evaluated in the lungs and in serum affecting gas diffusion and lung function [3, 4, 5].

The best described inherited risk factor for COPD is alpha-1 antitrypsin (AAT) deficiency. Primary AAT function is to inhibit neutrophil elastase [6, 7, 8]. In severe AAT deficiency, anti-elastase protection in the lung interstitium and alveolar zone is decreased to about 15–20% of normal limits, similar to the decrease in serum levels [9–12]. The majority of AAT deficiency cases (96%) have a PI*ZZ phenotype. The remaining cases belong to PI*SZ, PI*MZ, and other especially rare deficiency phenotypes [9]. AAT is a rare disorder because it is underdiagnosed worldwide; more than 80% of AAT deficiency patients remain unrecognized [10].

The potential role of systemic inflammation in the pathogenesis of lung function decline in COPD patients with different AAT phenotypes has not yet been well established.

The aim of our study was to evaluate possible associations of AAT level and lung function parameters in patients with COPD with different AAT phenotypes.

METHODS

Sample sources and subject selection

The study content was approved by the Lithuanian Bioethics Committee. A total of 1,167 patients with COPD, who gave their informed consent, were included in the study at the Department of Pulmonology and Immunology, Medical Academy, LUHS.

Only patients who met the GOLD spirometric criteria for COPD: 1) ratio of post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) less than 0.7, and 2) FEV_1 less than 80% of the predicted

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value – were included in the study [1]. Patients with chronic or acute inflammation were excluded from the study. After an appropriate physical examination, data on the symptoms of the patient and the diagnosis of COPD was also collected. Smoking history was also calculated in pack-years as the product of tobacco use (in years) and the average number of cigarettes smoked per day / 20 (years × cig. per day / 20).

Sample collection and evaluation

Blood samples were taken in serum tubes, clotted at normal room temperature for 35–65 minutes and centrifuged for 15 minutes at 4,000 rpm. Then, the samples were frozen at -70°C for further analysis. The serum levels of AAT were determined by nephelometry using commercial kits (Dade Behring Marburg GmbH, Marburg, Germany) according to the manufacturer instructions. AAT phenotyping was carried out by means of isoelectric focusing (LKB Multiphor II and LKB Macrodrive 5 Constant Power Supply, Amersham Pharmacia Biotech, Piscataway, NJ, USA), as previously described [13]. The analysis of C-reactive protein (CRP) in serum was done using standard assays (IBL International GmbH, Hamburg, Germany).

Statistical analysis

Descriptive statistics were used to tabulate the primary cohort database. Quantitative variables were expressed as means with standard deviations. Differences of quantitative data were assessed by the Kruskal–Wallis H-test. Correlations between variables were determined by the Spearman correlation test. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic descriptions of studied 1,167 COPD patients are shown in Table 1. Eighty-two percent of the patients were current (57%) or former (25%) smokers of 22.1 ± 12.2 pack-years, and 18% never smoked.

Phenotype distribution was as follows: 1,076 (92.2%) PI*MM, 40 (3.4%) PI*MZ, 39 (3.3%) PI*MS, 1 (0.1%) PI*SS, 3 (0.3%) PI*SZ, and 8 (0.7%) PI*ZZ.

The mean AAT serum level (g/l) was of 1.58 ± 0.43. As expected, we found significant differences in AAT serum concentrations between groups ($p < 0.05$) (Figure 1). The PI*ZZ group showed a markedly lower AAT blood level (0.40 ± 0.34) relative to the other AAT phenotype groups.

While analyzing lung function, the patients with AAT deficiency (PI*ZZ, PI*SZ, PI*SS) were grouped into one group. These individuals with severe AAT deficiency showed poorer spirometric FEV_1 (46 ± 20; $p < 0.05$) and FEV1/FVC (48 ± 16; $p < 0.05$) values than PI*MM, PI*MS, and PI*MZ patients (Table 2).

We found a statistically significant negative correlation between the AAT concentration and the FEV_1% predicted

Table 1. General data of study individuals

Variable	Values*
Age (years)	64 ± 12
Male/female	834 (71) / 333 (29)
Smoking status	
Smokers	660 (57)
Ex-smokers	294 (25)
Never-smokers	213 (18)

*Data are presented as n (%) or mean ± SD

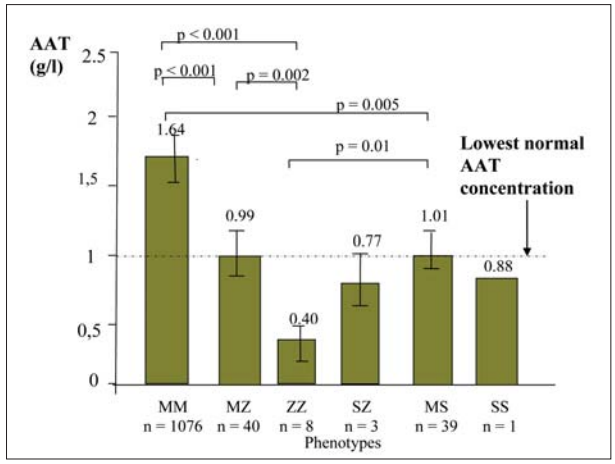

Figure 1. Serum alpha-1 antitrypsin (AAT) concentration in COPD patients with different AAT phenotypes

Table 2. Expresion of lung function and C-reactive protein (CRP) concentration in chronic obstructive pulmonary disease (COPD) patients with different alpha-1 antitrypsin phenotypes

Variable	MM n = 1,076	MS n = 39	MZ n = 40	SS, SZ, ZZ n = 12
FVC (% predicted normal)	74 ± 19	75 ± 15	73 ± 15	75 ± 17
FEV_1 (% predicted normal)	48 ± 17	51 ± 16	52 ± 18	46 ± 20
FEV_1/FVC (%)	54 ± 11	56 ± 11	57 ± 12	48 ± 16
CRP (mg/L)	9.6 ± 0.7	10.2 ± 0.8	11.3 ± 1.2	9.3 ± 1.5
COPD stage				
I	32 (3)	2 (5)	-	1 (8)
II	538 (50)	21 (54)	22 (55)	3 (25)
III	433 (40)	12 (31)	14 (35)	5 (42)
IV	73 (7)	4 (10)	4 (10)	3 (25)

Data are presented as n (%) or mean ± SD

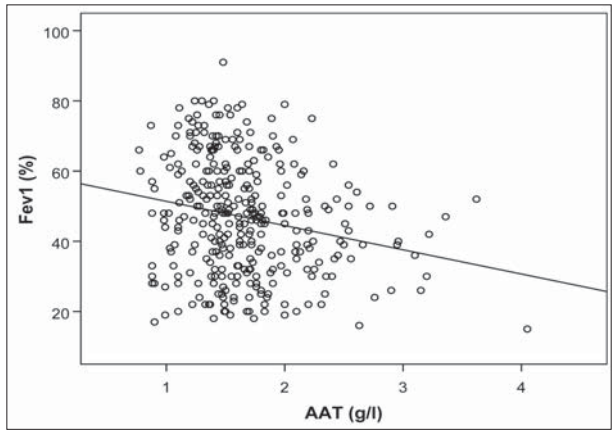

Figure 2. The correlation between the AAT concentration and FEV_1 in COPD patients without AAT deficiency (Spearman correlation coeficient)

Table 3. The correlation between the alpha-1 antitrypsin concentration and FEV_1 in chronic obstructive pulmonary disease patients without alpha-1 antitrypsin deficiency according to smoking status and sex

Patient group	n	r	Gender	n	r
Smokers	617	-0.511 ($p < 0.05$)	Male	415	-0.407 ($p < 0.05$)
			Female	202	-0.332 ($p < 0.05$)
Ex-smokers	249	-0.403 ($p < 0.05$)	Male	179	-0.398 ($p < 0.05$)
			Female	70	-0.178 ($p > 0.05$)
Never-smokers	210	-0.211 ($p > 0.05$)	Male	160	-0.166 ($p > 0.05$)
			Female	50	-0.152 ($p > 0.05$)

r – Spearman correlation coeficient

value in PI*MM phenotype ($r = -0.511$; $p < 0.05$) (Figure 2). While analyzing correlation between AAT concentration and FEV_1 in COPD patients according to smoking status and sex, we observed an inverse correlation in smokers and ex-smokers, but not in non-smokers. In males, this correlation was stronger than in females (Table3). Patients with elevated CRP were excluded from calculations. In addition, we detected that inverse correlations between CRP and FEV_1 have also been shown in COPD patients with the PI*MM phenotype ($r = -0.583$; $p < 0.05$). However, we didn't find such a correlation in COPD patients with AAT deficiency. In patients without the AAT deficiency, a significant positive association of blood AAT and CRP levels was detected ($r = 0.667$; $p < 0.05$).

DISCUSSION

The importance of the presented data is that circulating AAT inversely correlated with FEV_1 in COPD cases without the AAT deficiency. Such relationship had also been shown with healthy individuals [14, 15]. SAPALDIA project investigated associations of circulating AAT level with lung function in the general population and detected a negative correlation of serum AAT concentration with FEV_1 [14]. The amount of AAT that passively diffuses from the serum to the lung increases during an inflammation, which may be present in COPD [16]. This may indicate the increased need of AAT production to meet requirements of overcoming the release of various endogenous enzymes from inflammatory cells in the lungs, but its protective function may be overrun by the high level of secreted proteases [17]. However other studies have not found such a relationship between the serum AAT level and FEV_1% predicted value in COPD patients [18]. Possibly many other mechanisms might also be important for the pulmonary function, and not only for the inflammatory response.

Detected low AAT level in the PI*ZZ phenotype and the FEV_1 AAT ratio association may reflect a dual role of the AAT molecule as a pulmonary disease marker. The impact of AAT on pulmonary function seems to be a conclusion of context-dependent (i.e. AAT phenotype) and contrasting protective and proinflammatory effects in lung lining. On the one hand, elevated blood AAT level can show a beneficial shift in the antiprotease–protease balance, the center piece of the pathophysiological mechanism mediating the effect of most severe AAT deficiency on COPD. On the other hand, elevated blood AAT can also reflect low-grade inflammatory reaction in the lung [19, 20]. Significantly higher AAT concentration was even reported for AAT deficient (PI*ZZ) patients with COPD compared to PI*ZZ patients without COPD, further supporting the hypothesis that AAT concentration may also reflect an ongoing proinflammatory reaction [21]. Thus, our results support the hypothesis that the reduction of lung function may be a consequence of the presence of inflammatory stimuli.

Consistent with these findings, we could show a positive relationship between the AAT and CRP levels. High serum CRP concentrations in severe COPD individuals have been reported in other studies [5, 13, 14, 22]. Gan et al. [22] were the first to emphasize the importance of high CRP levels in COPD patients, showing the inflammatory process in even stable disease cases. Both CRP and AAT are acute-phase proteins. Several studies found CRP and AAT elevation in COPD patients, indicating that the inflammatory process is present in pathogenesis of the disease [5, 7, 21, 22, 23]. In addition, we find inverse correlations between CRP and FEV_1. Even in healthy individuals, an elevation of the CRP concentration over time was connected with a steeper FEV_1 decline [23, 24]. In these studies, FEV_1 was also inversely associated with blood CRP level. CRP reflects total systemic inflammation in many diseases and has been shown to upregulate the production of inflammatory cytokines [7]. The reasons for the inverse association between reduced lung function and systemic inflammation are not fully understood, but several mechanisms may be involved. Firstly, reduced pulmonary function may be responsible for the observed systemic inflammatory process. Inflammatory pulmonary epithelial cells have been shown to express small amounts of CRP and IL-6 [20, 25, 26]. Hence, the persistence of a systemic inflammatory process may result in damage to the airways, promoting the decline in FEV_1 in COPD patients. The data show that AAT has an immunomodulating capacity and acute increase in AAT level during various infectious and inflammatory states may enhance the magnitude of proinflammatory cells' reaction to endotoxic materials and subsequently accelerate the resolution of the inflammatory process.

CONCLUSION

We found that in patients without AAT deficiency, detected negative association of AAT level with FEV_1 and positive association with CRP level defined the importance of AAT as a biomarker of systemic inflammation for lung function in COPD. However, associations are complex and understanding the reactions of various mediators will require appropriately designed further studies.

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Повезаност нивоа алфа-1 антитрипсина и плућне функције код болесника са хроничном опструктивном болешћу плућа

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САЖЕТАК

Увод/Циљ Недостатак алфа-1 антитрипсина је добро познат наслеђен фактор ризика за хроничну опструктивну болест плућа (ХОБП). Међутим, низак ниво алфа-1 антитрипсина може узроковати различита смањења плућних функција.

Циљ нашег рада био је да се процени могућа повезаност нивоа алфа-1 антитрипсина и плућне функције код болесника с ХОБП са разним фенотипама алфа-1 антитрипсина.

Методе Концентрација серумског алфа-1 антитрипсина код болесника са ХОБП (n = 1167) у складу с критеријумима *GOLD* анализирана је коришћењем нефилометрије, а фенотип алфа-1 антитрипсина одређен је изолелекричним фокусирањем.

Резултати Код ХОБП болесника без недостатка алфа-1 антитрипсина (ММ) пронађена је значајна негативна повезаност плућне функције (FEV_1) са серумом алфа-1 антитрипсина (r =- 0,511, $p < 0,05$) и концентрацијом ЦРП (r = -0,583, $p < 0,05$); осим тога, ниво алфа-1 био је у позитивној повезаности са концентрацијом ЦРП (r = 0,667, $p < 0,05$).

Закључак Код ХОБП болесника без недостатка алфа-1 антитрипсина пронађена је значајна негативна повезаност са FEV_1 и позитивна повезаност са нивоом ЦРП доказала је значај алфа-1 антитрипсина као показатеља системске инфламације.

Кључне речи: хронична опструктивна болест плућа; алфа-1 антитрипсин; функција плућа

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Hand functions in type 1 and type 2 diabetes mellitus

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SUMMARY

Introduction/Objective Hand functions have an enormous impact on activities of daily living in patients with diabetes mellitus (DM), such as self-care, administering insulin injections, and preparing and eating meals.

The aim of the study was to evaluate hand functions and grip strength in patients with type 1 and type 2 DM.

Methods This was an observational case-control study investigating the hand functions and grip strength in patients with type 1 and type 2 DM. The study comprised 41 patients with type 1 DM aged 25–50 years sex- and age-matched, 40 non-diabetic controls, and 91 patients with type 2 DM aged 40–65 years sex- and age-matched 60 non-diabetic controls. Patients with documented history of diabetic sensorimotor neuropathy and adhesive capsulitis were excluded. The Duruoz Hand Index was used to assess the functional hand disability. Grip strength was tested with a calibrated Jamar dynamometer.

Results The Duruoz Hand Index scores in patients with type 2 DM were significantly higher than in persons in the control group ($p < 0.01$), but there was no significant difference between the type 1 DM and the control group ($p > 0.05$). Grip strength values of patients with type 1 DM were significantly lower compared to those in the control group ($p < 0.05$), whereas there was no significant difference between patients with type 2 DM and their control group. There was a negatively significant correlation between grip strength and the Duruoz Hand Index scores in patients with both type 1 and type 2 DM ($p < 0.05$).

Conclusion Patients with type 1 DM and type 2 DM have different degrees of hand disability as compared to healthy control groups.

Keywords: hand function; diabetes mellitus; grip strength

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic condition characterized by persistent hyperglycemia with resultant morbidity and mortality related primarily to its associated microvascular and macrovascular complications. DM is the leading cause of end-stage renal disease, adult vision loss, and non-traumatic limb amputations due to its classic micro- and macrovascular complications [1, 2]. In addition to these "classic" complications, patients with diabetes have a variety of musculoskeletal manifestations which cause disability and morbidity [1]. Diffuse idiopathic skeletal hyperostosis, osteoarthritis, osteoporosis, neuropathic arthropathy, calcium pyrophosphate dihydrate deposition disease, adhesive capsulitis, Dupuytren's disease, and carpal tunnel syndrome are frequently seen disorders. Musculoskeletal complications have been reported in about 36–75% of diabetic patients [3–7].

Moreover, patients with diabetes have reported to be more disabled in self-care tasks and housework than the non-diabetic ones, but there is less attention to upper extremity problems [8, 9]. These problems may be left unrecognized and untreated due to increased attention to other systems affected by diabetes.

Raje et al. [10] showed that patients with diabetes had higher symptom scores for hand and shoulder symptoms compared with control subjects. Mustafa et al. [11] conducted a cross-sectional study on 1,000 patients with type 2 DM. They found that 695 patients (69.5%) have had some sort of hand disorder.

Studies started to investigate grip strength as a further complication of diabetes affecting the hands. Grip and key pinch strength have been found to be lower in the hands of type 2 diabetics compared to the non-diabetic controls [9, 12]. The effect of the reduced hand strength on hand functional disability had also not been clearly demonstrated before. Occupational performance such as frequent daily measurements of blood glucose in patients with DM is very crucial.

We aimed to evaluate the hand strength and functional disability in patients with type 1 and type 2 DM.

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METHODS

This is an observational case-control study in which 41 patients with type 1 DM aged 25–50 years (18 female, 23 male) and sex- and age-matched 40 non-diabetic controls (19 female, 21 male), as well as 91 patients with type 2 DM aged 40–65 years (65 female, 26 male) and sex- and age-matched 60 non-diabetic controls (43 female, 17 male) were recruited from a clinic for diabetes of an education and research hospital. Non-diabetic controls were recruited from the relatives of the included patients, be it their spouses, parents, etc. The criteria for the inclusion into the study were as follows: the patients had diabetes, had no documented history of diabetic sensorimotor neuropathy nor adhesive capsulitis. The control subjects had no diagnosis of diabetes, pre-diabetes, or glucose intolerance, no documented history of trauma, cervical radiculopathy, nor any hand-related pain in the previous 12 months.

Body mass index (BMI) was calculated by using the formula of weight (kg) / height (m^2). The following three BMI categories were created: less than 25 kg/m^2, 25 to 29.9 kg/m^2, and 30 kg/m^2 or more [13]. Waist circumference was measured according to the International Diabetes Federation. Central obesity was defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women [14].

HbA1c, smoking habits, diabetes duration, and subjects who exercise regularly were noted parameters.

The Duruoz Hand Index (DHI) or Hand Function Disability Scale (HFDS) or Cochin Scale developed by Duruoz et al. [15] was used to assess the functional hand disability. It is a self-reported questionnaire developed to assess the hand ability in the kitchen, while performing personal hygiene, office tasks, during dressing and other general items. DHI consists of 18 questions that assess functional disability and handicap of the hand. Each answer is scored on a scale from 0 (no difficulty) to 5 (impossible to do). Scores from each of the five categories are summed to yield a total score range from 0 to 90. A higher score indicated poorer hand function [15]. It is also a reliable instrument for the assessment of hand functional disability in type 2 diabetes patients [16].

Grip strength was tested with a calibrated Jamar dynamometer (Smith & Nephew plc., London, UK). For each test of grip strength, the standard test position approved by the American Society of Hand Therapists was used [17, 18]. This testing position is described as sitting in a straight-backed chair with feet flat on the ground, the shoulder adducted and neutrally rotated, the elbow flexed at 90°, the forearm in a neutral position, and the wrist between 0° and 30° extension, and between 0° and 15° ulnar deviation. In all cases, the arm should not be supported by the examiner or by an armrest. The dynamometer is presented vertically and in line with the forearm to maintain the standard forearm and wrist positions. For each strength test the scores of three successive trials were recorded and the mean of three scores was used. Both dominant and non-dominant hands were tested.

Informed consent was obtained, and all procedures were conducted in accordance with the Helsinki Declaration of 1975 and approved by the local institutional clinical research ethical committee.

Statistics

Results were given as mean ± standard deviation (SD) and range. The χ^2 test was done to compare the categorical demographic variables, while Student's t-test was used for the intergroup comparisons of parameters with normal distribution, and Mann–Whitney U-test was used for the intergroup comparisons of parameters without normal distribution. Spearman correlation analysis in non-parametric variables was used to express the strength of the association between two variables. Linear regression analyses was used for multivariate analyses. A p-value of < 0.05 was taken as statistically significant. Statistical analysis was performed using NCSS 2007 and PASS 2008 Statistical Software (NCSS, LLC, Kaysville, UT, USA).

RESULTS

The characteristics of the study population are given in Table 1. Patients with type 2 DM were older, had higher BMI and waist circumference, and did less exercise than patients with type 1 DM, as expected.

Twenty (48.8%) patients with type 1 DM had diabetes for a period of time shorter than 10 years, and 21 (51.2%) patients had it for more than 10 years. Seventy-one (78.0%) patients with type 2 DM had it for less than 10 years, and 20 (22%) patients for more than 10 years. Six (15%) patients with type 1 DM had HbA1c < 6.5, and 34 (85%) had HbA1c > 6.5. Twenty-one (23.1%) patients with type 2 DM had HbA1c < 6.5, and 70 (76.9%) had HbA1c > 6.5 (Table 2).

The mean DHI scores of all groups and correlations between the groups are given in Table 3. DHI scores were significantly lower in patients with type1 DM than in type 2 DM patients ($p < 0.01$). Based on the DHI scores, there was no significant difference between the type 1 DM and the control group ($p > 0.05$). DHI scores in patients with type 2 DM were significantly higher than their control group ($p < 0.01$). There was no statistically significant correlation between the DHI scores and the duration of diabetes in patients with either type 1 or type 2 DM ($p > 0.05$). Also, there was no statistically significant correlation between the DHI scores and HgA1c levels in patients with either type or type 2 DM ($p > 0.05$).

Grip strength values are shown in Table 3. There was no statistically significant difference between grip strength values of the dominant and the non-dominant hand in either group. Dominant grip strength was used for statistical correlations. Based on the grip strength values, there was a significant difference between patients with type 1 DM and their control group ($p < 0.05$), whereas there was no significant difference between patients with type 2 DM and their control group. Patients with type 1 DM have significantly higher grip strength values than patients with type 2 DM ($p < 0.01$). There was a negatively significant correlation between the hand grip strength values of

Table 1. The characteristics of the study population

Variable		Type 1 DM (n = 41)	Control 1 (n = 40)	p	Type 2 DM (n = 91)	Control 2 (n = 60)	p
Age (years) (Mean ± SD)		37.80 ± 9.19	36.20 ± 6.58	0.371	53.27 ± 7.57	53.23 ± 5.45	0.972
Sex n (%)	Male	23 (56.1%)	21 (52.5%)	0.919	26 (28.6%)	17 (28.3%)	0.975
	Female	18 (43.9%)	19 (47.5%)		65 (71.4%)	43 (71.7%)	
BMI	Mean ± SD	25.58 ± 4.1	26.26 ± 4.71	0.491	30.30 ± 4.54	29.24 ± 4.66	0.167
	< 25	21 (51.2%)	19 (47.5%)	0.595	8 (8.8%)	9 (15.0%)	0.385
	25–30	16 (39%)	14 (35%)		37 (40.7%)	26 (43.3%)	
	> 30	4 (9.8%)	7 (17.5%)		46 (50.5%)	25 (41.7%)	
Waist circumference	Female: > 80 Male: > 94	8 (19.5%)	21 (52.5%)	0.002	78 (85.7%)	50 (83.3%)	0.867
	Female: < 80 Male: < 94	33 (80.5%)	19 (47.5%)		13 (14.3%)	10 (16.7%)	
Exercise	Never	24 (58.5%)	25 (62.5%)	0.933	67 (73.6%)	44 (73.3%)	0.410
	Non-regular	10 (24.4%)	9 (22.5%)		13 (14.3%)	12 (20.2%)	
	Regular	7 (17.1%)	6 (15%)		11 (12.1%)	4 (6.7%)	

BMI – body mass index

Table 2. HgA1c levels and the duration of diabetes mellitus (DM) in patients with type 1 and type 2 DM

Variable		Type 1 DM (n = 41) n (%)	Type 2 DM (n = 91) n (%)
HgA1c levels	< 6.5	6 (15%)	21 (32.1%)
	> 6.5	34 (85%)	70 (76.9%)
Duration of DM (years)	< 10	20 (48.8%)	71 (78%)
	> 10	21 (51.2%)	20 (22%)

dominant and non-dominant hands and the HgA1c levels in patients with type 1 DM ($p < 0.01$), whereas there was no significant correlation in patients with type 2 DM. There was no statistically significant correlation between the hand grip strength values and the duration of diabetes in patients with either type 1 or type 2 DM ($p > 0.05$).

Based on the exercise status, there was no significant correlation between the grip strength values and the DHI scores.

Results of the linear regression analysis are summarized in Table 4. Increased risk for poorer hand function was significantly associated only with female sex in patients with type 1 DM ($p < 0.05$).

DISCUSSION

The hand has a critical function in daily activities and may have an enormous impact on activities of daily living in patients with DM, such as frequent daily measurements of blood glucose. Studies investigating hand functions and grip strength in patients with DM yielded conflicting results. We assessed the hand function and grip strength in patients with type 1 and type 2 DM.

In our study, DHI scores in patients with type 2 DM were significantly higher than in persons in their control group, but there was no significant difference between the patients with type 1 DM and their control group. On the other hand, based on the grip strength values, there was no significant difference between the patients with type 2 DM and their control group, but there was a significant difference between the patients with type 1 DM and their control group.

Pfützner et al. [19] evaluated the dexterity in insulin-treated patients with type 1 and type 2 DM. The results showed that reduced dexterity skills were common in type 1 and type 2 DM patients, but type 1 DM patients and non-diabetic controls performed similarly in the dexterity tests. In this respect, the fact that type 1 DM patients and their controls had similar hand functions is not an interesting result of our study.

Casanova et al. [20] measured hand functions of patients with diabetes. Fifteen diabetes patients with a median age of 48 years, all having used insulin for a minimum of five years, were randomly selected from diabetes clinics. The Purdue Pegboard, O'Connor Tweezer Dexterity, and Smith Hand-Function tests were used. Hand functions were significantly decreased in the group with diabetes, and the decrease was out of proportion to patients' own subjective pretest assessments. These authors noted that diabetes patients' perception of their hand function appears to be much better than their real performance because of the insidious onset of the problem and gradual adaptation [20].

Table 3. DHI and grip strength values of all groups

	Type 1 DM (n = 41) Mean ± SD	Control 1 (n = 40) Mean ± SD	p	Type 2 DM (n = 91) Mean ± SD	Control 2 (n = 60) Mean ± SD	p
Duruoz Hand Index	0.97 ± 3.51	1.09 ± 3.26	0.874	3.74 ± 6.88	1.06 ± 3.2	0.005
Dominant hand grip strength (kg)	30.92 ± 12.03	36.79 ± 12.06	0.031	24.93 ± 10.72	25.73 ± 10.89	0.658
Non-dominant hand grip strength (kg)	30.30 ± 12.44	36.33 ± 12.38	0.032	24.58 ± 10.98	26.67 ± 10.71	0.250

DM – diabetes mellitus

Table 4. Linear regression analyses

Variable	Type 1 DM		Type 2 DM	
	B	p	B	p
Sex	3.9	0.002	1.260	0.623
Age	0.093	0.079	0.083	0.419
Exercise	-0.136	0.849	0.041	0.969
BMI	-0.027	0.882	-0.057	0.816
Duration of DM	0.089	0.289	0.127	0.327
HbA1c levels	0.046	0.846	-0.072	0.815
Waist circumference	0.084	0.281	0.124	0.242
Dominant hand grip strength	-0.032	0.587	-0.182	0.089

DM – diabetes mellitus; B – regression coefficient $p < 0.05$

De Carvalho e Silva et al. [21] studied the hand strength and functions in type 2 DM patients. They found that patients with type 2 DM have an impairment of hand functions and grip strength. Also, Savas et al. [9] and Cetinus et al. [12] found that grip strength values were lower in patients with type 2 DM than in the age-matched control subjects. However, based on the grip strength values, we found no statistically significant difference between the patients with type 2 DM and their control group. This conflicting result may be due to the shorter DM duration in patients with type 2 DM in our study.

It had been reported that hyperglycemia can affect contractile function and force generation in animal models [22]. In our study, there was a negatively significant correlation between the hand grip strength and HgA1c levels in patients with type 1 DM ($p < 0.01$), whereas there was no such significant correlation in patients with type 2 DM. When we take into account that musculoskeletal abnormalities may result from a prolonged disturbance of the glucose metabolism, 78% of type 2 DM patients in our study had diabetes for a period of time shorter than 10 years.

Lewko et al. [23] investigated the effects of poor hand functions in diabetes. They found that impaired hand function affects lower acceptance of the disease, the occurrence of depression, and reduces the patients' quality of life. Hence, the assessment of hand function is important.

CONCLUSION

Our findings reveal that hand functions are impaired in patients with type 2 DM, and grip strength values are decreased in patients with type 1 DM. Thus, type 1 and type 2 DM have different degrees of hand disability. It is important to assess hand functions to help patients with DM in daily activities.

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Функција шаке код болесника са шећерном болешћу типа 1 и типа 2

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САЖЕТАК

Увод/Циљ Функција шаке има велики значај у свакодневном животу дијабетичара у стањима као што су брига о себи, давање инсулина, припрема оброка и исхрана.
Циљ рада је био да оцени функције шаке и снаге стиска код оболелих од дијабетеса типа 1 и 2.

Методе Рад представља опсервациону студију случајева са групама усклађеним по полу и старости: 41 болесник са типом 1 дијабетеса (старости 25–50 година) са контролном групом од 40 здравих, и 91 болесник са дијабетесом типа 2 (старости 40–65 година) и контролном групом од 60 здравих особа. Болесници са дијабетичном неуропатијом и адхезивним синовитисом нису укључени у ово истраживање. За оцену функционалних могућности шаке коришћен је Дуруозов индекс шаке. Снага стиска тестирана је динамометром *Jamar*.

Резултати Дуруозов индекс шаке код оболелих од дијабетеса типа 2 у односу на контролну групу био је високо статистички значајан ($p < 0,01$), а није било значајне разлике између оболелих од дијабетеса типа 1 и контролне групе. Снага стиска код болесника са дијабетесом типа 1 у односу на контролну групу био је статистички значајан ($p < 0,05$), а није било значајне разлике између оболелих од дијабетеса типа 2 и њихове контролне групе. Пронађена је битна негативна корелација између снаге стиска и скора Дуруозовог индекса шаке код оболелих од дијабетеса типа 1 и типа 2 ($p < 0,05$).

Закључак Болесници са дијабетесом типа 1 и типа 2 имају различит степен неспособности шаке у односу на здраве особе у контролним групама.

Кључне речи: функција шаке, шећерни дијабетес, снага стиска шаке

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Skin tags associated with obesity and diabetes mellitus in patients with chronic kidney disease

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SUMMARY

Introduction/Objective Both chronic kidney disease and skin tags are associated with similar cardiovascular risk factors such as obesity, diabetes mellitus, dyslipidemia, hypertension, etc.
The aim of this study was to determine the prevalence of skin tags in patients with chronic kidney disease, and to assess the relationship between skin tags and cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, obesity, and metabolic syndrome.

Methods We evaluated 358 patients [149 (41.6%) female and 209 (58.1%) male, 197 (55%) predialytic and 161 (45%) dialytic] with chronic kidney disease. All the patients were examined for skin tags by the same clinician, and evaluated for body mass index, diabetes mellitus, hypertension, and dyslipidemia.

Results Skin tags were detected in 199 (55%) patients. Prevalence of skin tags was higher in males than in females ($p = 0.041$) and was also higher in diabetic patients than in nondiabetic ones ($p = 0.013$). Body mass index was higher in patients with skin tags when compared to patients without skin tags ($p = 0.047$). Skin tags were detected in 48.3% of normal, in 58% of overweight, and in 66% of obese patients ($p = 0.029$).

Conclusion The presence of skin tags is merely related to male sex, obesity, and diabetes mellitus in patients with chronic kidney disease.

Keywords: skin tags; obesity; diabetes mellitus; chronic kidney disease

INTRODUCTION

Chronic kidney disease (CKD) is a growing health problem worldwide that leads to end-stage kidney failure and cardiovascular complications [1]. CKD is defined as kidney damage and/or decreased kidney function expressed as glomerular filtration rate (GFR) for at least three months, regardless of the cause. CKD is classified into five stages based on the severity of the disease [2, 3]. The overall prevalence of CKD is 15.7% in Turkey. In addition, the prevalence rate of dyslipidemia is 83.4%, of hypertension 56.3%, of metabolic syndrome 46%, of obesity 29.2%, and of diabetes mellitus the prevalence is 26.6% in subjects with CKD in our country [4].

Skin tags are stalked or sessile papules the size of a pinhead or larger, with a color ranging from native skin to dark brown. They have been reported with an incidence of 46% in the general population [5]. Although the etiology is unknown, skin aging, obesity, diabetes mellitus, pregnancy, acromegaly, and genetic predisposition are thought to be associated with skin tags [5–12]. There are some studies showing associations between skin tags and diabetes mellitus, impaired glucose tolerance, insulin resistance, and disorders of lipid metabolism [8, 10–13]. In addition, skin tags are one of the independent predictors of the occurrence of cardiac disease [14].

As mentioned above, both CKD and skin tags are associated with similar cardiovascular disease (CVD) risk factors such as obesity, diabetes mellitus, dyslipidemia, hypertension, etc. Although there have been some reports that the presence of skin tags is associated with diabetes mellitus, hypertension, obesity, and atherogenic lipid profile, no data in the literature show the presence of skin tags in patients with CKD [5, 8, 10–13, 15].

The aim of this study was to determine the prevalence of skin tags in patients with CKD, and to assess the relationship between skin tags and other cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, obesity, and metabolic syndrome.

METHODS

We evaluated 358 patients [149 (41.6%) female and 209 (58.1%) male, 197 (55%) on predialysis and 161 (45%) on dialysis] with CKD. All the patients were examined by the same physician. Information on smoking habits was recorded.

All the patients were evaluated for blood pressure, body mass index, creatinine, lipids, glucose, glycated hemoglobin (HbA1c). Samples

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for plasma glucose, creatinine, HbA1c, and lipid level determinations were taken in the morning after at least an eight-hour fast. Fasting glucose levels were measured by enzymatic colorimetric assay method (GLU, Roche Diagnostics GmbH, Mannheim, Germany). Fasting cholesterol and triglyceride levels were measured by enzymatic colorimetric assay method (Roche Diagnostics GmbH). The levels of HbA1c were measured by the turbidimetric inhibition immunoassay (TINIA) method (HBA1C II, Roche Diagnostics GmbH).

CKD was defined as kidney damage with or without a decrease in GFR, which was calculated using a simplified version of the Modification of Diet in Renal Disease (MDRD) formula [$186 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742$ if women)] [16].

Height and weight were measured by the same person with the subjects wearing light clothing but not shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Overweight was defined as a BMI 25–30 kg/m^2, and obesity as a BMI of 30 kg/m^2.

All blood pressure measurements were made with calibrated mercury manometers (Rudolf Riester GmbH, Jungingen, Germany) in the right arm with the patient in a sitting position after a rest of five minutes. Hypertension was defined as a systolic/diastolic blood pressure of 140/90 mmHg or higher, and/or current antihypertensive treatment.

Dyslipidemia was defined as the presence of at least one of the following conditions: raised serum triglycerides (> 200 mg/dl), total cholesterol (> 200 mg/dl), LDL-cholesterol (> 100 mg/dl), low HDL-cholesterol (< 35 mg/dl for men and < 45 mg/dl for women), and/or current antilipidemic treatment.

Diabetes mellitus was defined as the presence of at least one of the following conditions: raised fasting plasma glucose level (≥ 126 mg/dl), plasma glucose level after two hours of oral glucose tolerance test (≥ 200 mg/dl), HbA1c (≥ 6.5%), and/or current hypoglycemic treatment.

Statistical Analysis

Statistical analysis was done by the SPSS for Windows, Version 10.0 (SPSS Inc., Chicago, IL, USA) statistical software. The results were presented as mean ± standard deviation. Continuous variables were tested for normality according to the Kolmogorov–Smirnov test. Univariate analysis of variance and Mann–Whitney U-tests were performed to compare the groups. For comparing categorical data, the χ^2 test was performed. The correlation analysis was done using Spearman's test. A p-value of < 0.05 was considered statistically significant.

RESULTS

The patients' age was 61.7 ± 32.4 years, GFR was 38.6 ± 20, CKD duration was 5 ± 1.57 years, and BMI was 27.7 ± 6.9 kg/m^2. In regard to wight, 31.1% of the patients were normal, 34.2% were overweight, and 34.7% of the patients were obese.

Skin tags were detected in 199 (55%) patients. A total of 143 (40%) patients were diabetic, 268 (75%) were hypertensive, 143 (40%) were dyslipidemic. Prevalence of skin tags was higher in male than in female patients (p = 0.041), and in diabetic patients than in nondiabetic patients (p = 0.013) (Table 1). BMI was higher in patients with skin tags when compared to patients without skin tags (p = 0.047). Skin tags were detected in 48.3% of normal patients, in 58% of overweight, and in 66% of obese patients (p = 0.029) (Table 2).

Table 1. Prevalence of skin tags in patients

Parameter		Skin tags		p
		Present (%)	Absent (%)	
Sex	Male	60	40	0.041
	Female	49	51	
Body mass index	Normal	48.3	51.7	0.029
	Overweight	58	42	
	Obese	66	34	
Diabetes mellitus	Present	66	34	0.013
	Absent	52.5	47.5	
Hypertension	Present	58.3	41.7	0.18
	Absent	51	49	
Dyslipidemia	Present	62	38	0.099
	Absent	54	46	
Dialysis treatment	Present	59.4	40.6	0.061
	Absent	50.1	49.9	
Proteinuria	Present	58.9	41.1	0.49
	Absent	60	40	
Cardiovascular disease	Present	57.4	42.6	0.51
	Absent	56.8	43.2	

Table 2. Comparison of parameters in patients with and without skin tags

Parameter	Skin tags		p
	Present	Absent	
Age (years)	62.2 ± 13.0	61.3 ± 16.4	0.79
Body mass index (kg/m^2)	28.3 ± 5.58	26.8 ± 8.3	0.047
Glomerular filtration rate (mL/min/1.73 m^2)	37.1 ± 19.1	41.1 ± 21.2	0.17
Duration of chronic kidney disease (years)	5 ± 1.5	5 ± 1.6	0.82

DISCUSSION

Skin tags, which appear to be associated with some endocrine diseases, are skin growths histologically characterized by a papillomatous acanthotic pattern in the epidermis [17]. Recent studies suggest an association between skin tags and type 2 diabetes mellitus, glucose intolerance, obesity, insulin resistance, atherogenic lipid profile, and cardiovascular disease [5, 7–13]. On the other hand, CKD is a growing health problem worldwide that leads to end-stage kidney failure and cardiovascular complications and/or risk factors [1].

As mentioned above, both CKD and skin tags are associated with similar CVD risk factors such as obesity, diabetes

mellitus, dyslipidemia, hypertension, etc. Although there have been some reports that the presence of skin tags is associated with diabetes mellitus, hypertension, obesity, and atherogenic lipid profile, no data in the literature show the presence of skin tags in patients with CKD [5, 8, 10–13, 15]. The main purpose of this study was to determine the prevalence of skin tags in patients with CKD, and to assess the relationship between skin tags and other cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, obesity and metabolic syndrome.

Skin tags have been reported with an incidence of 46% in the general population [5]. Skin tags were detected in 55% of our patients. Duration of CKD and GFR were not different in patients with and without skin tags. In this regard, our results suggest that the prevalence of skin tags was not increased in patients with CKD.

Recent studies suggest an association between skin tags and obesity. It has been reported that patients who have insulin resistance may develop acanthosis nigricans and skin tags with increasing incidence as BMI rises [7, 8, 12]. In addition to frequent skin irritation that occurs in obese patients, hormonal factors (oestrogen levels and position peripheral aromatization of androgens to oestrogen) and aging of the skin are also thought to contribute to the development of skin tags [6, 18, 19, 20]. The prevalence of obesity is 29.2% in patients with CKD [4]. Obesity prevalence was found to be 34.7% in our study population. We found higher BMI in patients with skin tags when compared to those without skin tags. In addition, skin tags prevalence was a gradual increment in overweight and obese patients. Our findings suggest that the relationship between obesity and skin tags in CKD patients is similar to that in normal population.

There have been a few reports that the presence of skin tags is associated with diabetes mellitus and insulin resistance [5, 8, 10–13]. The prevalence rate of diabetes mellitus is 26.6% in subjects with CKD in our country [4]. Forty percent of patients were diabetic in our study. We also detected high prevalence of skin tags in CKD patients with diabetes mellitus, which is comparable to normal population.

The prevalence rate of hypertension is 56.3% in subjects with CKD in our country [4]. In our study, 75% of patients were hypertensive. On the other hand, we detected a numerical but not a statistical increase in the prevalence of skin tags in patients with hypertension. The reason for this result may be associated with the development of hypertension due to CKD but is not the etiologic cause of CKD.

There are reports describing an association between skin tags and an atherogenic lipid profile [11, 12, 21]. This lipid profile is thought to be strongly associated with atherosclerosis, cardiovascular disease, and macroangiopathic diabetic complications. Crook [11] looked at the association between cardiovascular disease and skin tags in a small cohort study of four patients with the atherogenic lipid profile. The prevalence rate of dyslipidemia is 83.4% in subjects with CKD in our country [4]. In our study, 40% of patients were dyslipidemic. We detected a numerical but not a statistical increase of prevalence of skin tags in patients with dyslipidemia. Prevalence of skin tags was similar in patients with and without cardiovascular disease. We speculate that the increased risk of cardiovascular disease is not associated with skin tags in patients with CKD.

CONCLUSION

The presence of skin tags is merely related to male sex, obesity, and diabetes mellitus in patients with CKD. Further studies with large patient population are required to elucidate the association between the presence of skin tags and cardiovascular disease in patients with CKD.

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Кожни полипи удружени са гојазношћу и шећерном болешћу код болесника са хроничном бубрежном болешћу

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САЖЕТАК

Увод/Циљ Хронична болест бубрега и кожни полипи повезани су са кардиоваскуларним факторима ризика као што су гојазност, дијабетес мелитус, дислипидемија, хипертензија итд. Циљ рада је био да се утврди учесталост кожних полипа код болесника са хроничним бубрежним обољењем и да се процени однос кожних полипа и кардиоваскуларних фактора ризика као што су дијабетес, хипертензија, дислипидемија, гојазност и метаболички синдром.

Методе Испитано је 358 болесника: 149 (41,6%) жена и 209 (58,1%) мушкараца, и то предијализних 197 (55%) и на дијализи 161 (45%). Сви су испитивани од стране истог клиничара, а испитани су и индекс телесне масе, дијабетес мелитус, хипертензија и дислипидемија.

Резултати Кожни полипи су нађени код 199 (55%) болесника, чешће код мушкараца него жена ($p = 0,041$), и чешће код болесника са дијабетесом ($p = 0,013$). Индекс телесне масе био је већи код болесника са кожним полипима него код оних без њих ($p = 0,047$). Кожни полипи су откривени код 48,3% болесника са нормалном, код 58% болесника са прекомерном тежином, и код 66% гојазних болесника ($p = 0,029$).

Закључак Присуство кожних полипа повезано је са мушким полом, гојазношћу и дијабетесом код болесника са хроничним бубрежним обољењем.

Кључне речи: кожни полипи; гојазност; шећерна болест; хронично бубрежно обољење

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Pneumonia and in-hospital mortality after renal transplantation

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SUMMARY

Introduction/Objective Pneumonias remain one of the most frequent reasons for morbidity and mortality in the group of kidney recipients.
The objective of the study was to define the factors associated with a higher risk for in-hospital mortality from pneumonia after renal transplantations.

Methods A total of 124 patients with kidney transplants hospitalized with pneumonia for the period of nine years were studied. Different noninvasive and invasive diagnostic tests were used.

Results Forty-one of the patients died as a result of pneumonia or related complications during their hospital stay. The factors associated with the increased risk for in-hospital mortality were as follows: the development of pneumonia during the early postoperative period (during the first month after surgery) (HR = 2.027; p = 0.025) or between the first and sixth month after surgery (HR = 2.303; p = 0.026), dyspnoea (HR = 2.184; p = 0.007) and hypoxemia (HR = 2.261; p = 0.003). The presence of bilateral infiltrates (HR = 2.482; p = 0.001), failure of initial antibiotic therapy (HR = 3.548; p < 0.001), intubation and mechanical ventilation (HR = 4.635; p < 0.001) also increased the risk for the fatal outcome.

Conclusion Knowing the prognostic factors associated with the increased risk for in-hospital fatal outcome from pneumonia after renal transplantation makes it possible to differentiate the high-risk group of renal recipients who require early etiological diagnosis and strict control of the condition, in order to reduce the mortality from pulmonary infections in the group.

Keywords: pneumonia; mortality; recipient; transplantation, solid organ, renal

INTRODUCTION

The solid transplantation, as a treatment method of the final stage of organ insufficiency, has become increasingly significant in recent years. Renal transplantation (RT) is the most frequently performed organ transplant, accounting for approximately 60% of all cases. Of particular significance for the prognosis of the survival rate and the mortality among renal transplant recipients are pulmonary complications. According to different data in the literature, the frequency of post-RT pulmonary complications varies 5–37%. Most complications are caused by pulmonary infections, although their development after renal transplants is the lowest, compared to patients with other organ transplants (frequency of 8–16% and mortality rate of 5–8% per annum) [1, 2, 3].

The risk of infection after transplantation changes in time, especially with the modification of the therapy, and it varies depending on the immunosuppressive agents used. There are various therapeutic schemes, differing by drug interactions, side effects, as well as the risk of developing infections [4]. As a result of their inhibiting effects, the immunosuppressive drugs affect the endogenic barrier of the lungs against the penetration of infectious pathogens [4]. The immunosuppressive therapy, used after surgery, defines three sub-periods in the post-transplantation period, where different infectious agents causing pulmonary complications are prevalent – the first month after the operation, from the first to the sixth month after the transplantation, and late post-transplant period (more than six months after the surgery) [5, 6].

The main challenge when providing care for patients after transplantation is to choose the optimal immunosuppression, ensuring the balance between the prevention of rejection reactions and the minimization of the risk of infection [7]. This can be achieved with a strict monitoring of the immunosuppressive medications [8]. Nevertheless, pneumonias remain one of the most frequent reasons for morbidity and mortality in this group of patients [9, 10].

The aim of this study is to define the factors associated with a higher risk for in-hospital mortality from pneumonia after renal transplantations.

METHODS

Patients

A total of 124 post-RT patients diagnosed with pneumonia were included in the study. They were admitted to the Clinic of pulmonology

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of the Alexandrovska University Multiprofile Hospital for Active Treatment over a period of nine years. All the patients gave their written informed consent to participate. The protocols conformed to the guidelines of the 1975 Helsinki Declaration. All the patients had renal transplantation and were at least 18 years of age. Patients with mental disturbances or proven oncological diseases, including pulmonary neoplasms, were excluded from the study. The exclusion criteria were chronic pulmonary diseases like asthma and chronic obstructive pulmonary disease or dysfunctional graft with developed terminal renal insufficiency, and chronic hemodialysis treatment. A history of pulmonary tuberculosis successfully treated in the past did form part of the eligibility criteria. In cases of a second or subsequent pulmonary complication, only the first complication, registered for the respective patient, was used for the needs of the study and the data analysis.

Methods

Detailed medical history was prepared for each patient, and all the patients underwent complete clinical examination. When the criteria responsible for the development of pneumonia were present, the patients were hospitalized for treatment at the clinic. During the hospitalization period, the pulmonary and cardiac statuses were followed-up on a daily basis, along with a control of the vital signs – arterial pressure, pulse and respiration rate, body temperature, and 24-hour quantity of urine. The following hematological and biochemical blood tests were performed: complete blood count with differential leukocyte count, erythrocytes sedimentation rate, C-reactive protein (CRP), creatinine, urea, aspartate aminotransferase, alanine aminotransferase, potassium, sodium, chlorides, blood glucose, fibrinogen. The tests of all the patients also included electrocardiography and arterial blood gases (ABGs) analysis (equipment used – RapidLab 248; Siemens Healthineers, Erlangen, Germany). Spirometry and in some cases diffusion capacity analysis (equipment used – Ganshorn Medizin Electronic GmbH, Niederlauer, Germany) were performed in accordance with the requirements of the American Thoracic Society / European Respiratory Society Guidelines (Miller 2005). Microbiological tests of sputum, pleural effusion liquid or broncho-alveolar lavage, and of blood for aerobic and anaerobic microorganisms, fungi, and *Mycobacterium tuberculosis* were done. We used Realquality RQ-CMV standard kits by AB Analitica s.r.l., Padova, Italy, for the identification and quantitative determination of the Cytomegalovirus deoxyribonucleic acid. Posteroanterior radiography of all the patients was performed. In cases of diagnostic difficulties, high resolution computer tomography of the thorax was performed (device used – Aquilion 64-multi-slice, Toshiba Medical Systems Corporation, Otawara, Japan; following Vitrea 2 protocol of Vital Images, Minnetonka, MN, USA). Some of the patients underwent fiberoptic bronchoscopy with bronchoalveolar lavage, catheter-biopsy, and – if necessary –fibre-clamp biopsy (BF 1T30, Olympus Corporation, Tokyo, Japan). Cytological or histological examinations of the material from the bronchial mucosa or the lung parenchyma were all examined.

Statistical analysis

The statistical data processing was carried out using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). The adopted level of significance, eliminating the null hypothesis, was $p < 0.05$. The statistical analyses included a variational analysis of the quantitative variables – median, standard deviation, standard error of the median, and 95% confidence interval of the median, frequency analysis of qualitative variables, graphics. The χ^2 test and the Fisher's exact test were used for establishing the dependency between two qualitative variables, and the Kolmogorov–Smirnov and the Mann–Whitney methods for testing the normality of distribution of the quantitative variables. Quantitative indicators were assessed using a receiver operating characteristic (ROC) analysis. The probability ratio was calculated using logistic regression analysis, and the establishment of the effects of various factors and the risk estimation were carried out based on the Cox regression, using Kaplan–Meier survival curves.

RESULTS

A total of 124 kidney recipients with pneumonia were included in the study. The mean age of the patients was 41.23 ± 13.46 years. The male-to-female ratio was 78/46 (62.9% men and 37.1% women). According to the outcome of pneumonia, the patients were divided into two groups. In the first group, which was pneumonia (+), there were 83 patients recovered from pneumonia. The other 41 recipients in pneumonia (–) group died as a result of the pneumonia or related complications during their hospitalization. There was no significant difference between the two groups according to main demographic data – age, sex, smoking status, type and length of dialysis treatment before transplantation, immunosuppressive agents used in both patient groups, concomitant diseases ($p > 0.05$ for all).

In the pneumonia (+) group, three patients became ill during the first postoperative month, 36 patients between the first and sixth month after the transplantation, and 44 patients in the late post-transplantation period (more than six months after surgery). In the pneumonia (–) group, six patients became ill during the first postoperative period, 27 patients became ill between the first and sixth month after the transplantation, and eight patients in the late post-transplantation period. There is a statistically significant dependence between the period of development of pneumonia and the outcome of the disease ($p < 0.001$).

The effect of the period during which pneumonia occurs on the survival rate of the patients is shown in Figure 1.

The main clinical symptoms are similar in both groups ($p > 0.05$). The only statistically significant difference in clinical features between the two groups is the presence of dyspnoea at admission ($p = 0.033$). This symptom occured more frequently in the pneumonia (–) group.

The major hematological and biochemical parameters are shown in Table 1. Statistical differences between their values in the groups of patients according to the outcome of pneumonia were observed for CRP and lymphocytes. The calculated ROC curve for CRP is shown in Figure 2. The area below the curve is 0.702 (95% CI, 0.584–0.819), p = 0.003.

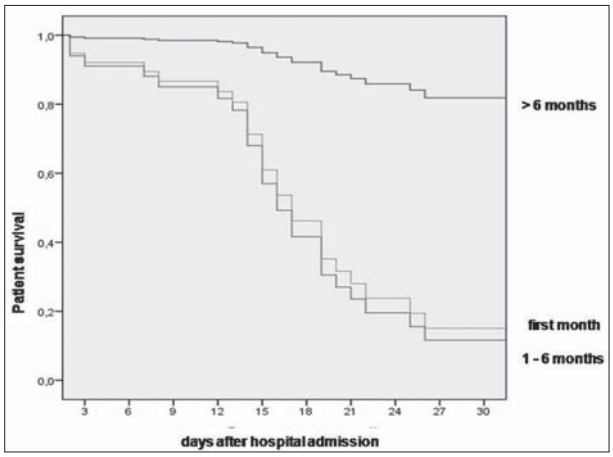

Figure 1. Kaplan–Meier plot – effect of the period after the transplant on the survival rate in patients with pneumonia

Table 1. Comparison of the hematological and biochemical parameters between the two groups

Laboratory indicator	Median ± SD Pneumonia (+)	Median ± SD Pneumonia (–)	p
CRP	54.60 ± 77.285	94.32 ± 94.100	0.026*
Erythrocytes	51.19 ± 31.688	55.30 ± 26.913	0.530
Leukocytes	9.175 ± 4.6359	9.656 ± 4.3531	0.583
Neutrophils	10.072 ± 11.8294	15.200 ± 21.3843	0.069
Lymphocytes	2.573 ± 3.8850	1.535 ± 2.5872	0.026*
Monocytes	0.965 ± 1.9900	0.777 ± 0.8372	0.301
Eosinophils	0.164 ± 0.4307	0.126 ± 0.1667	1.000
Basophils	1.02 ± 0.136	1.04 ± 0.192	1.000
Thrombocytes	266.59 ± 103.618	236.01 ± 132.407	0.062
Hemoglobin	117.00 ± 23.261	111.22 ± 18.331	0.442
Fibrinogen	5.1842 ± 1.66059	5.9019 ± 1.92601	0.559
Creatinine	205.94 ± 165.943	270.69 ± 210.343	0.321
Albumin	33.75 ± 1.03	32.00 ± 0.96	1.000

CRP – C-reactive protein
*Statistically significant

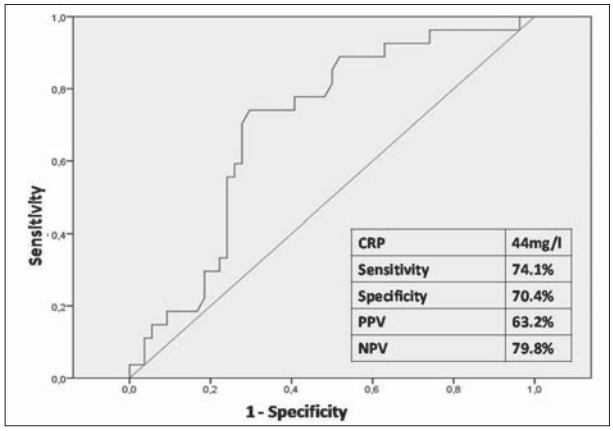

Figure 2. ROC curve of CRP as a predictor of the fatal outcome of pneumonia

The ABGs analysis shows that at admission 38 patients (45.78%) of those that subsequently recovered and 35 (85.37%) of the subsequently deceased patients had hypoxemia (p = 0.001). Figure 3 shows the ROC curve for PaO_2 in the ABGs at admission. The area below the curve is 0.703 (95% CI, 0.591–0.815), p = 0.003.

The ABGs analysis, performed on the third day of the treatment, revealed hypoxemia in 23 (27.71%) of the subsequently recovered and in 39 (95.12%) of the subsequently deceased patients (p < 0.001). Figure 4 shows the ROC analysis comparing both groups, based on the outcome of the disease and the PaO_2 values, obtained from the ABGs analysis on the third day of the treatment. The area below the curve is 0.884 (95% CI, 0.814–0.955), p < 0.001.

There was a statistically significant difference in the localization of the X-ray alterations between the two groups (p < 0.001). The predominant radiological findings in the pneumonia (–) group were bilateral changes. They increased the risk of fatal outcome (HR = 2.482; 95% CI, 1.439–4.279; p = 0.001).

A failure of the antibiotic treatment administered and a need to re-evaluate it was determined in 21 (25.3%) recipients in the pneumonia (+) group and in 38 (92.68%) patients in the pneumonia (–) group. The two groups differ statistically (p < 0.001) (Figure 5).

In the pneumonia (–) group, three (7.31%) recipients were subjected to non-invasive ventilation (NIV) and 31 (75.61%) to invasive ventilation. In the pneumonia (+) group, seven (8.43%) patients were subjected to NIV, and two (2.41%) to invasive ventilation (p < 0.001). The effect of the need for intubation and mechanical ventilation

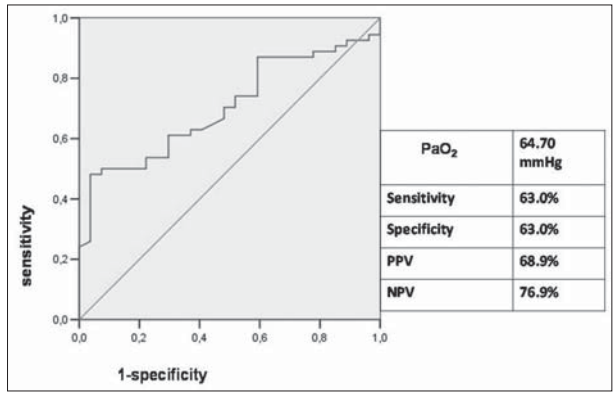

Figure 3. ROC curve of PaO_2 on the first day, as a lethality predictor

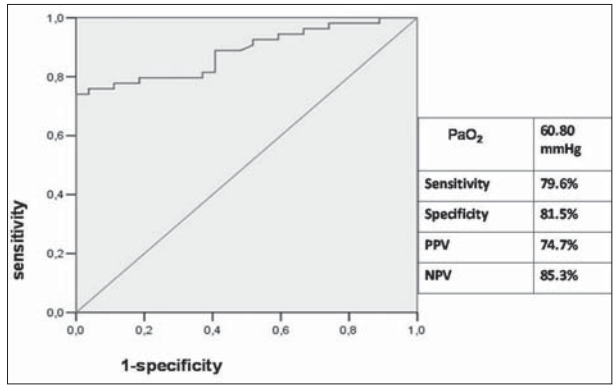

Figure 4. ROC curve of PaO_2 on the third day, as a lethality predictor

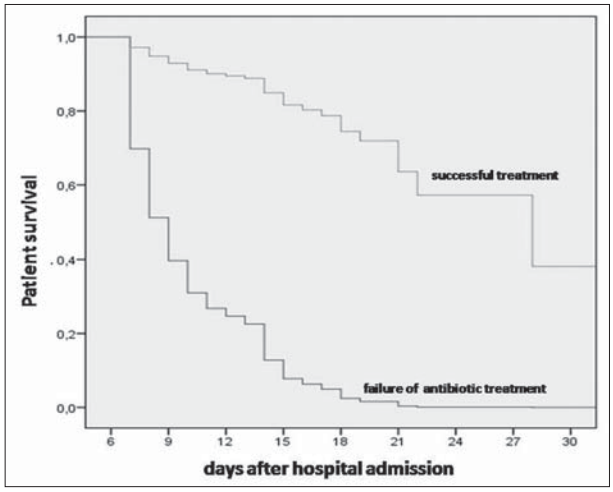

Figure 5. Effect of adjusting the antibiotics therapy on the survival rate of pneumonia patients

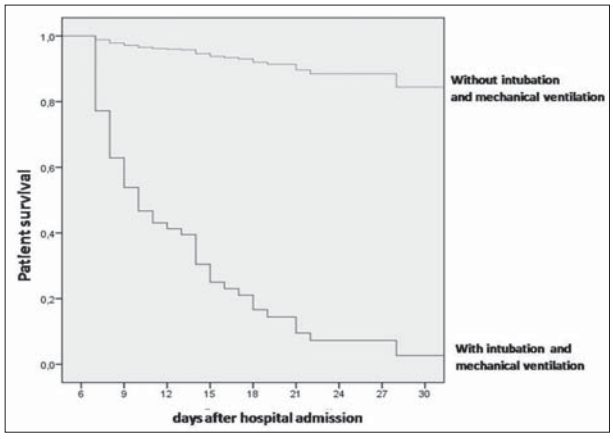

Figure 6. Effect of mechanical ventilation on the survival rate of pneumonia patients

Table 2. Indicators for the assessment of the fatal outcome risks

Indicator	HR	95% CI	p
1st month after renal transplantation	2.027	1.092–3.761	0.025
1–6 months after renal transplantation	2.303	1.104–4.803	0.026
Dyspnoea	2.184	1.239–3.849	0.007
Hypoxemia	2.261	1.314–3.890	0.003
Bilateral radiological changes	2.480	1.439–4.279	0.001
Failure of initial antibiotic therapy	3.548	2.418–5.205	< 0.001
Intubation and mechanical ventilation	4.635	2.276–9.437	< 0.001

HR – hazard ratio

on the survival rate of pneumonia patients is shown in Figure 6.

The risk factors for an in-hospital fatal outcome of pneumonia in patients after renal transplantation are shown in detail in Table 2.

DISCUSSION

The frequency of pneumonia, reported after RT varies 2.9–30%, as these are the lowest rates, compared to other organ transplantations [11, 12]. According to our results, the mortality rate resulting from pneumonia is 33.06%. The available literature provides inconsistent data on the mortality of pulmonary infections. Some authors report a rate of 15–20% [13]. Other studies show mortality rates of 21–35%, as there are certain differences between the mortality from pneumonia, acquired in public (8%), and Hospital-acquired (nosocomial) cases (58%) [14, 15].There is a statistically significant dependency between the period of the development of the pulmonary infection and the outcome of the disease ($p < 0.001$). The pneumonia outcome depends on the amount of time which passes after the transplantation before the infection develops [16]. The mortality rate is higher among patients who acquire pneumonia in the early post-transplantation period, i.e. between one and six months after surgery. The development of pneumonia during the early postoperative period (during the first month) increases the lethal outcome risk 2.027-fold (HR = 2.027; 95% CI, 1.092–3.761; $p = 0.025$). The development of pneumonia one to six months after surgery increases the risk of an unfavorable outcome 2.303-fold (HR = 2.303; 95% CI, 1.104–4.803; $p = 0.026$). At the same time, most of the successfully treated patients developed pneumonia in the late post-transplantation period.

Clinical symptoms of pneumonia do not differ from those in immunocompetent patients. The prevailing complaints of patients with the fatal outcome were dyspnoea. A statistically significant dependency between the outcome of pneumonia and the presence of dyspnoea at admission was determined ($p = 0.033$).The dyspnoea increases the risk of the unfavorable outcome 2.184-fold (HR = 2.184; 95% CI, 1.239–3.849; $p = 0.007$).

The analysis of the laboratory indicators revealed typical changes in infection markers, also observed in immunocompetent patients with pneumonia – increased CRP, leukocytosis with neutrophilia, lymphopenia, monocytosis. Also observed were slight anemic syndrome and increased levels of creatinine and fibrinogen. Statistically significant differences between the values of the laboratory results in the groups of patients, according to the pneumonia outcome, were observed only for CRP and lymphocytes. The analysis of the CRP ROC curve showed that CRP at 44mcg/L reveals the highest sensitivity (74.1%) and specificity (70.4%) as a fatal outcome predictor. In multivariate analysis, Diadar et al. [17] also found that high CRP is associated with significant risk for death from pneumonia.

Patients with post-RT pneumonia show increased rates of hypoxemia. At the same time, low levels of PaO_2 on admission or in the course of treatment are a risk factor for the fatal outcome of pneumonia [18]. Our results show that the ABGs analysis at admission revealed hypoxemia in 85.37% of the patients who subsequently died ($p = 0.001$). The PaO_2 values below the normal range increase the risk of the fatal outcome 2.261 times (HR = 2.261; 95% CI, 1.314–3.890; $p = 0.003$). According to the ROC analysis, the PaO_2 level of 64.7 mmHg has both the highest sensitivity and specificity (63%) as a predictor of the fatal outcome. If PaO_2 is observed dynamically, hypoxemia was determined in 95.12% of the deceased patients ($p < 0.001$) on the third day of the treatment. The analysis of the ROC

curve on the third day of the treatment showed the PaO_2 value of 60.8 mmHg with very high sensitivity (79.6%) and specificity (81.5%) as a predictor of the fatal outcome. These results coincide with the manuals prepared to date, in which PaO_2 values below 60 mmHg are considered a risk factor for the fatal outcome of pneumonia.

Several previous studies showed that multilobar radiographic pulmonary infiltrates were significantly associated with mortality [19, 20]. In our study, X-ray changes have diverse localization, as the presence of bilateral infiltrates increase the risk of the fatal outcome 2.482 times (HR = 2.482; 95% CI, 1.439–4.279; p = 0.001).

The early initiation of the treatment with appropriate antibiotics is of great importance for the outcome of pneumonia after RT. In the case of therapy failure, risk of mortality increases significantly [21, 22, 23].

According our results, a failure of the originally started antibiotics treatment and its subsequent re-evaluation in the course of treatment was observed in 92.68% of the patients in the pneumonia (–) group (p < 0.001).The need for adjusting the antibiotics therapy increases the risk of the fatal outcome 3.548-fold (HR = 3.548; 95% CI, 2.418–5.205; p < 0.001).

Due to the occurring complications in the course of pneumonia, some patients had to undergo NIV or invasive ventilation. Mechanical ventilation increases the risk of the fatal outcome in patients with pneumonia. This fact has been confirmed by numerous studies carried out previously [15, 24, 25]. Prolonged mechanical ventilation is mentioned in a number of publications as the main risk factor for the development of nosocomial pneumonias [14, 15]. At the same time, in recent years, a significant volume of data has been accumulated on the role of the NIV in the treatment of acute respiratory insufficiency in immunosuppressed patients [26]. A randomized study by Antonelli et al. [27], involving 25 patients post RT, showed that NIV, due to hypoxemic respiratory failure, significantly reduced mortality rates (p = 0.05). Hilbert et al. [28] reported a lower rate of use of intubations (46% compared to 77%) and lower mortality rate (50% compared to 81%) (p ≤ 0.05 for both) among immunocompromised patients with acute respiratory failure and NIV, compared to those observed in conventional treatment [28].

The results of our study are similar to the previous publications. We have established a statistically significant correlation between the outcome of the disease and the type of ventilation administered (p < 0.001). The group of the recovered patients is dominated by those with non-invasive ventilation – seven kidney recipients (8.43%). In the pneumonia (–) group, 31 (75.61%) patients had been intubated and mechanical invasive ventilation had been administered to them. The need for intubation and mechanical ventilation increases the risk of the fatal outcome 4.635 times (HR = 4.635; 95% CI, 2.276–9.437; p < 0.001). Most patients on NIV recovered. At the same time, NIV is not statistically significant for the outcome of the disease. The results are probably due to the small number of patients treated with NIV.

The markers of inflammation, hypoxemia, and hypocapnea from the ABGs analysis, as well as the bilateral infiltration changes, shown by the radiological tests of the lungs, may be used as predictors for the outcome of the disease and the occurrence of complications. The need for re-evaluation of the antibiotics treatment in the course of the disease is an independent risk factor for the development of complications and the fatal outcome. That fact may be used when determining the high-risk groups of renal recipients with pneumonia, requiring increased attention and strict control in the course of treatment.

Our study has not determined any factors associated with increased risk of developing pneumonia. No comorbidities which may have an aggravating effect on the course of pneumonia have been taken into account. No long-term evaluation of the survival rate after pneumonia in this group of patients has been made. We studied only in-hospital death and did not analyze the mortality thereafter.

CONCLUSION

Based on the results that we have obtained, it is possible to prepare an algorithm with prognostic factors associated with a more severe course of pulmonary infections and an increased risk of the occurrence of complications and the fatal outcome. This makes it possible to differentiate a high-risk group of patients requiring early etiological diagnosis or strict control of the condition, in order to reduce the mortality from pneumonia after a renal transplantation.

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Упала плућа и болничка смртност после трансплантације бубрега

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САЖЕТАК

Увод/Циљ Пнеумоније су један од најчешћих разлога морбидитета и морталитета код прималаца бубрега.
Циљ овог рада је био да дефинише факторе повезане са већим ризиком од морталитета од упале плућа у болници после пресађивања бубрега.

Методе Анализирана су 124 болесника са пнеумонијом и пресађеним бубрегом хоспитализована у периоду од девет година. Коришћени су различити неинвазивни и инвазивни дијагностички тестови.

Резултати Због пнеумоније или сродних компликација умро је 41 болесник током боравка у болници. Фактори повезани са повећаним ризиком од морталитета у болници били су следећи: развој пнеумоније током раног постоперативног периода (до првог месеца) (*HR* = 2,027; *p* = 0,025) или од првог до шестог месеца после операције (*HR* = 2,303; *p* = 0,026), диспнеја (*HR* = 2,184; *p* = 0,007) и хипоксемија (*HR* = 2,261; *p* = 0,003). Присуство билатералних инфилтрата (*HR* = 2,482; *p* = 0,001), неуспех почетне антибиотске терапије (*HR* = 3,548; *p* < 0,001), трахеална интубација и механичка вентилација (*HR* = 4,635; *p* < 0,001) такође су повећавали ризик од смртног исхода.

Закључак Познавање прогностичких фактора повезаних са повећаним ризиком од смртног исхода од пнеумоније у болници после трансплантације бубрега пружа могућност одређивања групе болесника високог ризика, која захтева рану етиолошку дијагнозу и строгу контролу стања да би се смањила смртност од плућних инфекција код прималаца бубрега.

Кључне речи: пнеумонија; смртност; прималац; трансплантација, солидни орган, бубрег

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Significance of the correlation between the serum prostate-specific antigen and the percentage of prostate cancer volume in postoperative biochemical progression

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SUMMARY

Introduction/Objective Radical prostatectomy (RP) is the best form of treatment of patients with locally confined prostate cancer (PC). Biochemical progression (BP) of the disease occurs in 27–53% of patients after RP.

The aim of our analysis was to assess the significance of the correlation of preoperative prostate-specific antigen (PSA) values and the percentage volume of PC in biochemical progression in patients with RP and the biopsy Gleason score of 6 and 7.

Methods The analysis included the results of treatment of 228 patients with the committed radical retropubic prostatectomy for localized PC in the 2007–2011 period. According to the Gleason grade system values, three groups were identified – 6 (3 + 3), 7 (3 + 4) and 7 (4 + 3). According to the preoperative PSA values the following three groups were determined and monitored: ≤ 4 ng/ml, 4.1–10 ng/ml, and ≥ 10.1 ng/ml. Biochemical progression was defined as two consecutive increases of PSA values ≥ 0.2 ng/ml after RP. The percentage of tumor volume (PTV) is determined by a visual assessment of the percentage of PC in each microscopic sample. Four PTV groups were determined: 0–5%, 6–25%, 26–50%, and 51–100%.

Results Biochemical progression was registered in 19 patients. Most frequent PTV in the group of patients with BP and from biopsy and RP was 6–50%, an average of 30%.

Conclusion Our study showed predictive significant connections between preoperative PSA values and the values of PTV after operational treatment and that these are independent parameters in the assessment of treatment results.

Keywords: prostate cancer; radical prostatectomy; prostate-specific antigen; tumor volume; biochemical recurrence

INTRODUCTION

Prostate cancer (PC) is the most common tumor in older men and one of the leading malignant tumors in the world. According to the results of epidemiological studies, diagnostics of PC in each year ranges from 26% to 28% of all malignant tumors [1]. Thanks to early diagnosis and numerous therapeutic modalities, mortality caused by PC declines each year and currently stands at 9–11%. Radical prostatectomy (RP) is the best form of treatment of patients with locally confined PC, who are expected to survive longer than 10 years. Biochemical progression (BP) of the disease occurs in 27–53% of patients after RP [2]. BP after RP is defined as the elevation of the value of prostate-specific antigen (PSA) in the absence of diagnostic metastases [2–5]. Together with the Gleason grade system (GGS) and the stage of the disease, serum PSA values have represented the leading standard PC parameters for decades [1–4]. The first results of work based on an estimate of the PC volume in diagnostic biopsies and material from RP and its questionable character in assessing the progression of the malignant disease have emerged in the 1990s. The assessment of PC volume depended on the implementation of the recommendations of the macroscopic treatment of prostate tissue, as well as computerized or other methods of its determination [6–12]. Despite the large number of positive correlations with tumor volume with BP, PC volume analyzed through GGS and the stage of the disease has not gained the importance of an independent prognostic parameter [7–11].

The aim of our analysis was to assess the significance of the correlation of preoperative PSA values and the PC percentage volume in biochemical progression in patients with RP and the biopsy GGS score of 6 and 7.

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METHODS

The analysis included treatment results of 228 patients who underwent radical retropubic prostatectomy for localized PC in the 2007–2011 period. The material from biopsies and RP of 113 patients with GGS values of 6 and 7 was used for the analyses of this group. Status of the lymph nodes in all the patients was negative. Postoperative follow-up included the period from 29 to 77 months, the average being 56 months. The patients did not receive preoperative hormonal or radiation therapy. The diagnosis of PC was determined according to standard clinical parameters, with ultrasound-guided transrectal biopsy (TRBP), which was followed by noting preoperative and postoperative PSA values, clinical and pathological stage of the disease, GGS score from biopsy and operational material, as well as the tumor volume percentage. According to GGS values, the following three groups were identified: group 1 – GGS 6 (3 + 3) (Figure 1); group 2 – GGS 7 (3 + 4) (Figure 2); and group 3 – GGS 7 (4 + 3) (Figure 3).

Macroscopic treatment of the prostate tissue, seminal vesicles, and groups of lymph nodes, was performed with the use of protocol-labeled samples according to topography changes, including the analysis of the prostate apex and the status of the entire margin [11]. The volume of histologically processed tissue ranged 70–100% of the total weight of the prostate. Prolonged tissue fixation in 10% formalin was applied, after which parasagittal sections 2–3 mm wide were made. Histologic type, tumor grade, and standard WHO grade (1 to 3 degrees) as GGS and pathological stage of the PC were determined from paraffin embedded prostate tissue obtained from RP, treated with standard hematoxylin and eosin staining. The postoperative stage in all the patients was revised and fully adapted to the seventh edition of the official AJCC/UICC protocol in 2009 [12]. Serum levels of PSA were determined by Hybritech monoclonal immunoassay method (Hybritech, Inc., San Diego, CA, USA). According to the preoperative PSA values, the following three groups were determined and monitored: group 1 – PSA values of ≤ 4 ng/ml; group 2 – PSA values of 4.1–10 ng/ml; group 3 – PSA values of ≥ 10.1 ng/ml. The first postoperative result of serum PSA was reached after three months. Biochemical progression was defined as two consecutive increases of PSA values greater than 0.2 ng/ml after RP [2, 3]. The percentage of tumor volume (PTV) is determined by a visual assessment of the percentage of PC in each microscopic sample. Data such as the status of the margin, the minimum and broad infiltration, and transcapsular expansion were analyzed as individual data by slides and customized folder. The total field of PC was estimated visually, according to the map. The PTV was determined from the weight of the prostate without seminal vesicles and according to assumed specific gravity of the prostate for a little more than 1 g/cm^3 [13]. Macroscopic and microscopic analyses were made by a single pathologist. The following four groups were determined: group 1 – PTV of 0–5%; group 2 – PTV of 6–25%; group 3 – PTV of 26–50%; and group 4 – PTV of 51–100%. The patients were monitored postoperatively 21 to 83 months, three months during the first year of treatment and then every six months. Data are presented as number (percent) or mean ± standard deviation, depending on the data type. Group differences were analyzed using Student's t-test,

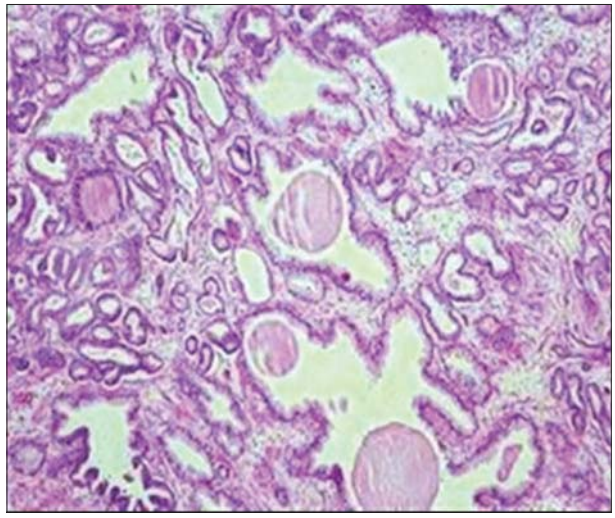

Figure 1. Prostate cancer GGS 6 3 + 3; H&E, ×40

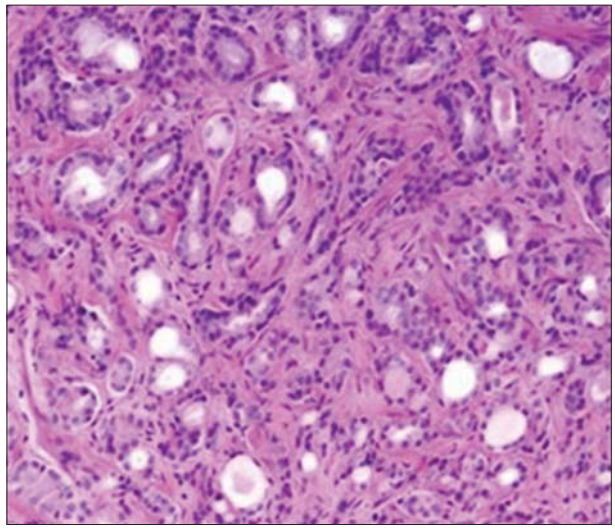

Figure 2. Prostate cancer GGS 7 3 + 4; H&E, ×40

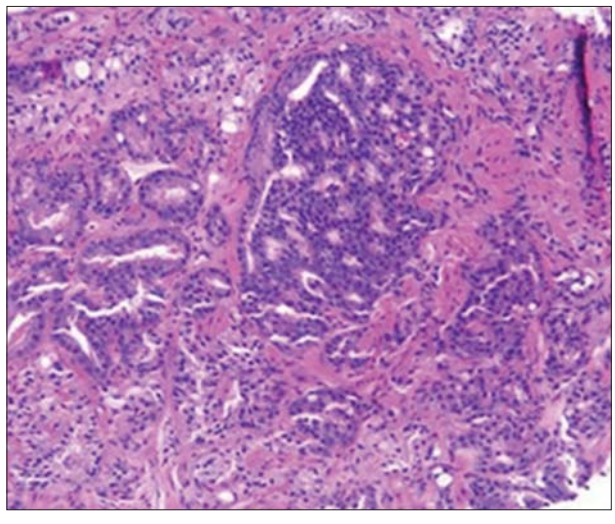

Figure 3. Prostate cancer GGS 7 4 + 3; H&E, ×40

Mann–Whitney U-test and χ^2 test (Pearson's and trend test). Cox regression was used to model the relationship between independent variables and biochemical progression of PC. All the data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) statistical software. All p-values less than 0.05 were considered statistically significant.

RESULTS

The average age of patients with RP was 64 years (the range being 50–76 years) and the average value of preoperative PSA was 9.4 ng/ml (1.4–20 ng/ml). In the analyzed group, PSA levels were up to 4 ng/ml in four patients, 4.1–10 ng/ml in 71 (62.8%) patients, and more than 10 ng/ml in 38 (33.6%) patients. Only one patient (5.2%) with intermediate PSA values developed BP after RP, and 18 (94.8%) patients with PSA values above 10 ng/ml BP developed after RP. Clinical stage T1 was determined in 60 patients (53.1%), T2 in 47 patients (41.6%), and T3 in six patients (5.3%). After RP, pathologic stage T2 was diagnosed in 64 patients (56.6%), and T3 in 49 patients (43.4%). GGS scores in the biopsy material were as follows: GGS 6 (3 + 3) in 56 patients (49.6%), GGS 7 (3 + 4) in 52 patients (46%), and GS 7 (4 + 3) in five patients (4.4%). GGS findings from RP according to the same groups were as follows: group 1 in 12 patients (10.6%), group 2 in 75 patients (66.4%) and group 3 in 26 patients (23%). Table 1 shows the comparative values for the entire group and the group of patients with BP after RP.

According to PTV values of the biopsy material, two patients (1.8%) were distributed into PTV group 1, 87 patients (77%) into PTV group 2, 19 patients (16.8%) into PTV group 3, while the highest PTV values (group 4) were found in five patients (4.4%). After RP, only one patient (0.9%) remained in PTV group 1, as much as 82 patients (72.5%) were in PTV group 2, 28 patients (24.8%) were in PTV group 3, and only two patients (1.8%) were in PTV group 4, with PTV in the range of 51–100%. With Cox regression analysis it was found that PSA and PTV with RP have statistical significance in the univariate analysis. In the multivariate analysis, PSA is close to the very limits of statistical significance in correlation with the tumor volume (TV) from RP (model 2) and PSA, TV from RP (model 4). The patients' age was analyzed because of associated comorbidities and subsequent life expectancy. Models of analysis of the parameters listed in Table 2.

BP was registered in 19 patients (16.8%). It was exhibited over a period of 24 months, with a median of 18 months. In one patient, BP was found 69 months after RP. The average age of patients in the group with BP was 64 years (54–74 years). In assessing BP, statistical significance existed in the clinical ($p < 0.001$) and in the pathological stage of prostate cancer ($p = 0.005$). According to the PSA group, in the majority of patients with BP (a total of 18 patients, 94.8%), preoperative PSA levels were higher than 10 ng/ml and the levels were in the gray zone (4.1–10 ng/ml) in only one patient (5.2%). The average values of PSA at BP amounted to 12.4 ng/ml (the range being 5.7–19.9 ng/ml). Clinical stage T1 existed in five patients (26.3%) with BP, T2 in 11 patients (57.9%), and T3 in three patients (15.8%). In relation to the biopsy GGS scores, most of BP was registered in 10 (52.6%) patients with GGS 7 (3 + 4) score; six patients (31.6%) had GGS 6 (3 + 3) score, and three patients (15.8%) had GGS 7 (4 + 3) score. Regarding GGS score from RP, BP developed in only one patient (5.3%) with GGS 6 (3 + 3) score, in nine patients (47.4%) with GGS 7 (3 + 4) score, and in nine patients (47.4%) with GGS 7 (4 + 3) score. Postoperative stage T3 was determined in 14 (73.7%) patients with BP, and T2 stage was determined in five patients (26.3%).

Most frequent PTV (for 6–50% PTV) in the group of patients with BP and from TRBP from RP was in groups 1 and 2 (an average of 30%).

Table 1. Comparative values for the entire group and the group of patients with BP after RP

Parameter	Entire group n (%)	BP n (%)
Number of patients	113	19 (16.8)
Years of age		
Average	64	64
From – To	50–76	54–74
Monitoring time (months)		
Average	47	56
From – To	21–83	29–77
Preoperative PSA (ng/ml)		
Average	9.4	12.4
≤ 4.0	4	0
4.1–10	71	1 (5.2)
≥ 10.1	38	18 (94.8)
Clinical stage		
T1	60 (53.1)	5 (26.3)
T2	47 (41.6)	11 (57.9)
T3	6 (5.3)	3 (15.8)
GGS of TRBP		
6	56 (49.6)	6 (31.6)
7 (3+4)	52 (46)	10 (52.6)
7 (4+3)	5 (4.4)	3 (15.8)
PTV from TRBP (%)		
0–5	2 (1.8)	0
6–25	87 (77)	15 (79)
26–50	19 (16.8)	2 (10.5)
51–100	5 (4.4)	2 (10.5)
Pathological stages		
pT2	64 (56.6)	5 (26.3)
pT3	49 (43.4)	14 (73.7)
GGS of RP		
6	12 (10.6)	1 (5.2)
7 (3+4)	75 (66.4)	9 (47.4)
7 (4+3)	26 (23)	9 (47.4)
PTV from RP (%)		
0–5	1 (0.9)	0
6–25	82 (72.5)	10 (52.7)
26–50	28 (24.8)	7 (36.8)
51–100	2 (1.8)	2 (10.5)

BP – biochemical progression; PSA – prostate-specific antigen; TRBP – transrectal biopsy; PTV – percentage of tumor volume; RP – radical prostatectomy; GGS – Gleason grade system

Table 2. Models of parameter analysis

Models	p-value	HR	95% CI	
			Low	High
Model 1. Univariate analysis				
PSA	0.001	1.183	1.073	1.304
PTV from RP	0.002	1.051	1.019	1.084
Age	0.694	1.016	0.938	1.100
GGS from RP	0.012	2.814	1.258	6.298
Model 2. PSA and PTV from RP				
PSA	0.014	1.145	1.028	1.274
PTV from RP	0.081	1.031	0.996	1.067
Model 3. PSA and GGS from RP				
PSA	0.011	1.150	1.032	1.281
GGS from RP	0.182	1.790	0.762	4.207
Model 4. Age, PSA, PTV from RP				
PSA	0.006	1.171	1.046	1.310
PTV from RP	0.060	1.034	0.999	1.071
Age	0.176	1.061	0.974	1.155
Model 5. Age, PTV from RP and GGS from RP				
Age	0.393	1.037	0.954	1.126
PTV from RP	0.086	1.036	0.995	1.078
GGS from RP	0.171	1.988	0.743	5.315
Model 6. PSA, PTV from RP, GGS from RP				
PSA	0.027	1.134	1.015	1.268
PTV from RP	0.244	1.024	0.984	1.066
GGS from RP	0.501	1.399	0.526	3.721
Model 7. PSA, PTV from RP, GGS from RP				
Age	0.172	1.062	0.974	1.158
PSA	0.013	1.159	1.031	1.303
PTV from RP	0.209	1.027	0.985	1.069
GGS from RP	0.487	1.414	0.533	3.752

HR – health risk; PSA – prostate-specific antigen; PTV – percentage of tumor volume; RP – radical prostatectomy; GGS – Gleason grade system

Table 3. Statistically significant parameters for the development of biochemical progression (BP) after radical prostatectomy (RP)

Parameters	BP		p-value
	Yes	No	
Age	64.2 ± 6.4	63.9 ± 5.7	0.881
PSA	12.5 ± 3.9	8.8 ± 3.7	< 0.001
PTV from BP	23.4 ± 18.7	19.8 ± 13.6	0.024
PTV from RP	29.7 ± 11.4	21.7 ± 9.7	0.001
GGS from RP			
6 (3+3)	11 (91.7%)	1 (8.3%)	0.023
7 (3+4)	66 (88%)	9 (12%)	
7 (4+3)	17 (65.4%)	9 (34.6%)	
kT			
T1	5 (8.3%)	55 (91.7%)	0.002
T2	11 (22.9%)	37 (77.1%)	
T3	3 (60%)	2 (40%)	
pT			
T2	5 (7.8%)	59 (92.2%)	0.003
T3	14 (28.6%)	35 (71.4%)	

PSA – prostate-specific antigen; PTV – percentage of tumor volume; GGS – Gleason grade system

Determined according to TRBP, the most common PTV existed in 15 patients (79%), and in 10 patients (52.7%) determined from RP. In the group with BP, high statistical significance was found for preoperative PSA levels ($p < 0.001$), for PTV from biopsy material ($p = 0.024$), and for PTV from RP ($p = 0.001$). Statistical significance was observed in the group with BP and according to GGS from biopsy ($p = 0.016$) and from operating materials ($p = 0.023$). Table 3 presents parameters statistically significant for the development of BP after RP.

DISCUSSION

The first results of the TV aspect in localized PC in the 1990s pointed to its prognostic significance. However, it was lacking the monitoring of patients through the postoperative PSA levels that have not yet been widely applied in the world [9, 13]. At the same time, there were recommendations that TV should not be a routine part of the pathologist report, because it has no predictive value, particularly in relation to the benefits of GGS [8]. One of the reasons for the prognostic significance of TV in PC is the absence of a unified position on the right time and manner of further treatment in case of BP manifestation. The expression of PSA progression represents a heterogeneous event of PC. The results of some studies show that PSA progression precedes clinical diagnostic dissemination of PC over a period of several months to several years. In some studies, there were no significant differences in the 10-year survival rate of patients either with or without PSA progression after RP [14].

Maintenance of the differences in the assessment of the real limitations of PC in the selection of patients for the treatment of RP, assessed through serum PSA values, is the lack of studies in the 21st century. Within the intermediate levels of serum PSA, PC is diagnosed in 33% of patients. Intermediate PSA values represent important information about the limitations of the tumor because, after RP, the diagnosis is reached in 53–81% of patients with localized PC. After RP, locally advanced PC can be diagnosed in more than 30% of patients [14, 15]. In our analyzed group of intermediate PSA values, out of the total number of patients, only one patient developed BP in the postoperative pT3 stage.

Divided opinions on the importance of PTV are the result of the application of various methods of its determination. These methods include the maximum diameter or multiple fields of tumor growth calculated through a sophisticated computerized method or method of visualization of certain block sections [16–19]. In our work, we applied imaging method for the percentage of PC. The most frequent PTV in patients with BP, determined in TRBP and RP, was in group 1, with the distribution of PTV being 6–25%. This result is in line with the threshold PTV values of prostate cancer > 20%, which is mentioned in several clinical studies. In a study by Hinkelammert et al. [19], the predictive value of PTV as an independent factor for the development of BP after RP, for the value of PTV > 20%, was demonstrated through a multivariate analysis. Song et al. [20] pointed out the significance of the results for a range of TV from 14% to 29%. However, for the same chosen method of determining TV, predictive significance in other studies is not determined [4, 7, 9].

The results of our analysis showed a positive correlation between preoperative PSA values, postoperative stage, and PTV. We found BP in 73% of patients with stage pT3 and PTV of about 30%. Similar results are found in a study by Blackwell et al. [21], where it is demonstrated that the preoperative value of PSA is significant in predicting not only TV, but also pathological stage and the risk of spread of the disease. During the follow-up of patients after RP, there was no appearance of BP in 83.2% of patients during 29–77 months. The results of our analysis are similar to the results of a major study by Ramos et al. [22], derived from 1,850 RPs, which showed that BP does not present in 82% of patients with PTV > 20% during the five-year period of monitoring [22]. In a paper by Swanson and Basler [23], PTV greater than 25% appears as a significant predictor of BP in 57–88% of patients in the five-year follow-up period after RP, and in 25% of patients with PTV below 25%. BP is expressed in a lower percentage in 19 (16.8%) patients from our group, but over a period of two years. High statistical significance of GGS correlation with BP is presented in Table 3. There was an equal representation of GGS 7 (3 + 4) score and GGS 7 (4 + 3) score at 47.4%. This information is not common as, this is linked to a more aggressive behavior of PC with GGS 7 (4 + 3) score in most studies, which is diagnosed in more than 69% of patients with BP after RP [4].

CONCLUSION

This is a study made at a single institution, with a retrospective comparison of PTV with standard parameters, with a small group of patients. There were no deaths during the study period. The study showed the predictive significant connections between preoperative PSA values and the values of PTV after operational treatment. It also showed that these are independent parameters in the assessment of the results of treatment, in particular in the group of patients with with PTV values of 6–50%, which also carry the greatest risk for BP.

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Значај корелације серумских вредности простата специфичног антигена и процента волумена карцинома простате у постоперативној биохемијској прогресији

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САЖЕТАК

Увод/Циљ Радикална простатектомија (РП) представља најбољи облик лечења болесника са локално ограниченим карциномом простате (КП). Код 27% до 53% болесника након РП ипак долази до биохемијске прогресије (БП) болести. Циљ анализе била је процена значаја корелације преоперативних вредности простата специфичног антигена (ПСА) и процента волумена КП у БП код болесника са учињеном РП и биопсијским Глисон градусом 6 и 7.

Методе У анализу је било укључено 228 болесника са учињеном ретропубичном РП због локализованог КП у периоду од 2007. до 2011. године. Према ГГС вредностима издвојене су три групе: 6 (3+3), 7 (3+4) и 7 (4+3). Према преоперативним вредностима ПСА групе установљене су и праћене следеће три групе: ≤ 4 *ng/ml*, 4,1–10 *ng/ml* и ≥10,1 *ng/ml*. Биохемијска прогресија дефинисана је као два узастопна пораста вредности ПСА већа од 0,2 *ng/ml* након РП. Проценат тумор волумена (ПТВ) одређен је као визуелна процена процентуалне заступљености КП у сваком појединачном микроскопском узорку. Одређене су четири групе ПТВ: 0–5%, 6–25%, 26–50% и 51–100%.

Резултати Биохемијска прогресија регистрована је код 19 болесника. Најзаступљенији ПТВ у групи болесника са БП и из ТРБП и РП био је 6–50%, просечно 30%.

Закључак Наша студија је показала предиктивни значај везе преоперативних вредности ПСА и добијених вредности ПТВ после оперативног лечења те да су ово независни параметри у процени резултата лечења.

Кључне речи: карцином простате; радикална простатектомија: простата специфични антиген; волумен тумора; биохемијска прогресија

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Treatment of tibial shaft fractures with Mitković type external fixation – Analysis of 100 patients

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SUMMARY

Introduction/Objective Tibial shaft fractures (TSF) are one of the most common fractures. External fixation (EF) may be used to treat TSF.
The aim of this study was to analyze the treatment of TSF with Mitković EF.

Methods The study included 100 patients with TSF treated with Mitković EF as the primary and definite method of treatment. The results are compared to those in the literature.

Results The patient group comprised 67% male and 33% female patients aged 10–71years. TSF is common in adult males in the fourth and fifth decades of life. The most common cause is falling with the twisting of the leg (59%). Closed fractures were observed in 76 patients (57.4% of type A AO, 25.4% of type B AO, and 17.1% of type C AO), and open fractures in 34 patients (50% of type I GA, 32.35% of type II GA, and 17.64% of type III GA). The average time period from injury to surgery was 2.5 days (the range being 4 hours to 9 days). Bone healing was achieved in 93% of patients. The average healing time was 18.4 weeks (the range being 11–32 weeks). The distribution of complications is as follows: 10% for minor pin site infections; 4% for major pin site infections; 6% for nonunion; 1% for acute respiratory distress syndrome; 2% for osteitis. There was no deep vein thrombosis nor neurovascular damage. EuroQol score was excellent in 82% of the patients.

Conclusion Mitković EF can be used for treating all types of TSF. Functional results of treatment by this method are excellent. The data analysis of the series does not differ from the data in the literature.

Keywords: tibial fracture, etiology, pathology, surgery; fracture fixation, instrumentation, methods; external fixators; osteosynthesis

INTRODUCTION

Tibial shaft fractures (TSF) are common long bone fractures of great importance. The National Center for Health Statistics (NCHS) reports an annual incidence of 492,000 fractures of the tibia and fibula in the United States [1].

Treatments of these injuries are being debated – whether they are non-surgical or surgical. This can also be said about the method of surgical treatment used [2].

The role of external fixation (EF) in the treatment of these injuries is great and EF is widely used for surgical treatment in accordance with the indication. There are three methods of using EF for the treatment of TSF: 1. EF as the primary and definitive treatment [3]; 2. EF combined with internal fixation [4, 5]; and 3. Conversion of EF to internal fixation [6].

Mitković EF has been used for a long time for surgical treatments of TSF [7, 8]. Biomechanical tests of this type of EF showed remarkable stability of fixation and good biochemical conditions for bones healing [9].

The aim of this study is to describe the method of Mitković EF with the M20 external fixator in surgical treatment of TSF, to examine the effectiveness of this method by analyzing 100 patients treated by this method, and to compare our results with the data in the literature.

METHODS

Patients

This study included 100 patients with TSF who were surgically treated in the 2011–2015 period at the Department of Orthopedic Surgery of the Kosovska Mitrovica Health Center. The surgical treatment was carried out in accordance with the following indications: 1. open TSF; 2. unstable TSF; 3. "damage control" surgery; 4. fractures with "indicators of instability", such as soft tissues damage, involvement of apophysis or articular surface, the excessive distance of fragments, etc [10]. All the patients were treated using the Mitković EF method with the M20 external fixator. EF we used as the primary and definitive treatment method.

In this study, we analyzed the age, gender structure, and the causes of injury. For the clas-

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sification of fractures, we used the AO classification of closed fractures and Gustilo–Anderson (GA) classification of open fractures. At the end of the treatment, we analyzed the outcome, the way we treated the patients, and the treatment complications. The patients' quality of life after the treatment was examined with EuroQol-5d scoring system.

The surgical technique and treatment methods

M20 is a unilateral fixator using pins that we placed in the tibia in the "safe zones" [11]. It is very important to set the correct position of M20 with convergent pins, placed at an angle of at least 60 degrees. The fixator body must be placed between fixator pins in the axis of the tibial diaphysis. Only in this way M20 shows its exceptional biomechanical properties [9]. The proper position of the M20 fixator is shown in Figure 1.

We placed pins before the closed or open reduction of bone fragments, after which we placed the rest of the fixator construction. We used four pins, but depending on the weight of the patient, the type of the fracture, the degree of comminution, and the estimated length of the carrying fixator, we can place more than four pins. Minimal osteosynthesis can be done in the zone of fractures in open reduction. In a few cases, when TSF included the involvement of the distal tibia, we made a combined construction: dynamic EF of the ankle joint and standard EF for TSF, for additional stabilization, as shown in Figure 2 [12].

In similar fractures (TSF with the fracture of the proximal tibia) we performed an EF combined with internal fixation, shown in Figure 3.

In cases of closed TSF, we always use closed reduction of bone fragments and EF after obtaining adequate position of bone fragments. In several cases with an inadequate position of the bone fragments after closed reduction, we did open reduction with a minimally invasive approach. After two weeks, we allowed the partial reliance on the injured leg. Pin site is carried out after three to four days.

In cases of open TSF, we used the following protocol [8]: early surgery (within six hours of injury if possible), profuse irrigation of the wound, extraction of any foreign bodies, hemostasis, debridement of soft tissues, EF (neurovascular procedure if necessary), and drainage. We used the following combination of antibiotics: cephalosporins of the third and fourth generation and aminoglycosides. In the cases of heavily infected wounds we used metronidazole as the third antibiotic. Anti-tetanus prophylaxis was given to all patients with open fractures according to the protocol. After that, each patient was again carefully examined and further course of treatment or the need for new surgery was determined.

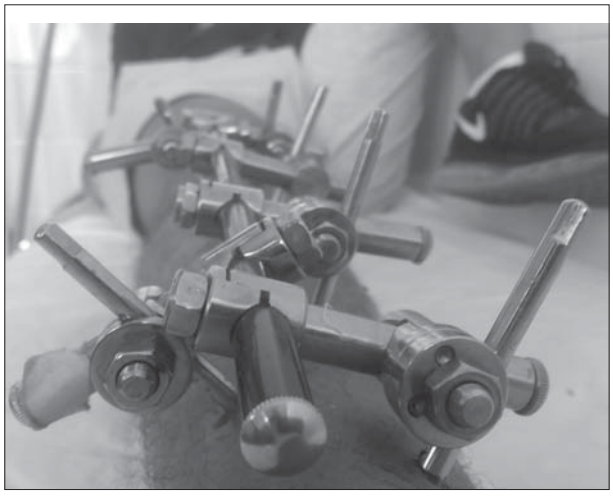

Figure 1. Proper position of the Mitkovic M20 external fixator (for **Figures 2–14** please click on the figure)

We used EF in children after the careful assessment of their age, weight, type of fracture and the need for surgical treatment [13]. We placed fixator pins outside the zone of the epiphysis, while the rest of the treatment is similar to treatment done to adults.

We used nadroparin for thromboprophylaxis according to the protocol in all the patients except children.

RESULTS

Our study included 67 (67%) male and 33 (33%) female patients. The classification of our patients according to age is given in Table 1. Our youngest patient was 10 years old and the oldest one 71 years old. Based on this, we can say that our study shows that adult men in their thirties and forties are the age group injured most frequently.

We treated four children with TSF, aged 10, 12, and 13 years. For two children, it was open fractures type I GA, one child had an AO type B fracture, and one child was with a bilateral TSF (shown in Figure 4).

The most common cause of injury was indirect force (falling on the leg with twisting of the foot or the whole lower part of the leg), with 59% of the cases, followed by the action of a direct force, such as traffic traumatism, with 22%, hitting the lower leg, with 17%, and gunshot injuries, with 2% of the cases.

TSF was closed in 76 patients (type A AO with 57.4%, B AO with 25.4%, and C AO with 17.1%). The patients were surgically treated on average within 2.5 days of the hospitalization, and after four hours in the earliest cases (in patients with threatening compartment syndrome and polytraumatized patients in "damage control" surgery) and no later than 9 days (the patient with heart problem). In 64 (84.21%) patients we achieved a satisfactory position of bone fragments using closed fracture reduction, even in fractures with great bone comminution, shown in Figure 5. In other cases we performed an open reduction of fractures and EF, using a minimally invasive approach. In four cases we used minimal internal osteosynthesis (screw,

Table 1. Classification of patients by age

Patient age	n (%)
2nd decade	10 (10%)
3rd decade	16 (16%)
4th decade	26 (26%)
5th decade	23 (23%)
6th decade	13 (13%)
> 60 years	12 (12%)

wire, or hemicortical pin). Hemicortical pin for additional stabilization is shown in Figure 6.

Our study included 34 patients with open TSF. The majority of patients was with small damage of skin and soft tissue: I GA in 17 cases (50%) and II GA in 11 cases (32.35%). Six (17,64%) patients were with severe soft tissue damage of III GA (1 IIIa GA, 3 IIIb, and 2 IIIc). All the patients with open TSF were surgically treated within six hours of hospitalization. We used the above listed combination of antibiotics. The antibiotics were given immediately after admission to hospital and before the surgery. We continued to administer the antibiotics in type I GA patients up to 72 hours after the operation. To type II GA and III GA patients, the antibiotics were given at least 7 or 14 days, depending on when the sterile microbiological findings were obtained.

All the patients with III GA open fractures had a daily wound care and periodic debridements if necessary. In two patients, the Thiersch transplant skin graft was made.

In one patient, multiple injuries of a. tibialis posterior were found. After a careful wound care, repeated debridements, subsequent secondary sutures, and Thiersch skin transplant, we achieved a satisfactory result. The patient is shown in Figures 7 and 8.

In another case, a patient with an open IIIc GA TSF on the right leg and a II GA open fracture of the left ankle joint was hospitalized with signs of severe traumatic shock due to severe bleeding and signs of serious violations of the blood vessels in the upper part of the lower leg, shown on Figures 9 and 10. He was injured in a car accident and spent nearly two hours stuck under the truck. After initial reanimation we did a surgical procedure of "damage control," an urgent bilateral EF. Reanimation of the patient lasted several hours and included five units of blood transfusion in addition to other procedures. Due to the severity of injuries of blood vessels in the upper part of the right lower leg the patient was referred to the relevant tertiary institution after receiving the overall status that allowed the transport of the patient. Despite the surgical procedures on blood vessels, the amputation of the right leg above the knee was performed in the end.

We had two patients with gunshot injuries of the lower legs. In both cases we achieved excellent results. One of them is shown in Figures 11 and 12. In this patient, we combined a classical surgical treatment with hyperbaric oxygen therapy, which proved to be a good combination for a faster healing of wounds.

The average time for fracture union was 18.4 weeks (the range being 11–32 weeks). We achieved the bone union in 93% of the patients. The decision to remove the fixator was made on the basis of clinical and radiographic findings and the length of treatment. In patients that seemed to have adequate healing we conducted a simple test shown in Figure 13. We removed the fixator and kept pins in the bone, allowed full reliance on the injured leg and followed the clinical and radiographic findings after a few days. If the clinical and radiographic findings were normal, we removed the pins. We continued with the EF treatment in patients who felt pain in the region of the fracture or where there were changes in radiographic findings. After the removal of EF we applied plaster to four patients in order to protect the resulting union. These were our oldest patients.

Table 2. Soft tissue complications in closed tibial shaft fractures

Complication	n (%)
Epidermolysis bullosa	8 (8%)
Dermoabrasion	4 (4%)
Skin necrosis	2 (2%)
Threatening compartment syndrome	2 (2%)

Table 3. The presence of complications during treatment

Complication	n (%)
Minor pin infection	10 (10%)
Major pin infection	4 (4%)
Nonunion	6 (6%)
ARDS	1 (1%)
Osteitis	2 (2%)
Amputation	1 (1%)

ARDS – acute respiratory distress syndrome

Table 2 shows the complications of soft tissue in closed fractures. The most common complication was epidermolysis bullosa. We removed blisters and dried the spots with an antibiotic spray. Minor injuries to the skin (dermabrasions and less frequently postcontusion skin necrosis) were treated carefully. In two patients that were threatened with the compartment syndrome we made an emergency fasciotomy of the lower leg.

The most common complication in our study was related to the pin-tract infection (PTI) in 14 (14%) patients. Although the literature cites multiple classification systems related to the problem of PTI, we used a simple classification on minor and major infections, described by Ward in 1984 [14]. In all the patients with problems related to pin site (pain, swelling, secretion, erythema, itching, etc.) we did a microbiological analysis of the pin insertion using a swab, then we manually tested the pin stability and did an X-ray examination. The patients with minor infections were treated with daily pin site care and antibiotic therapy (positive microbiological analysis) and a careful assessment of the pin stability. The patients with major infections were treated in hospital. In patients with positive microbiological analysis, the signs of pins instability, and radiographic signs of bone osteolysis around the pins, we removed the pins and placed them in a different location.

Nonunion was found in six (6%) patients (two with closed TSF, four with open TSF), shown in Table 3. For the treatment of nonunion, the Ilizarov EF was applied in two (2%) patients, whereas the Mitković EF with compression–distraction device was used in four (4%) patients, shown in Figure 14. In all the patients we achieved bone healing.

The EQ-5D (EuroQol) questionnaire was used to assess these patients at the end of treatment. Excellent results were achieved in 82% of the patients.

In our study we did not have patients with DVT and injuries of neurovascular bundles while placing pins. Also, we did not have any mechanical damage to the M20 construction, in terms of bending or fracture of the structure.

DISCUSSION

The TSF are common injuries that remain challenging to treat because of the wide spectrum of fracture patterns and soft tissue injuries. Understanding the indications for surgical and nonsurgical treatment of these fractures is essential for good outcome [15].

The debate on TSF treatment is ongoing. Operative treatment can be performed with several different implants. Intramedullary nailing (IMN) with a huge biomechanical stability seems to be the implant of choice. The use of EF is still the implant of choice in the first line treatment of multiple traumas according to the damage control principles [16].

EF of TSF with the M20 fixator is a simple and effective method to enable the safe healing of fractures, early mobilization of patients, early weight-bearing, as well as early rehabilitation [17].

The previous three citations describe the dilemma we had during our research. Can EF be used as a universal method of treatment in patients with TSF, and how to properly select patients for surgical treatment? Currently, the data on using IMN as the method of choice in treating TSF are dominant. The role of EF is mainly reduced to a temporarily osteosynthesis, in polytraumatized patients in the procedure of "damage control" and the treatment of open TSF. The use of IMN is described in the literature even for the most serious III GA open fractures. [18].

In our institution, the Mitković EF has been in use since 1998 and 375 patients with TSF have been surgically treated so far. In the beginning, we treated patients with high bone comminution and open TSF. Functional results of treatment of such fractures were excellent and we expanded the list of indications for surgery in patients with unstable closed fractures as well as patients who had "indicators of fracture instability." EF is particularly suitable for the treatment of segmental TSF and other high bone comminution (gunshot injuries, traffic traumatism, etc.). According to McMahon et al. [19], IMN has the fastest time to fracture union in segmental TSF; however, there are concerns regarding an increased deep infection rate in open segmental TSF. In this subgroup, the data suggest that the EF provides the most satisfactory results. In our 15-year use of the M20 fixator for TSF, we never had a mechanical damage to the M20 structure. In patients who had no problems with the PTI, a remarkable biomechanical stability of the Mitković EF enabled long-term use of fixators, but good stability is guaranteed only with an adequately positioned fixator and a proper pin site care. Only in this way does the Mitković EF show its exceptional biomechanical properties [9].

Gender structure (67% of male and 33% of female patients) and injuries most common in the fourth and fifth decades of life correspond to the data in the literature [1]. The most common cause of injury was the effects of indirect forces, which was the case in 59% of the patients, followed by the effect of a direct force, with 41% of the patients. The distribution of fractures classified in the AO system followed the cause of injury (54% for AO type A, 27% for type B, and 19% for type C), and corresponded to the intensity distribution of forces.

EF was used in four children on the basis of a careful assessment of the child's age, weight, and the type of fracture. Children adapted very quickly to the method of treatment and functional results of the treatment were excellent. According to Kinney et al. [20], the initial treatment outcomes between the operative fixation and closed reduction of the displaced tibia fractures in adolescents are similar, but patients must be counseled about the high failure rates with closed reduction. In a study covering 106 adolescents, Marengo et al. [21] reported that the average patient age at the time of injury is 13.5 ± 1.3 years (the range being 11.3–16.1). The mean patient weight was 57 ± 8 kg. This study demonstrates that the use of elastic stable intramedullary nailing for displaced TSF in children and adolescents weighing 50 kg (110 lb) or more, or older than 13 years, is not contraindicated.

Average healing time of 18.4 weeks and achieving bone union in 93% of the cases is in accordance with the data in the literature.

Distribution of complications (shown in Table 3) is similar to the data in the literature. Beltsios et al. [3] published similar information. In our study, the most common complication was PTI (14%). Ramos et al. [22] reported a similar pin site problems. Proper identification of PTI and a quick response is of the utmost importance, as pin instability is the instability of the entire EF [14].

Tibial nonunion is estimated to constitute 2–10% of all tibial fractures. The incidence is greater with high-energy injuries and open fractures [23]. In our series, we had 6% of nonunions, which does not deviate from the data in the literature. In all the patients we achieved bone healing and good functional results.

There was a significant positive correlation in patients with TSF between functional outcomes and the EQ-5D score [24]. In our study, an excellent result was achieved in 82% of the patients (EuroQol 5D), but the level decreased with the severity of injuries (fasciotomy, grade IIIB / IIIC open fracture, and amputation). Giannoudis et al. [25] state that patients with these injuries still report long-term problems with their health-related quality of life, though to varying degrees.

CONCLUSION

Properly placed Mitković EF can be used to treat even the most serious TSF fractures as it provides optimum biomechanical conditions for bone healing and excellent stability of osteosynthesis. Closed reposition of TSF and EF is a method of treatment and provides exceptional results. EF has a precious role because it is used in treatment of open TSF. A combination of early surgery, profuse wound irrigation, removal of all foreign bodies, debridement of avital tissues, fracture stabilization using the external EF, early reconstruction of soft tissue defects, antibiotic and tetanus prophylaxis, is a method of choice in open TSF treatment, even in type III GA, the most complex open TSF. This

method of TSF treatment gives excellent functional results, and allows for the possibility of early rehabilitation in a very short period of time after surgery, particularly in patients with closed TSF and which are performed by closed reduction of fragments. The patients were generally tolerant to long-term treatments using EF. In our study, the quality of life of patients described by EuroQol 5D scoring system proved to be excellent in 82% of the cases. We believe that early surgical treatment is of extreme importance in patients with TSF. The average healing time of 18.4 weeks and bone union in 93% of the cases is in accordance with the data in the literature. In this study, we showed the number, type, and method of treatment of complications, and our data do not deviate from the data in the literature. In a larger percentage of patients (14%), pin site problems can be considered regular attendant problems related to EF in the region of the lower leg during prolonged wearing of EF. Proper identification of pin site problems, adequate response, and treatment are of utmost importance.

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Лечење прелома потколенице спољашњом фиксацијом по Митковићу – анализа 100 болесника

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САЖЕТАК

Увод/Циљ Преломи потколенице (ПП) једни су од најчешћих прелома и могу се лечити спољашном фиксацијом (СФ). Циљ овог рада је био да анализира резултате лечења ПП помоћу СФ по Митковићу.

Метод Студијом је обухваћено 100 болесника са ПП лечених СФ по Митковићу као примарним и дефинитивним методом лечења. Резултати су упоређени са литературним подацима.

Резултати Група болесника састојала се од 67% мушкараца и 33% жена, старости 10–71 године. ПП најчешће задобијају одрасли мушкарци у четвртој и петој декади живота. Најчешћи узрок је пад са извртањем ноге (59%). Затворених прелома је било код 76 болесника (тип А АО 57,4%, тип Б АО 25,4% и тип Ц АО 17,1%). Отворених прелома је било код 34 болесника (тип I ГА 50%, тип II ГА 32,35% и тип III ГА 17,64%). Просечно време до оперативног захвата било је 2,5 дана (4 ч – 9 дана). Зарастање је постигнуто код 93% пацијената, а просечно време зарастања је било 18,4 (11–32) недеље. Компликације лечења су биле: минор инфекција клина 10%, мајор инфекција клина 4%, незарастање 6%, АРДС 1%, остеитис 2%. Дубоких венских тромбоза и неуроваскуларних оштећења није било. Анализа квалитета живота помоћу *EuroQol* скора била је одлична код 82% болесника.

Закључак СФ по Митковићу се може употребити за лечење свих типова ПП. Функционални резултати лечења овом методом су одлични. Подаци добијени анализом серије не одступају од података у литератури.

Кључне речи: преломи потколенице, етиологија, хирургија; фиксирање прелома, инструменти, методе; спољни фиксатори; остеосинтеза

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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Female street sex work in Belgrade as a risk environment for a syndemic production – A qualitative study

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SUMMARY
Introduction/Objective Although female street sex workers are contextually vulnerable to numerous health-endangering factors, they also contribute in re-producing them. This synergetic production is approached by syndemic theory developed within medical anthropology.
The objective of the study is to present an analysis of the results of a qualitative ethnographic study conducted in Belgrade, Serbia in 2015, and reflect upon social environment factors influencing syndemic development of medical conditions.
Methods The risk environment factors enhancing possibilities of developing particular medical conditions were investigated by applying qualitative anthropological methodology, emphasizing semi-structured in-depth interviews, a standard qualitative sample, and respondents' self-reporting.
Results Social environment of sex work, generally considered risky due to sexually and blood-transmitted diseases, in this study also proved as receptive for many other illnesses, whose syndemic character has been insufficiently addressed. The study confirmed the syndemic nature of street sex work.
Conclusion The social science perspective should be used in health policy conceptualization and implementation not only during latter stages, i.e. in the interpretation of the social conditions influencing medical related issues, but during early stages of understanding how those conditions and issues circularly constitute each other.
Keywords: medical anthropology; qualitative research; street sex work; risk environment; syndemics: health policy

INTRODUCTION

Street sex work in Belgrade is identified by previous research as an environment capable of generating various epidemiological risks, most notably those related to HIV/AIDS and sexually transmitted infections (STI) [1]. The population of female street workers (FSWs), highly vulnerable to such risks in itself, makes altogether with their male clients the so-called "bridge population," which holds the potential for transmitting diseases to a wider population, otherwise at not so high HIV- or STI-related risk [2]. Both working and living conditions of street FSWs make them susceptible to some other diseases, the infectious ones, like hepatitis C virus (HCV) or tuberculosis (TBC), or the non-contagious ones caused by alcohol or drug abuse. FSWs are also prone to be the victims of physical and non-physical violence, as well as of stress caused by social stigma and poverty [3, 4]. As street sex work contextually perpetuates numerous health-endangering factors, we argue it is the syndemic environment [5].

Syndemic theory, developed within medical anthropology, addresses the empirically observed tendency of pathologically different health conditions to co-occur and overlap in certain populations in relation to their living conditions [6, 7]. Studies inspired by this notion stress "elucidating specific biological, behavioral, emotional, or other mechanisms of adverse interaction among co-morbid diseases, and the social environments of sufferers that facilitate multiple disease clustering and deleterious interactions" [8]. Syndemic theory is not a medical theory designed to predict and explain exact co-occurrence but a social science medical related research program which aims to backup epidemiological research by suggesting likeliness of having such developments when social factors like poverty, poor housing, social exclusiveness, or violence regularly co-occur within a population.

The social environment of (the street) sex work plays a significant part in producing factors responsible for worsening health conditions and is regularly researched as a type of risk environment in which mutual fuelling of diverse health problems proved to be understood best by applying qualitative research methods, as developed in social science [5, 9, 10, 11].

Our aim is to present results of the qualitative ethnographic study and reflect upon social environment factors influencing syndemics development and production within population of street FSWs in Belgrade. By identifying and interpreting these factors we seek to demonstrate the importance of the interplay between social and medical factors of the diseases

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particularly affecting this population, and thus demonstrate the need for an interdisciplinary interpretation of health-related policy issues.

METHODS

Sixteen adult street FSW in Belgrade were interviewed during 2015. Each interview has been performed after the written consent, lasted approximately 60-90 minutes, was tape-recorded and transcribed for analytic purposes. Participants were chosen according to predefined criteria [1, 3], and according to the standard structure of sample in qualitative research (sixteen participants [12], two participants [13], three participants [14], seven participants [15]). They were provided with information on aims, purpose, and ethics of this study, and have been let known that they can retreat at any time and without obligation to explain.

In-depth, semi-structured interviews used in this study are designed to enable informants to feel as comfortable as possible, to provide them with the themes of interest to which they can choose to respond or not, and to offer them the time necessary to present and explain their thoughts, stances, attitudes or beliefs. The purpose of in-depth interviewing is to gain first-hand accounts of experience on the matter of research by the respondents themselves, i.e. it is purposively based on self-reporting [16–21].

The interviews were devised after the study topic guide, a standard orientation tool in qualitative research, containing principle topics of interest according to the aim of the research. The topic guide and the corresponding coding frame (Table 1) were modified after the one used in pivotal studies of FSW in Serbia (1, 3).

These broad topics enabled the coverage of the set of more precise concerns regarding FSWs' social setting, such as daily routines; initiation into sex work; relations to partners and/or pimps; their micro-social environments; services provided or not; amount of money for which they are willing to perform services they otherwise do not engage in; their socioeconomic status and health expenditures particularly; health status, including if they recall the occasions when they were harmed by an infectious disease or physical violence, or were diagnosed with a chronic or mental illness; the ways they take care of their health, including social service status and attitudes towards healthcare providers; the troubles and health-related consequences of the lack of legal status of their profession; violent nature of their working environment, etc.

The basic criteria for including the participants in this study were as follows: women who have been offering

Table 1. The coding frame

First-level code	Second-level codes
1. Personal information	1.1 Living conditions 1.2 Family
2. Sex work initiation	2.1 Reasons 2.2 First experience (where, how, expectations, clients, condom use) 2.3 Influence of other SWs/friends 2.4 Environment (police, location, negotiations)
3. Personal sex work organization	3.1 Ways of reaching clients 3.2 Place of service provision 3.3 Pimps, protection, other persons involved 3.4 Negotiations (location, types of service, payment, condom use, influences) 3.5 Hours (seasons) 3.6 Earnings, costs (tips, types of sex work, condom use, client type)
4. Clients	4.1 Client types and numbers (regular, one-time) 4.2 Client description (where from, age, marital status, etc.) 4.3 Client preferences 4.4 Drug use
5. Condom use	5.1 Reasons 5.2 Purchase and provisions 5.3 Environment (role of external factors)
6. Sex work without a condom	6.1 Reasons 6.2 Client refusal 6.3 Environment (role of external factors)
7. Drug use	7.1 Drug use patterns (especially as related to sex work) 7.2 Drug use and alcohol use with clients 7.3 Drug use and alcohol use with other SWs 7.4 Injecting drug use (access to sterile equipment and sharing) 7.5 Environment (role of external factors)
8. Violence	8.1 Client violence (reasons, how often, strategy) 8.2 Police violence (reasons, how often, strategy)
9. Risk	9.1 Perceptions (HIV/STI risk) 9.2 Non-HIV risk (e.g. violence, arrest) 9.3 Risk behavior change and risk reduction
10. STI/HIV	10.1 Past experiences 10.2 Knowledge of STI/HIV
11. Testing	11.1 HIV testing, diagnosis and experience 11.2 STI testing, diagnosis and experience

STI – sexually transmitted infections; SWs – street workers

Table 2. Results

No.	Age	FSW experience	IDU	Health status	Education	Marital status	Children	Health insurance	Tested for HCV, HIV at least once
1	29	11	+	Chlamydia, HCV+	SE	S	/	+	+
2	22	6	/	Broken rib, pneumonia, alcohol abuse, HPV	PE	S	/	/	+
3	33	12	/	Pediculosis pubis, alcohol, injuries from being beaten up, pneumonia	PE	Sep.	1	/	+
4	22	1	/	Epileptic, broken arm, BV	PE	M	/	/	/
5	21	10	/	Alcohol abuse, gonorrhea, mental disorder	iPE	S	/	/	/
6	30	11	+	Pediculosis pubis, TBC	SE	D	1	+	+
7	19	3	+	HCV+, mental disorder	PE	S	/	+	+
8	29	2	+	HCV+, heart issues	PE	M	1	+	+
9	25	6	/	Gonorrhea, injuries from being beaten up	PE	S	/	+	+
10	29	5	+	Alcohol abuse, mental disorder, injuries from being beaten up	PE	M	/	+	+
11	31	16	+	HCV+, HIV+	PE	S	/	/	+
12	33	8	+	Genital herpes, heart issues	iPE	Sep.	/	/	+
13	26	3	/	HCV+, pediculosis pubis	PE	S	/	/	+
14	23	5	/	BV, TBC, alcohol	iPE	S	/	/	/
15	22	2	+	HIV+, TBC	PE	S	/	/	+
16	38	14	/	Genital herpes, HPV, BV	PE	S	2	/	+

FSW – female street worker; IDU – injecting drug user; D – divorced; S – single; M – married; Sep. – separated; PE – primary education; iPE – incomplete primary education; SE – secondary education; HCV – hepatitis C virus; HPV – human papillomavirus BV – bacterial vaginosis; TBC – tuberculosis

commercial sex services in the streets for at least five years; have provided commercial sex services in the previous thirty days; abuse alcohol and/or drugs; and have medically documented reports on two or more conditions, or have had them in the last three years. Out of many known sites of sex work, FSWs from the vicinity of the Main Railway Station, the Blue Bridge ("Plavi most"), and another purposively undisclosed location in the urban core of Belgrade were interviewed.

RESULTS

All of the participants stated that they have been initiated in sex work in their teens. All of the injecting drug users (IDUs), exactly one half of the responders, claimed that they had commenced providing sexual services before they began injecting drugs, mostly heroin. Alcohol abuse has been reported as more frequent among those who do not inject drugs, as well as injuries caused by physical violence and STI. On the other hand, HIV and HCV infections were reported as more frequent among FSWs who inject drugs, while mental disorders and other illnesses are nearly evenly distributed.

The following co-occurrences of medical conditions were self-reported by IDUs: chlamydia and HCV; pediculosis pubis and TBC; HCV and mental disorder; HCV and heart issues; mental disorder and injuries from being beaten up, together with alcohol abuse; HCV and HIV; genital herpes and heart issues; HIV and TBC.

Participants who do not inject drugs reported co-occurrences of the following medical conditions: bacterial vaginosis and TBC, together with alcohol abuse; HCV and pediculosis pubis; gonorrhea and injuries from being beaten up; gonorrhea and mental disorder, together with alcohol abuse; epilepsy, broken arm, and bacterial vaginosis; pediculosis pubis, injuries from being beaten, and pneumonia, together with alcohol abuse; broken rib, pneumonia and human papillomavirus, together with alcohol abuse; chlamydia and mental disorder.

All of the diagnoses were self-reported, i.e. they do not necessarily correspond to a professional medical opinion but illustrate the perception and knowledge of the respondents themselves.

Basic social features of street FSWs

In contrast to the places of their work, the participants live mostly in distant suburban neighborhoods. They normally rent small apartments or single rooms, the latter sharing running water with other tenants. Most of them often move, seeking lower rent.

Eleven of them claimed that they do not have a pimp, but seven of those stated that they live with their boyfriends, which is usually close to or even the same as having a pimp, according to the previous findings [1]. Others who admitted having a pimp claimed the pimp was also their boyfriend.

Only two respondents reported they have completed secondary school, and three of them stated that they did not complete elementary school. All of the informants claimed domestic disturbance in their pre-sex work family lives: their parents divorced and consequently they were being neglected by the remaining parent and their step-parent; they were abandoned by a parent and left with financial hardship; they were being abused by parents or siblings (including half-siblings); they went away from home after completing primary education to search for a job due to economic hardships of their families; they had chronically ill parent(s) not capable of taking full care of them, etc. A few of them maintain relations with their parents in order to take advantage of remaining on their health insurance policies.

Their common claim was that they have engaged in sex work either for having no qualifications or/and for seeing the sex work as an opportunity for earning easy money. Some of them thought of the sex work as a temporary solution but the claim that they would like to find the way out of it was unanimous (though admitting they are not actively looking for another job).

Basic health-related risk features of street sex work social environment

Knowledge about illness related to risks produced by sex work is gained either personally or transmitted by other FSWs. It is subject to change and so is its related behavior: it could be empowered positively (as a result of the outreach work of some health institutions like JAZAS) or negatively, for example, when money shortage is urging them to hustle for clients no matter what the weather conditions or clients' request are, when they abandon safety procedures on obviously false, albeit habitual, presupposition "that condoms are efficient only in heterosexual intercourse" [21, 22].

The respondents' usual claim is that they do not work without using a condom, but when asked if they recollect whether they used it or not on the last four to 10 occasions, it is found they mostly did not. The unprotected sex could bargain them a bit higher price for their services; the other usual answer is that clients prefer it that way or that the clients could get nasty if they firmly oppose. Oral sex is regularly provided without a condom and all of the participants were positive about providing such a service. Some of them are reluctant and others are disgusted by the notion of ejaculation into the mouth or over the body. Nevertheless, they state that they can hardly avoid direct contact with clients' sperm, and by knowing that, they do not try to do it at all.

Save for three of the participants who claimed they have never provided anal sex, and two more that are willing to provide it upon request, the others do it now and then, mostly if they cannot earn money needed at the moment, and mostly without any protection. Some of the respondents reported they agree upon such service only if the client uses a condom, but also admit that a "fair price" to do it without a condom is convincing enough to them.

Pre-sex hygiene is mostly not an issue for FSWs and their clients. Providing services takes place out in the open, in hidden or visually not distinctive places (dark parking lots, remote parts of parks or woods); indoors (purposely rented rooms in the vicinity of the sex work route); in vehicle cabins. It usually has to be quick. Using lubricants is the only reported preparation for sex, and using wet wipes is the most usual way of cleaning oneself after providing sex service.

Providing services in vehicle cabins is the least favored by the FSWs, so they try to avoid it whenever possible. Not going to the client's place of residence is a rule, as they fear clients can get rough there or even try to rob them or force them to the sexual acts they are unwilling to perform. Nevertheless, violent acts happen at the regular working places by clients refusing to pay after being provided the sex service; clients incapable of performing the sexual act; clients of ill temper or "control freaks" – all of them physically harm street workers now and then.

Three main resources of physical violence were indicated: boyfriends/pimps; clients; and police officers. While the violence committed by policemen could be described as brutality, that produced by boyfriends/pimps and clients could result in more serious health consequences. As previously reported, police violence is restricted to brutal treatment when having FSWs arrested, like pushing, slapping and cuffing; there are also random tries of coercing sex by the policemen that is noted for threats of being arrested or ousted from the territory the FSWs are working in [23].

Violence produced by boyfriends/pimps and clients usually results from quarrels, bad temperament, mental instability, etc., and it can result in serious injuries, from deep bruises and black eyes to broken arms and ribs. The syndemic-specific problem in that regard is that FSWs are unanimously reluctant to seek help from police or social service and to go to ask for medical help. When suffering from fractures, they usually wait for a day or two before seeing medical doctor, trying to ease themselves with analgesics. The main reason they hesitate to seek the institutional help is the fear of being recognized as illicit sex solicitors and treated with neglect by both healthcare workers and police officers, as reported for Serbia and worldwide [24–27]. The second most important reason is the fear of retribution by those who hurt them, which stems again from the highly uncertain legal and social position FSWs occupy in Serbia.

Most of the respondents do not have healthcare insurance and rely only on private medical practitioners. They seek medical help only if they cannot resist the health problems or when those prevent them from working. "Petty" problems such as cold, fever, coughing or "bearable" pains do not prevent them from working, nor do their menstrual periods, for most of their duration.

Those participants who inject drugs attribute equal shares of their injecting habits to doing it alone and to doing it with another injector or injectors (the same goes for alcohol use or abuse). Sharing of the injecting equipment, including cooking together, occurs whenever the usual injecting routine is ruptured. It usually follows prolonged periods of money shortage or as a kind of sociality – exactly the same pattern as with the IDU in Belgrade in general [28]. Regular alcohol consumers admit to drinking with clients although they know they shouldn't, for safety reasons. Those who binge drink are strict about the rule of not drinking with clients, as they fear things can get out of control and they can end up physically hurt. Their diet and clothing show certain pattern as well. As they spend most of their time outside their dwelling places wearing clothing pieces suitable for their work, due to their working hours (from some time in the late afternoon until deep into the night, depending on the season and weather), their costume usually does not follow the weather conditions and stays light during the course of the year. Their diet is all but regular and is predominantly based on fast food. They eat when they can during the day, usually having two main

meals – one after they return from work and the other before work, but not very close to it, as they do not want to be "heavy" when going to work, fearing they can feel nausea if they perform sexual acts with their stomachs full.

DISCUSSION

Social environment of sex work is widely considered risky to sexually and blood-transmitted diseases, as confirmed by numerous studies [1, 3, 21, 22, 23, 29, 30]. However, it proved to be receptive for many other illnesses as well, whose syndemic character has been insufficiently addressed. Congruence between results presented here and in several similar studies indicates that certain social behavior works in favor of syndemic production, regardless of drug use. While it is intuitively expected that HCV will be more frequent among the IDU in general than within the non-injecting FSWs, frequency of the alcohol abuse among the non-injectors comes as a kind of a counterweight; that is, sex work is hard to cope with individually without substance abuse [31].

Physical violence to which street FSWs are exposed almost regularly, illegal status of their profession, and inability/unwillingness to access public healthcare and social services confirm such findings, making them double-excluded, i.e. personally and socially stigmatized. However, it is important to stress the limitation of this study: no questions on a chosen medical doctor have been asked.

Gender shows to be an issue as well, for their week social position is likely attributed to their "biopolitical" vulnerability, i.e. the interaction of biological factors with social and political ones in causing higher health-related risks among women [32].

Their adhesiveness to STI comes then not only from the nature of their work but from the lack of proper medical care, prevention and treatment alike. Faced with judgment and reportedly neglect by law, institutions and the general public, they dispose not only aversion towards asking for protection from violence but also coercion, unwilling to reveal profession-related circumstances of their injuries or health conditions to medical professionals. Furthermore, their self-reported lack of healthcare insurance prevents them from receiving help from medical specialists, as seeing private medical practitioners is scarcely affordable to most of them. Their hygienic habits stem at least partially from the need to be as quick as possible when their service is over, in order not to be caught in the act. Constantly in economic deprivation, they do not hesitate engaging in unprotected sexual acts in order to earn more money or to prevent clients from going to another sex worker. Street FSWs rank lowest in the sex work world, thus charge low for their services, which faces them with the need of having as much clients as possible per working hour.

The way of providing services at places which are health- and hygiene-wise highly problematic; the fact of them being up and on their feet outdoors for almost all and every night; the presence of stress, uncertainty, lack of formal education; and constant economic deprivation, illegal status of the profession and generally poor living conditions all act as social impellers of health endangerment and must not be excluded from the explanation for their increasing susceptibility to different health issues when compared to the general population [24].

An urge to acknowledge the value of qualitative social research in addressing socially-and culturally-specific medical issues has already been recognized in other social contexts [33, 34, 35]. In that regard, it would be of utmost importance to consider the methodological specificities of research among vulnerable populations [36, 37, 38]. As the study confirmed a clear syndemic basis for such co-occurrences, it should be further investigated and taken into account in policy development and implementation.

Prevention and harm reduction recommendations

A wider and more aggressive national strategy and action plan regarding the use of condoms, including during oral sex, should be deployed. More frequent outreach education of FSWs on STI and easing their access to condoms should be a priority.

Stronger outreach of medical support to FSWs should be considered in relation to their stigmatization, which results in reluctance or even aversion towards healthcare professionals and institutions.

Policing actions more oriented towards clients of FSWs should be introduced.

National policy plans and actions on women empowerment in the society should include and emphasize the category of FSWs as a vulnerable population and a group at most risk in regard to partner violence, and sexually and gender-related violence.

CONCLUSION

The study confirmed that the street sex work is such an environment where the risk of multiple diseases is produced in the syndemic mode. Besides STI, as the most obvious possible consequence of the very nature of their work, the FSWs are faced with frequent substance – heroin and alcohol – abuse. This increases their proneness to other infections, mostly HCV but also HIV and pulmonary diseases, as well as to the non-infectious medical conditions like mental health problems or heart issues. The illegal status and overall social image of their profession, together with chronic scarcity, make them additionally vulnerable to various types of violence.

NOTE

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Женски улични сексуални рад у Београду као ризично окружење за изазивање синдемије – квалитативно истраживање

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САЖЕТАК

Увод/Циљ Уличне сексуалне раднице контекстуално су подложне бројним факторима који угрожавају здравље, али и саме учествују у њиховом репродуковању. Овој синергији смо приступили из перспективе теорије синдемије, развијене у оквирима медицинске антропологије.

Циљ рада је био анализа резултата квалитативног етнографског истраживања спроведеног у Београду током 2015. године и указивање на факторе социокултурног окружења који утичу на синдемијски развој болести.

Метод Употребом стандардне квалитативне антрополошке методологије приступили смо чиниоцима ризичног окружења који увећавају могућност појаве специфичних обољења. Нагласак је стављен на полуструктурисане интервјуе и анализу података о којима извештавају сами испитаници.

Резултати Друштвено окружење сексуалног рада, које се у начелу сматра ризичним од сексуално и крвљу преносивих болести, у овом истраживању се показало као подложно за ширење многих других болести чији синдемијски карактер до данас није довољно проучен. Истраживање је потврдило синдемијски карактер уличног сексуалног рада.

Закључак Перспектива друштвених наука може допринети концептуализацији и имплементацији здравствене политике, како у фазама тумачења друштвених услова који утичу на појаву медицински релевантних стања, тако и за разумевање тога како се медицинска стања и друштвени услови у којима они настају међусобно конституишу.

Кључне речи: медицинска антропологија; квалитативно истраживање; улични сексуални рад; ризично окружење; синдемија; здравствена политика

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PRELIMINARY REPORT / ПРЕТХОДНО САОПШТЕЊЕ

Clinical analysis and surgical treatment of frontal sinus mucoceles – 10 years' experience of seven cases

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SUMMARY

Introduction/Objective A mucocele is a benign cystic but extremely expansive change in paranasal cavities, first described in literature by Langenbeck in 1820. The etiology of mucoceles is still a subject of debate. It is assumed that the obstruction of the frontal sinus duct and drainage impairment into the middle nasal meatus, as a consequence of a chronic infection, trauma, or tumor, represent one of the main causes of their occurrence.

The aim of this study was to describe ophthalmological and clinical properties of frontal sinus mucoceles.

Methods Our retrospective study covered a period of 10 years during which seven patients with mucocele in the frontal sinus were operated on.

Results Predisposing factors for the appearance of frontal sinus mucoceles were observed in six out of seven patients – the existence of a previous surgical intervention in two patients, the existence of a previous injury in four, and one patient did not exhibit the existence of predisposing factors. Four out of seven mucoceles were located in the rear segments of the frontal sinus. The destruction of the anterior sinus wall was observed in one patient, while the process propagation toward the endocranium and the orbit was present in three out of the seven patients. Postoperative epistaxis was noted in two out of three patients treated with transfacial approaches.

Conclusion Transcranial and transfacial approaches are treatment methods for advanced mucoceles with a present intraorbital, intracranial, and endonasal process propagation.

Keywords: mucoceles; frontal sinus; diagnostics; surgery treatment

INTRODUCTION

A mucocele is a benign cystic but extremely expansive change in paranasal cavities, first described in literature by Langenbeck in 1820 [1].

The etiology of mucoceles is still a subject of debate in scientific circles and it has not been defined in great detail. It is assumed that the obstruction of the frontal sinus duct and drainage impairment into the middle nasal meatus, as a consequence of a chronic infection, trauma or tumor, represent one of the main causes of their occurrence [2].

Growth and development of mucoceles are very slow and can last for several years. The appearance of symptoms is associated with complications of the process spreading outside the sinuses, as a consequence of bone destruction, or with a secondary infection in terms of mucopyocele [3].

Given the direct contact of the frontal sinus with the brain parenchyma, orbit and nasal cavity, a possible extension of mucoceles towards them represents one of the complications of advanced and, in most cases, late diagnosed mucoceles.

Ophthalmological disorders in terms of diplopia, upper lid ptosis, proptosis, bulbus dislocation, and periorbital swelling represent the symptoms of the process spreading toward the orbit [4]. Intracranial extension developed as a consequence of the posterior sinus wall destruction may cause meningitis, meningoencephalitis, pneumocephalus, brain abscess, and cerebrospinal liquid extravasation [5]. Mucocele expansion toward the nasal cavity leads to nose obstruction and the appearance of anosmia [6]. Headaches and swelling in the orbit area represent the key reasons why patients turn to doctors.

The aim of this study was to describe ophthalmological and clinical properties of these lesions, analyze used surgical approaches, and present the incidence of recurrence and complications of surgical treatments.

METHODS

The conducted study is retrospective. It covered a period of 10 years during which, after surgical examinations, complete diagnostics, and preparation, seven patients with pathohistologically confirmed mucocele in the frontal sinus were operated on. All the patients were operated on using endotracheal anesthesia at the Department of Maxillofacial Surgery, Clinic of Dentistry, Faculty of Medicine in Niš,

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Serbia, between 2002 and 2012. The analysis included the sex and age of patients, the presence of a chronic disease, predisposing factors, clinical characteristics, surgical approach type, recurrence, and postoperative complications in all patients. The minimal period of monitoring each patient was two years.

Prior to surgical treatments, in the observation stage, multi-slice computed tomography was done in all the patients to determine the location of mucoceles, the presence of bone destruction of sinus walls, and the extension rate toward the orbit, brain parenchyma, or nasal cavity.

RESULTS

The mean age of the mentioned group of patients was 56, with the age range being 28–65 years. As for the sex, four out of the seven patients included in the study were male.

The presence of chronic diseases was noted in six out of the seven patients – chronic artery hypertension in five, diabetes mellitus in two, and chronic obstructive pulmonary disease in only one patient (14%).

Predisposing factors for the appearance of frontal sinus mucoceles were observed in six out of the seven patients,

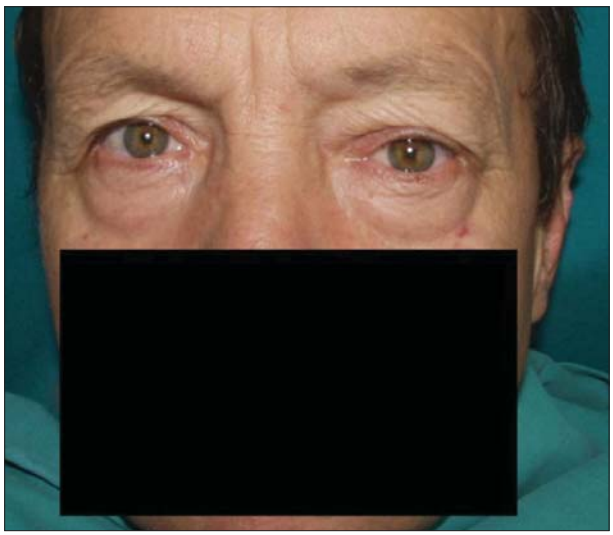

Figure 1. Temporal sinus mucocele with endocranial and intraorbital propagation; the presence of exophthalmos accompanied by inferior dislocation of bulbus with no defects in the visual field

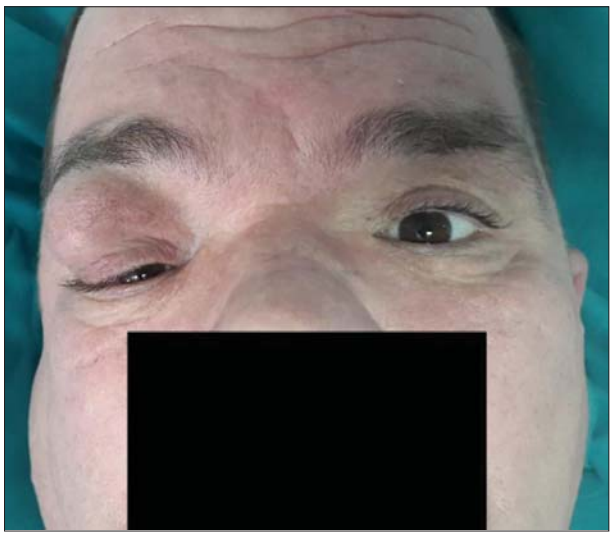

Figure 3. Frontal sinus mucocele with intraorbital extension; the presence of enophthalmos, inferior dislocation of the bulbus without diplopia and defects in the visual field area

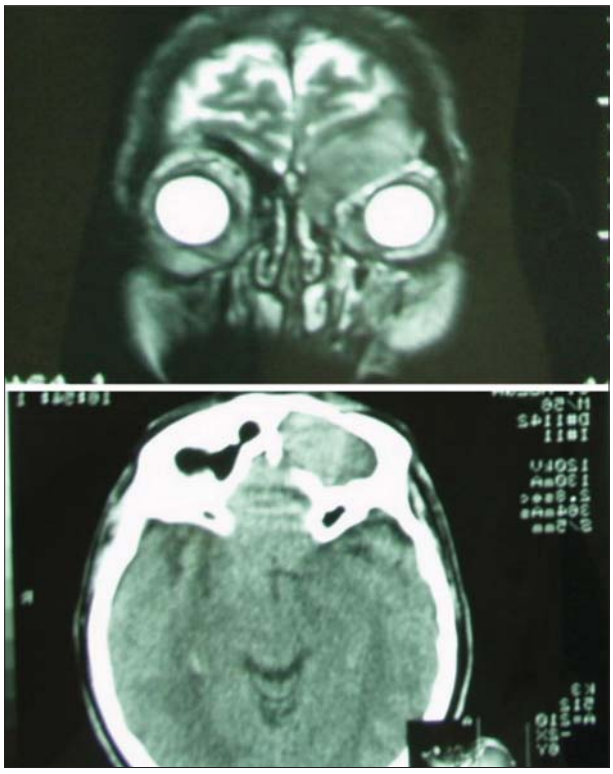

Figure 2. Hypodense formation in the left frontal sinus and left orbit; process extension presents frontobasally and toward the left orbit

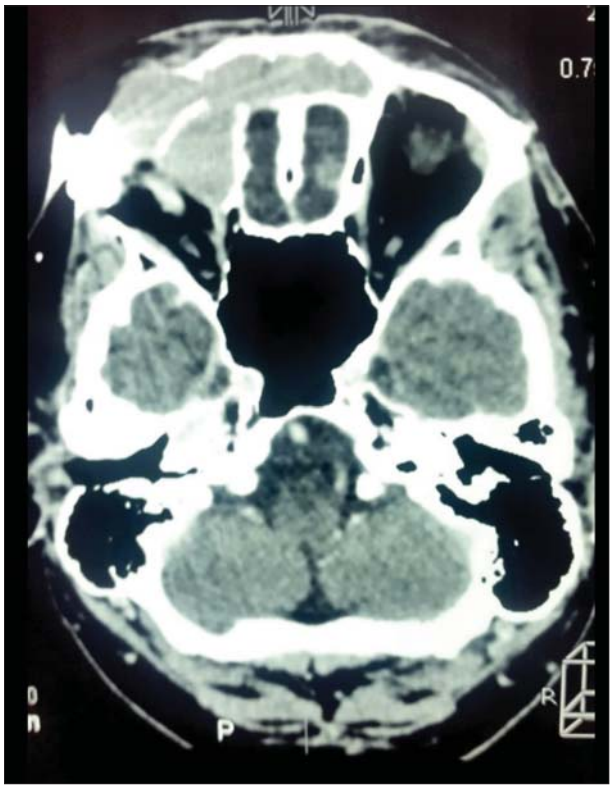

Figure 4. Hypodense formation in the right frontal sinus with signs of the sinus floor destruction and penetration into the right orbit

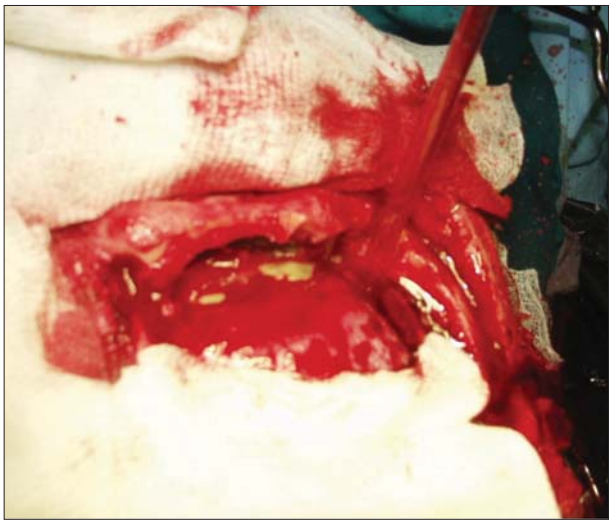

Figure 5. Post bifrontal craniotomy condition; mucopyocele in the left frontal sinus

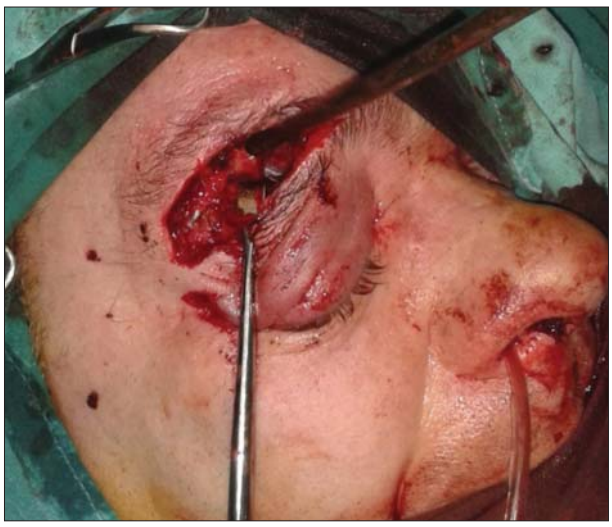

Figure 6. Post frontal sinus mucocele and orbit extirpation condition; drainage performed through the nose

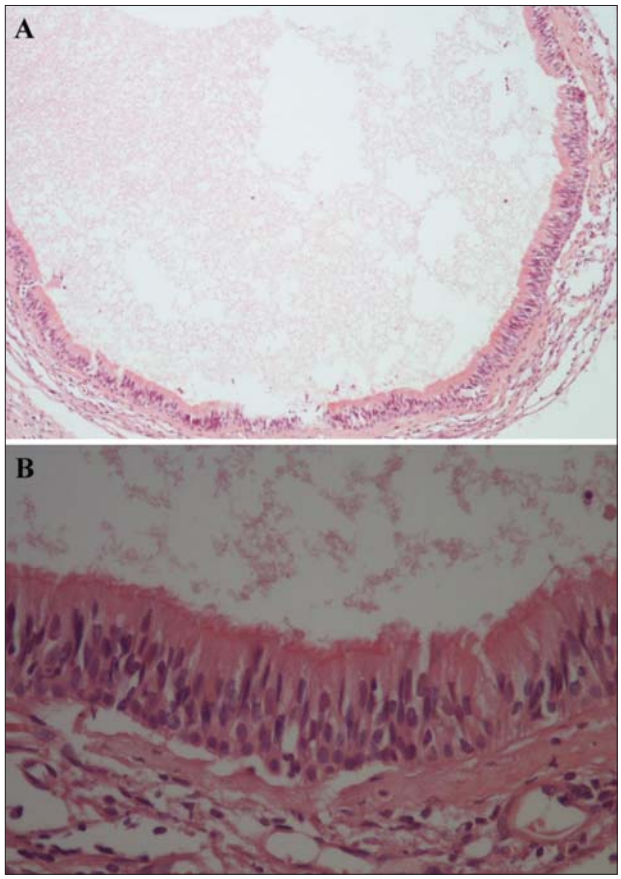

Figure 7. Cyst showing pseudostratified columnar ciliated epithelium containing mucous cells (H&E; A: × 4; B: × 20)

the existence of a previous surgical intervention in two, the existence of a previous injury in four out of the seven patients, whereas one patient did not exhibit the existence of predisposing factors.

Four out of seven mucoceles were located in the rear segments of the frontal sinus. The destruction of the anterior sinus wall, dura infiltration, and intracranial propagation process were observed in one patient, while in three the process propagation toward the endocranium and the orbit was present (Figures 1 and 2).

In three cases, the process extension toward the orbit was present along with the mentioned ophthalmological disorders (Figures 3 and 4). The occurrence of diplopia was observed in two cases.

In four patients, bifrontal craniotomy was performed after the bicoronary approach due to possible exploration of the anterior cranial fossa, frontal sinuses, and orbits. The tumor formation was completely separated from the dura, periorbital tissue, and orbit content. Bone defects were found in the area of the frontal sinus posterior wall, orbit roof, and upper third of the medial orbit wall. The posterior sinus wall was reconstructed with Palacos® (Heraeus Medical, Hanau, Germany) biosynthetic material, placed between the dura of the posterior sinus wall. Bone defects in the orbit roof and medial wall area were reconstructed with free bone transplants from calvaria and titanium meat. Dura defects were reconstructed with fascia lata (Figure 5). A pericranial flap characterized by good vascularization, appropriate voluminosity, and minimal morbidity of the donor site was placed on the sinus floor over the nasofrontal opening in order to separate the sinus from the nasal cavity and thus prevent infection.

In three patients, the transfacial approach according to Lynch–Howarth was used, with the extension toward the lateral border of the supraciliary region. The mucocele tissue was separated from the periorbital tissue, with lacrimal glands and oculogyric muscles preserved. The average size of the orbit roof and frontal sinus floor defects was 2 × 1 cm. The existing bone defect in all cases was reconstructed with titanium meat. Moreover, in all patients, a Silastic® tube was placed endonasally to keep the sinus duct passable, and then removed after six weeks (Figure 6).

Histologically, the lesions were characterized by dilated epithelium lined ducts filled with mucin, often associated with extravasation of mucin into the stroma. The cysts were lined by flat or low cuboidal epithelium (Figure 7).

The appearance of major postoperative complications was not recorded. In two out of three patients treated with

transfacial approaches, postoperative epistaxis was noted and stopped using frontal nose tamponade.

Recurrence was observed in one out of three cases treated with the transfacial approach. After a performed re-intervention and a three-year-long monitoring of patients, recurrence was not recorded. Recurrence in patients treated with the transcranial approach was not recorded.

There were no cases of endonasal spreading of the frontal sinus mucocele in the study.

DISCUSSION

Mucoceles are most often located in the frontal sinus (60–89%), ethmoid sinus (16%), whereas they are extremely rare in the maxillary (3%) and sphenoidal (1%) sinus [7]. This conclusion is supported by the fact that the frontal sinus excretory duct is 15–20 cm long, and 1–2 mm wide, often with the uneven lumen. It is more frequent in men. The highest incidence is among the population between 55 and 65 years of age [8].

The etiology of frontal sinus mucoceles is multifactorial and still has not been clarified in detail. Pathological entities whose presence may lead to disorders of drainage through the nasofrontal duct represent a dominant factor in their occurrence. Most often, they include chronic sinusitis, allergic reactions on the level of sinus mucosa, injuries, anatomic sinus and excretory duct anomalies, tumors, etc.

In a retrospective study which included 72 patients with mucoceles in paranasal cavities, Obeso et al. [9] determined that 35% of their examinees stated they had underwent previous surgical interventions on the sinuses, thus indicating a possible iatrogenic cause of their occurrence.

The most common mechanism of bone destruction of sinus walls is a continuous pressure which leads to bone ischemia, necrosis, and resorption. The obstruction of the sinus excretory duct and a consequent infection result in the accumulation of lymphocytes and neutrophils which, by creating cytokine molecules, lead to enzymatic osteolysis of sinus walls [10]. It has been determined that the fibroblasts from paranasal cavities with existing signs of infection create greater amounts of prostaglandin E2 and collagenases, compared to the mucosal fibroblasts with physiological characteristics that have the key role in increased osteolysis processes of sinus walls and a consequent mucocele expansion [11].

Bacteriological findings of mucoceles are negative in most cases. In cases of a present infection, the presence of *Staphylococcus aureus*, *Haemophilus* species, and Gram-negative bacilli types was determined. Dominant anaerobic bacilli include *Propionibacterium acnes*, *Peptostreptococcus, Prevotella* and *Fusobacterium* species [12].

The diagnostics of mucoceles includes a detailed anamnesis, clinical examination, and the use of additional radiological methods, computed tomography (CT) and magnetic resonance imaging (MRI) above all. CT with contrast is the most reliable and most used method for the determination of the bone destruction rate, whereas MRI is used for complicated cases with intracranial process spreading or a present infection due to its ability to precisely determine the contact of a mucocele with the brain parenchyma and orbit content [13]. CT findings are characterized by the appearance of the so-called jagged bone, formed as a consequence of alternating bone remodeling processes.

Bulbus proptosis, present in 85% of cases, is a pathognomonic sign of mucocele spreading toward the orbit [14]. The spreading of the process from the direction of the sinuses leads to anterior dislocation of the bulbus, while processes from the ethmoidal sinus lead to lateral dislocation.

Dermoid cysts, histiocytosis, tuberculosis, fungal infections, fronto-orbital cholesterol granulomatosis, secondary deposits, orbit and sinus tumors represent pathological entities which are included in the differential analysis of frontal sinus mucoceles [15].

The treatment of frontal sinus mucoceles is surgical, with the aim to establish the anatomical and functional integrity of sinuses. Depending on the size of the process and the engagement of surrounding anatomic structures, the extensity of a surgical intervention ranges from a minimal invasive endoscopic surgery to craniotomy with or without sinus obliteration [16].

Inability to completely remove mucoceles and establish patency of the nasolacrimal duct, as well as the extension of the process toward the orbit or brain parenchyma, represent indicators for open approaches [17].

The aim of a surgical treatment is to entirely remove changes along with the repair of intraorbital and intracranial complications, form drainage into the nose through the nasofrontal duct, or to remove the whole mucosa with duct and sinus obturation. In the case of posterior sinus wall erosion and dura involvement, the bicoronary approach, radical mucocele removal, cranialization and obturation of the nasofrontal duct are indicated [18]. Transfacial approaches are indicated in case of the process extension toward the orbit and nose with crucial preservation of posterior sinus wall continuity [19].

The advantages of transfacial and transcranial approaches compared to endoscopic approaches are reflected in the possibility to explore the whole sinus, prevent blind curettage and possible dura damage, create adequate space for possible sinus obliteration, and prevent recurrence.

The prognosis of frontal sinus mucoceles is usually good, with an extremely low recurrence rate (10%) [20]. Regardless of the previous statement, long-term monitoring of patients after surgical treatments is recommended.

CONCLUSION

The specificity of the anatomic region represents one of the reasons for the spreading of mucoceles toward the orbit, nasal cavity, and anterior cranial fossa, as well as for the occurrence of symptoms due to which patients initially consult doctors.

The diagnosis of frontal sinus mucoceles is set based on a detailed anamnesis, clinical examination, and the use of additional radiological methods.

The treatment of frontal sinus mucoceles is always surgical. Endoscopic surgery and marsupialization of a change are an indicator for smaller, early-diagnosed mucoceles. Transcranial and transfacial approaches represent treatment methods for advanced mucoceles with a present intraorbital, intracranial, and endonasal process propagation.

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Клиничка анализа и хируршко лечење мукокела чеоног синуса – 10 година искуства са седам болесника

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САЖЕТАК

Увод/Циљ Мукокела је бенигна цистична али веома пространа промена у параназалним шупљинама. Етиологија је још увек предмет дискусије, а претпоставља се да су неки од главних узрока њеног јављања опструкција дренаже фронталног синуса и оштећења у средњем носном меатусу, као последица хроничне инфекције, трауме или тумора.
Циљ овог истраживања је био да се опишу клиничке карактеристике и хируршко лечење мукокела фронталног синуса.

Методе Ретроспективна студија за период од 10 година и седам болесника са мукокелама фронталног синуса.

Резултати Предиспонирајући фактори за настанак мукокеле фронталног синуса су уочени код шест болесника: претходне хируршке интервенције код два болесника, претходне повреде код четири болесника, а код једног не постоје предиспонирајући фактори. Четири мукокеле су се налазиле у задњим сегментима фронталног синуса. Уништење предњег синусног зида уочено је код једног болесника, а код три болесника процес се простирао у ендокранијум и орбиту. Код два од три болесника са трансфацијалним приступом јавила се постоперативна епистакса.

Закључак Транскранијални и трансфацијални приступи су методе лечења за напредне мукокеле са интраорбиталном, интракранијалном и ендоназалном пропагацијом.

Кључне речи: мукокела; фронтални синус; дијагностика; хируршко лечење

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Transapical transcatheter aortic valve implantation in a patient with small body weight complicated by severe hypotension – an enigma successfully solved by echocardiography

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SUMMARY

Introduction Transcatheter aortic valve implantation is currently considered an alternative treatment for older patients with severe aortic valve stenosis and increased surgical risk, but can be associated with multiple life-threatening complications.

Case outline An 83-year-old woman with severe symptomatic aortic stenosis, body weight of 29 kg and body surface area of 1.1 m^2 underwent transcatheter aortic valve implantation via transapical access. Severe hypotension occurred before the valve implantation, due to temporary distortion of the mitral valve apparatus by stiff wire, leading to acute mitral regurgitation. This complication was immediately recognized by continuous transesophageal echocardiography and managed by simple wire retrieval instead of applying mechanical circulatory support. After rewiring and predilatation of the stenotic aortic valve, a 23 mm balloon-expandable transcatheter stent-prosthetic valve was successfully implanted.

Conclusion This case demonstrates that continuous imaging during transcatheter aortic valve implantation is key to rapid diagnosis of life-threatening complications, associated with the procedure, especially during the early learning curve in transapical approach.

Keywords: transcatheter aortic valve implantation; transapical approach; acute mitral regurgitation

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has now become the standard of care for the high- and intermediate-risk elderly patients with symptomatic severe aortic stenosis [1, 2]. Two routes of delivery for TAVI are commonly employed for the balloon expandable valve – the transfemoral and the transapical route (Figure 1 a and b). In patients in whom a transfemoral approach is not feasible, a subclavian, direct aortic (all three approaches represent retrograde delivery), or transapical approach (anterograde delivery) can be utilized.

A mortality benefit has been shown for TAVI compared with conservative treatment in patients deemed inoperable, and the procedure was proven to be at least non-inferior to surgical aortic valve replacement in high- and intermediate-risk patients [1, 2].

Acute hypotension during TAVI is a complication mainly due to aortic/annular rupture, landing zone trauma, ventricular perforation, cardiac tamponade, severe aortic or mitral regurgitation, or ventricular dysfunction due to coronary occlusion [3, 4, 5]. Whatever the cause, hypotension might initiate a downward spiral of ischemia and myocardial dysfunction, leading to shock [3]. Accurate positioning and deployment of the transcatheter heart valve (THV) may be complicated by marked septal hypertrophy because of prominent angulation of the left ventricular outflow tract diameter and difficulty on maintaining coaxial alignment of the guidewire, sheath, and valve delivery catheter [6]. This may be particularly apparent during the transapical approach when the apical cannula position is fixed.

In this paper, we present a case of acute hemodynamic deterioration during transapical TAVI, due to temporary distortion of the mitral valve apparatus by stiff wire leading to acute mitral regurgitation and hypotension, which was immediately recognized by transesophageal echocardiography (TEE) and managed by simple wire retrieval instead of applying mechanical circulatory support. Continuous imaging is key to rapid diagnosis of life-threatening complications, associated with the procedure.

CASE REPORT

We report a case of a frail 83-year-old woman with severe symptomatic aortic stenosis. Based on the frailty, the patient was considered unsuitable for conventional surgery. The patient's body weight was 29 kg, and body surface area 1.1 m^2. Due to very tortuous aorta and small

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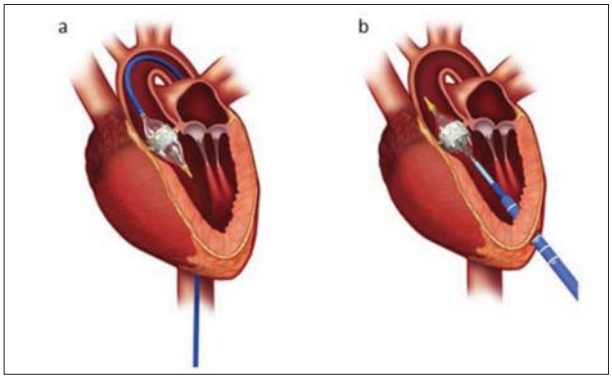

Figure 1. Schematic diagram of the delivery routes for transcatheter aortic valve implantation commonly employed for the balloon expandable valve; (a) the transfemoral (retrograde), and (b) the transapical (anterograde) route (courtesy of Edwards Lifesciences)

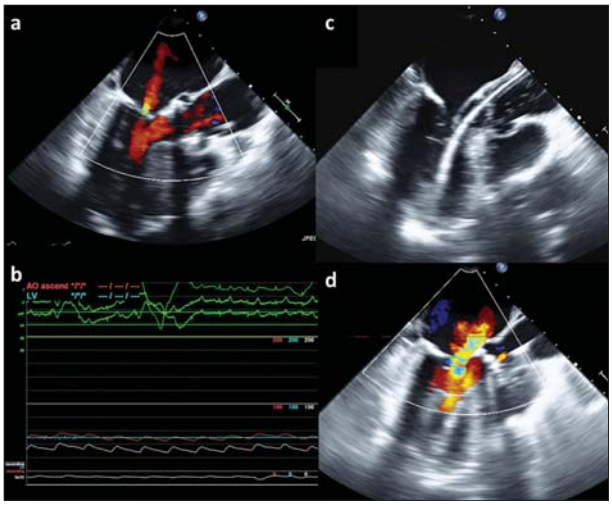

Figure 2. Severe hypotension and acute severe mitral regurgitation due to a distortion of the mitral apparatus by the stiff wire; transesophageal echocardiogram revealed (a) mild mitral regurgitation; (b) invasive pressure monitoring showed severe hypotension; (c) transesophageal echocardiogram: Lunderquist Stiff Wire is poorly positioned in the left ventricle and is causing tethering of the anterior mitral leaflet; (d) transesophageal echocardiogram: significant mitral regurgitation due to malpositioned stiff wire in the left ventricle.

iliofemoral arteries, TAVI was performed by the transapical approach. The left coronary artery and the right coronary artery ostium heights were 13 mm and 16.5 mm, respectively. The left ventricular outflow tract diameter, sinus of Valsalva diameter, and sinotubular junction diameter were 15.9 × 23.3 mm, 29.2 × 29.6 × 31.9 mm, and 22.8 × 23.7 mm, respectively. The mean aortic gradient was 38.7 mmHg. The left ventricular ejection fraction was calculated to be 75% using a modified Simpson method. Indexed aortic valve area was 0.51 cm^2/m^2; mild mitral regurgitation (Figure 2a) and trace aortic regurgitation were recorded.

The TAVI procedure was performed under general anesthesia and continuous TEE guidance in the hybrid operating room. An anterior left mini-thoracotomy was performed to obtain access to the apex of the left ventricle. After the puncture of the apex, a guide wire was malpositioned into the left atrium due to narrow left ventricular outflow tract diameter and severe left ventricle concentric hypertrophy, which was documented in fluoro, as well as

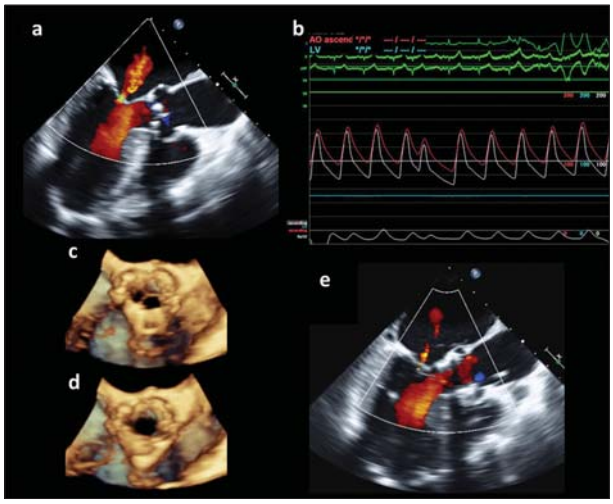

Figure 3. Successful management of the severe hypotension and deployment of the transcatheter stent-prosthetic aortic valve; transesophageal echocardiogram after wire removal revealed (a) mild mitral regurgitation; (b) invasive pressure monitoring showed recovery of blood pressure; 3D transesophageal echocardiogram revealed normal valve function in diastole (c) and systole (d); 2D transesophageal echocardiogram revealed only mild mitral regurgitation after the balloon-expandable transcatheter stent-prosthetic aortic valve implantation (e)

in echo images. The wire was removed from the left atrium and was difficult to replace through the narrow aortic valve. Second puncture was attempted in order to redirect the wire across the aortic valve. After the second puncture, 7 Fr 25 cm sheet was placed, and 4 Fr Judkins catheter was advanced with Radifocus wire (Terumo Corporation, Tokyo, Japan), and exchanged for the Lunderquist Stiff Wire (Cook Medical, Bjaeverskov, Danemark). Immediately after, severe hypotension was recorded (37/22 mmHg) (Figure 2b), and patient became hemodynamically unstable. Continuous TEE monitoring revealed mitral apparatus distortion which lead to the retraction of the anterior mitral leaflet causing severe mitral regurgitation due to leaflet malcoaptation (Figure 2 c and d). This was successfully managed without mechanical support by removing the stiff wire (Figure 3 a and b). We recrossed the aortic valve using a softer wire (Amplatz Extra Stiff Wire, Cook Medical), which did not cause the mitral apparatus distortion. A 23 mm Sapien XT valve (Edwards Lifesciences Inc., Irvine, CA, USA) was successfully implanted following predilatation with a 20 mm balloon (Figure 3 c, d, and e).

DISCUSSION

We report a case with mitral apparatus distortion and hemodynamic deterioration due to severe mitral regurgitation detected by TEE during transapical TAVI. Continuous imaging is key to rapid diagnosis of life-threatening complications associated with the procedure. A wire can be passed underneath a mitral chordae utilizing the antegrade apical approach [6, 7]. Sliding forward a wire or a catheter over the wire might result in temporary distortion of the mitral valve apparatus, leading to acute mitral regurgitation [3]. If resistance to catheter advancement is noticed or transient mitral regurgitation is assessed by TEE, this

should alert the operator to the possibility. To avoid the subchordal passage, rewiring or the use of a balloon flotation catheter might be considered.

It is critically important to have communication between the echocardiographer and other TAVI team members about the qualitative features of the left ventricular outflow tract and septal geometry [7]. Accurate positioning and deployment of the THV may be complicated by marked septal hypertrophy because of prominent angulation of the left ventricular outflow tract and difficulty on maintaining coaxial alignment of the guidewire, sheath, and valve delivery catheter. This may be particularly apparent during the transapical approach when the apical cannula position is fixed. In addition, a hyperdynamic hypertrophied septum may cause the THV to be superiorly displaced during balloon inflation or unsheathing of the valve [3].

During the immediate implantation period, echocardiographic imaging is essential even though precise valve placement can be performed with fluoroscopic imaging alone [8, 9]. Echocardiographic imaging provides rapid and accurate assessment of the valve position, valve shape, leaflet motion, and gradients following the THV deployment. Color Doppler imaging provides prompt and precise feedback to the operator about the presence, location, and severity of aortic regurgitation, as well as coronary patency and mitral valve function [7, 9, 10]. Left ventricular dysfunction or aortic root catastrophe can be assessed within seconds as potential etiologies in this setting of hemodynamic compromise [11, 12].

The presented case report showed the importance of continuous TEE monitoring during the TAVI procedure. TEE seems be useful to clarify the etiology of sudden hemodynamic deterioration. Furthermore, it provides invaluable information with regard to treatment of severe hypotension during transapical TAVI by simple wire retrieval instead of applying mechanical circulatory support. TEE with general anesthesia remains to be an important option, especially during the early experience with transapical or transfemoral TAVI.

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Транскатетерска имплантација аортне валвуле трансапикалним приступом код болеснице са малом телесном масом и тешком хипотензијом – загонетка решена ехокардиографским прегледом

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САЖЕТАК

Увод Транскатетерска уградња аортне валвуле представља алтернативно лечење старијих болесника са тешком стенозом аортне валвуле и високим хируршким ризиком, а може бити праћена бројним компликацијама.

Приказ болесника Болесница стара 83 године, тешка 29 *kg* и површине тела 1,1 m^2, са тешком симптоматском аортном стенозом, подвргнута је транскатетерској уградњи вештачке аортне валвуле трансапикалним путем. Пре уградње валвуле јавила се акутна митрална регургитација и тешка хипотензија узрокована дисторзијом митралне вавлуле чврстом жицом. Ова компликација је одмах препозната ехокардиографским прегледом и решена једноставним повлачењем жице натраг и репозицијом жице, уместо применом механичке циркулаторне подршке. После поновног пласирања жице и предилатације стенотичне аортне валвуле успешно је транскатетерским путем након надувавања балона уграђена вештачка стент валвула пречника 23 *mm*.

Закључак Континуирано праћење болесника помоћу трансезофагусне ехокардиографије за време транскатетерске уградње аортне валвуле представља кључ за брзу дијагнозу компликација које могу да се јаве у току ове процедуре, посебно у раној фази криве учења трансапикалног приступа.

Кључне речи: транскатетерска уградња аортне валвуле; трансапикални приступ; акутна митрална регургитација

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Recanalization of coronary artery chronic total occlusion by retrograde approach

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SUMMARY

Introduction Chronic total occlusion (CTO) is defined as a 100% obstruction of the blood vessel lumen with Thrombolysis in Myocardial Infarction grade 0 flow in the occluded segment at least three months old. Advancement of technological devices and techniques used during the percutaneous coronary interventions (PCI) in the past years brought more success in blood vessel recanalization. According to the latest guidelines for myocardial revascularization, the CTO treatment should be considered when there are symptoms or objective proof of viability or ischemia in the occluded area.

The aim of this work is to present two cases with a recanalization of the coronary artery CTO by the retrograde approach.

Outline of cases The first patient had a single vessel coronary disease which led to a decision to first attempt PCI. During the attempt of antegrade recanalization, the guidewire penetrated subintimally, risking blood vessel dissection below the occluded area as well as serious complications. Retrograde approach enabled easier and safer passing of guidewire through the occlusion and then successful establishment of the antegrade flow. In the second case, the antegrade approach was also first attempted. Since it could not pass through the occluded area despite changing several guidewires, the strategy was changed during the intervention. It was continued with the retrograde approach, which led to the successful revascularization.

Conclusion These two cases demonstrate that retrograde approach and new technological improvements in dedicated guidewires can be implemented in everyday angiography practice for successful recanalization of CTO lesions.

Keywords: coronary artery occlusion; chronic total occlusion; percutaneous coronary interventions; retrograde approach

INTRODUCTION

Chronic total occlusion (CTO) is defined as a 100% obstruction of the blood vessel lumen with Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow in the occluded segment which is at least three months old, it is assumed that CTO with good collaterals is the same as a 90% narrowing of a coronary blood vessel [1]. By a functional examination of collateral circulation, Werner et al. [2] proved that angiographically well-developed collaterals cannot provide enough blood supply to the occluded segment. Even in patients with well-preserved ventricular function, collaterals provide good "flow reserve" in less than 10% of the cases [2]. Hence, the symptoms of stable angina pectoris can be manifested since, under stress, there is inadequate perfusion in some segment of the myocardium through collateral circulation. However, it needs to be stated that the risk of developing some form of acute coronary syndrome as a consequence of CTO is rare [3].

Recanalization of CTO represents one of the biggest challenges in interventional cardiology. The advancement of technological devices and techniques used during percutaneous coronary intervention (PCI) in the past years brought more success in blood vessel recanalization [4]. According to the latest guidelines for the myocardial revascularization, the CTO treatment should be considered when there are symptoms or objective proof of viability or ischemia in the area of occluded artery [5]. Not only that the successful revascularization of CTO contributes to the improvement of functionality and relief of anginal discomforts, but it also leads to the better left ventricular systolic ejection function and has positive correlation in relation to the long-term survival [6–9].

The success of the CTO revascularization is smaller than in other lesions and it largely depends on operators' experience, good analysis of the lesion itself, and available technical devices. Until 2005, the success of CTO revascularization had remained unchanged for a long period of time and was around 60–70%. Since the CTO revascularization was significantly less successful, the representation of these procedures was therefore small and did not exceed 10%, so the patients were more frequently referred to coronary artery bypass grafting (CABG) [10, 11].

Introducing modern techniques [controlled antegrade and retrograde subintimal tracking (CART), reverse CART, knuckle wire technique],

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modern retrograde approach to CTO revascularization gained in importance and started being used more frequently especially when antegrade approach failed. In more complex lesions, the operators from the beginning choose retrograde approach due to its better efficacy [12, 13].

Here, we present our initial experience in two cases of successful revascularization of CTO by the retrograde approach.

CASE REPORT

Case 1

A 61-year-old male patient was admitted to the Institute of Cardiovascular Diseases of Vojvodina in February 2015 for elective coronarography due to stable angina pectoris CCS 2 and previous anterior wall myocardial infarction from November 2013, when he underwent conservative treatment in the regional center. The stress test demonstrated signs of anterior wall ischemia. Echocardiography examination registered hypokinesis on medioapical and anteroseptal area and slightly decreased ejection fraction of 50%.

The patient underwent diagnostic coronarography, which found single-vessel coronary disease along with the chronic occlusion of the proximal left anterior descending (LAD) segment. Since it was an over 20 mm long lesion with calcifications, the J-CTO score was 2, i.e. a lesion difficult for revascularization. The case was presented at the Board of Cardiologists and Cardiac Surgeons, who suggested the attempt of CTO LAD opening.

The recanalization of CTO LAD with the antegrade approach was tried first. Judkins left 4 guiding catheter (Launcher, Medtronic, Minneapolis, MN, USA) was placed in the left main coronary artery (LMCA) and right amplatz 1 guiding catheter (Launcher, Medtronic) was placed in the right coronary artery (RCA). The catheter in the RCA was used to show the area below the occlusion through collateral circulation and for better orientation during the wire passing through the occlusion. Since the guidewires Fielder XT and Confianza (Asahi Intecc Co., Ltd., Nagoya-shi, Japan) could not be advanced and there was a great possibility of subintimal guidewire penetration and blood vessel dissection below the occluded area, we decided to try recanalization using the retrograde approach (Figure 1).

The guidewire Runthrough NS (Terumo Corporation, Tokyo, Japan) was placed through the donor RCA and was used for positioning of the Corsair microcatheter (Asahi Intecc Co., Ltd.) below the septal collaterals. Then the Sion guidewire (Asahi Intecc Co., Ltd.) was used for crossing through the septal collaterals and positioning the Corsair in the LAD below the occluded area. Arter passing through the occlusion site with the Sion guidewire, microcatheter Corasire was placed in the LMCA. Afterwards, the externalization of Asahi RG3 guidewire was performed through the catheter in the LMCA. Balloon dilatation of the occlusion was done using the externalized guidewire Asahi RG3, establishing antegrade flow.

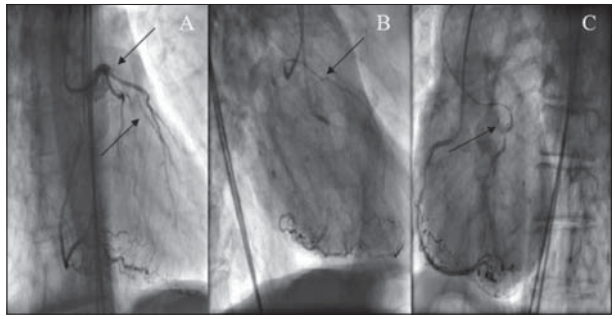

Figure 1. A) The upper arrow shows the occluded area, while the lower arrow shows distal part of the blood vessel being shown through the collateral circulation; arrows in images B and C show subintimal guidewire penetration though the occluded area

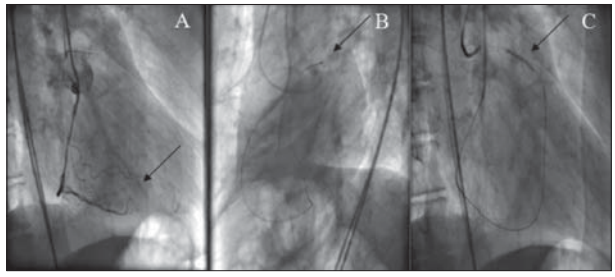

Figure 2. A) The arrow shows the guidewire in the Corsair at the septal collateral channels between the right coronary artery and the left anterior descending artery (LAD); B) the arrow showing the Corsair below the occlusion in the LAD; C) after the guidewire was passed through the occlusion, it was used to perform percutaneous transluminal coronary angioplasty of the occlusion in the LAD

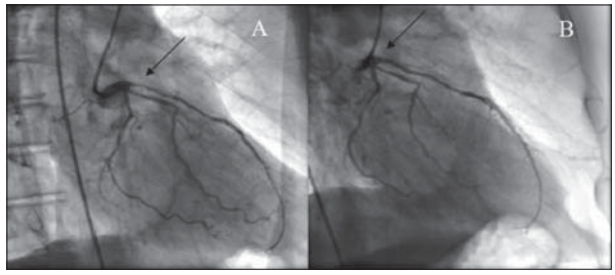

Figure 3. A) The result after percutaneous transluminal coronary angioplasty of the LAD and the establishment of the antegrade flow; B) the arrow indicates where the drug-eluting stent was implanted with the optimal result

A new Runthrough NS guidewire was placed in the LAD through the catheter and a drug-eluting stent Biomatrix Flex 18 × 2.75 mm (Biosensors International, Newport Beach, CA, USA) was implanted giving optimal result (Figures 2 and 3).

Case 2

A 56-year-old male patient was admitted to the Institute of Cardiovascular Diseases of Vojvodina in January 2015 for planned PCI of CTO on the LAD and the circumflex coronary artery (Cx). The patient was hospitalized at our hospital in December 2014 due to the inferior wall ST-elevation myocardial infarction (STEMI) when primary PCI was performed with an implantation of one stent in the RCA and one in the posterolateral branch. Since the Syntax score was 23.5, the Board of Cardiologists and Cardiac Surgeons decided that the PCI of CTO on the

LAD and significant Cx lesion should be attempted, and in case the CTO LAD recanalization was unsuccessful, the surgical myocardial revascularization should be done. The J-CTO score of the LAD lesion was 2 since it was over 20 mm long and had calcifications, or, in other words, it was a lesion difficult for revascularization.

The recanalization of CTO LAD using the antegrade approach was first attempted. Two guiding catheters were placed, one EBU 3.5 (Launcher, Medtronic) in the LMCA and left Amplatz 1 (Launcher, Medtronic) was placed in the RCA. Initially, it was planned for the catheter in the RCA to serve as a retrograde visualization aid of the artery below the LAD occlusion. Since none of the guidewires – Fielder XT and Gaia second (Asahi Intecc Co., Ltd.) – could pass the occlusion, we decided to switch to the retrograde approach (Figure 4).

The Runthrough NS guidewire (Terumo Corporation) was placed through the donor RCA and was used for the positioning of the Corsair microcatheter (Asahi Intecc Co., Ltd.) below the septal collaterals. The Sion guidewire (Asahi Intecc Co., Ltd.) passed through septal collaterals, distal occlusion cap, and then through the occlusion itself. The guidewire was then placed in the left guiding catheter in the LMCA. The advancement with the Corsair was continued, placing it also through the occlusion in the left guiding catheter in the LMCA. The Runthrough NS guidewire was placed in the Corsair microcatheter which was in the LMCA guiding catheter. The Corsair was then gradually removed and the Runthrough NS guidewire was released below the occluded LAD area (Figure 5). The intervention continued using the antegrade approach. After the predilatation, the antegrade flow was established and two drug-eluting stents, Promus Premier 32 × 2.5 mm (Boston Scientific, Marlborough, MA, USA) and Resolute 26 × 2.5 mm (Medtronic) were implanted showing optimal results (Figure 6).

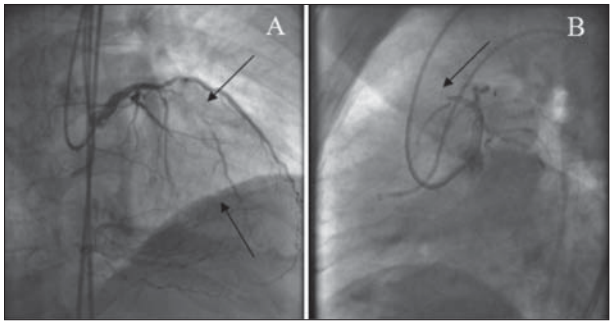

Figure 4. A) The upper arrow shows the area of occlusion in the LAD, the lower arrow points to the transseptal collaterals; B) the arrow points to the occluded area as well as the coronary guide that could not advance further in the occluded area

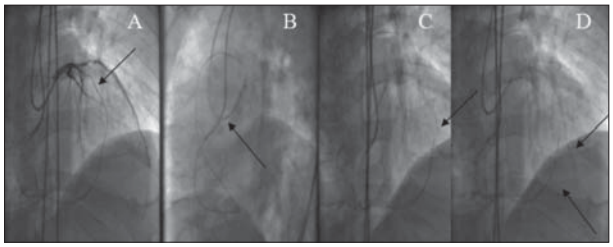

Figure 5. A) The guidewire in the occluded area is shown as well as the Corsair, which is below the occluded area; B) the Corsair placed in the catheter which is in the left coronary artery; C) the Corsair is returned to the septal collateral while the guidewire, placed antegradely in the Corsair, is being released; D) The guidewire is placed in the LAD and is used to continue the intervention while the Corsair is being removed

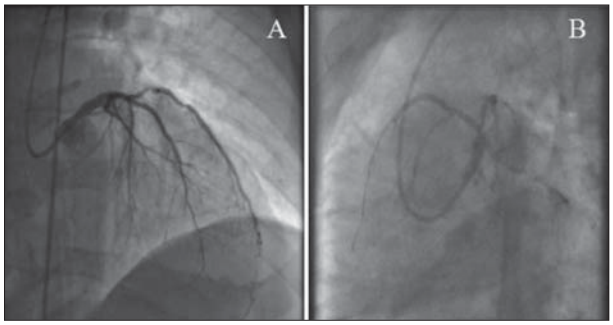

Figure 6. Both A) and B) show the optimal result after the implantation of two stents

DISCUSSION

CTO represents one of the biggest and most demanding challenges in the interventional cardiology. Registering CTO along with the lesions in other coronary blood vessels strongly influences the decision making for surgical myocardial revascularization (CABG).

The exact prevalence of chronic total occlusions in general population is still unknown. However, some studies have shown that CTO can be found in 24% of patients who underwent coronarography and that it is found in 52% of cases where patients have at least one lesion > 70% [14, 15]. To estimate the difficulty of guidewire crossing through CTO and to plan revascularization strategy, the J-CTO score is used. It is based on assigning one point for each of the five factors that influence the complexity of CTO revascularization (prior failed attempt to revascularize the CTO, blunt stump, calcification, lesion bending, and occlusion length). Based on the scoring system, the lesions are classified as easy (J-CTO 0), intermediate (J-CTO 1), difficult (J-CTO 2), and very difficult (J-CTO 3) [16].

Introduction of modern techniques in CTO recanalization by Japanese experts, primarily retrograde approach, contributed to the more frequent use of CTO revascularization by percutaneous coronary intervention [17].

The use of intravascular diagnostic procedures, particularly intravascular ultrasound (IVUS), significantly increased the sureness of performing PCI CTO. Unlike optical coherence tomography, which can only be used after the establishment of the antegrade flow, IVUS needs no contrast during scanning and enables guidewire position checking during the occlusion crossing.

Pathohistology has demonstrated that CTO segments are thinner and softer in the distal than in the proximal cap. Therefore, the distal cap is more suitable for guidewire penetration in relation to the proximal cap, and this is the mechanism underlying the advantage [18].

Due to the complexity of PCI of CTO lesions, the risk of complications is slightly bigger than during PCI of other

lesions. Therefore, it is more common for complications to occur, such as blood vessel perforation, periprocedural myocardial infarction, and stent slipping. Radiation injuries and contrast-induced nephropathy are also possible due to the length and complexity of the procedure [19, 20].

UK National Institute for Cardiovascular Outcomes Research analyzed the data from 13,500 patients who underwent elective PCI of one or more CTO lesions in the period from 2005 to 2009. The results showed that the successful PCI is strongly related to the reduction of all causes of mortality [21].

In time, the success of CTO revascularization significantly increased from previous 50–60% up to 90% primarily due to experienced operators as well as the use of modern techniques and the growing use of the retrograde approach [12].

It should be pointed out that there is still insufficient amount of randomized clinical trials that demonstrate the advantages of different approaches to CTO revascularization as well as their long-term patient benefit.

We have presented two cases of an unsuccessful antegrade approach to CTO revascularization where both interventions were immediately continued with a successful retrograde approach.

The first patient had a single-vessel coronary disease, J-CTO score 2 (difficult). For that reason it was decided to first attempt PCI, and then, if it failed, to undertake CABG. During the attempt of the antegrade recanalization, the guidewire was penetrating subintimally with the risk of blood vessel dissection below the occluded area and the risk of serious complications. The use of the retrograde approach enabled easier and safer passing of the guidewire through the occlusion as well as the successful establishment of the antegrade flow. Then, the antegrade guidewire was placed and used for the stent implantation. It should be noted that, in these types of cases, the use of dual lumen catheter for antegrade guidewire placement is highly recommended because it significantly lowers the risk of blood vessel dissection. In this case, due to the lack of dual lumen catheter, it was not used.

The second case showed a patient who initially had a three-vessel coronary disease which was, since he had had STEMI, first treated with the PCI. In this case, the J-CTO score was also 2 (difficult). Afterwards, the coronary disease could be completely solved with the percutaneous coronary intervention or the hybrid procedure, i.e. surgical revascularization of the LMCA system. It was also initially tried with the antegrade approach but, in spite of changing several guidewires, we were not able to pass through the occluded area. The strategy was changed during the intervention and was continued with the retrograde approach. Since the distal cap was softer, the guidewire followed by the microcatheter went through the occluded area, enabling the intervention to continue and finish with the Randezvous technique, establishing the antegrade flow [22].

Pure retrograde technique was used in both cases. It should be stated that there are numerous other techniques that increase the technical success rate of CTO revascularization by 20%. Successful treatment of lesions in both patients permitted further continuation of the medical treatment.

These two cases demonstrate that the retrograde approach and new technological improvements in dedicated guidewires can be implemented in everyday angiography practice for successful recanalization of CTO lesions. Therefore, we expect that this approach will be used more frequently in our center to improve the clinical outcome of these patients.

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Реканализација хроничне тоталне оклузије коронарне артерије ретроградним приступом

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САЖЕТАК

Увод Хронична тотална оклузија (ХТО) дефинише се као 100% опструкција лумена крвног суда са *TIMI* 0 протоком у том сегменту, у периоду од најмање три месеца. Напредак технолошких средстава и техника које се користе током перкутане коронарне интервенције (ПКИ) довео је до веће успешности у реканализацији крвног суда. Према званичном водичу за реваскуларизацију миокарда, решавање ХТО треба размотрити у случају присуства симптома или објективних доказа вијабилности и исхемије у подручју оклудиране артерије.

Циљ овог рада је приказ два болесника са реканализацијом коронарних артерија код ХТО ретроградним приступом.

Приказ болесника Код првог болесника се радило о једносудовној коронарној болести, и то је био разлог да се прво одлучи за покушај ПКИ. Приликом покушаја антероградне реканализације жичани водич је продирао субинтимално уз ризик настанка дисекције крвног суда испод подручја оклузије; самим тим постојао је висок ризик за настанак озбиљних компликација. Примена ретроградног приступа је омогућила лакши и безбеднији пролазак жичаног водича кроз оклузију и успешно успостављање антероградног протока. И у другом случају иницијално је покушано са антероградним приступом, али се није могло проћи кроз подручје оклузије. Настављено је ретроградним приступом, што је резултирало успешном реваскуларизацијом.

Закључак Ретроградни приступ заједно са новим технолошким достигнућима и специјализованим жичаним водичима може се увести у свакодневну праксу ради успешне реваскуларизације ХТО.

Кључне речи: оклузија коронарних артерија, хронична тотална оклузија; перкутане коронарне интервенције, ретроградни приступ

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Transvenous lead placement and its pre-sternal tunneling to the contralateral side as a solution for a pacemaker system upgrade in the case of subclavian vein thrombosis

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SUMMARY

Introduction Chronic right ventricular pacing can deteriorate cardiac function. Consequently, pacemaker system upgrades are more frequently indicated. These interventions can be hindered by venous thrombosis. In literature, it is rarely described that this problem is resolved by implanting a new lead for left ventricle (LV) stimulation on the opposite side of the previously implanted pacemaker and then subcutaneously transferring it to the old pocket.

Case outline A 75-year-old male patient was hospitalized due to a planned pacemaker upgrade in December 2015. A dual-chamber pacemaker had been implanted due to sinus node dysfunction in 2011. During the previous 18 months he had been complaining about symptoms of heart failure. An upgrade to the cardiac resynchronization therapy (CRT) with a new CRT-P device was indicated due to the LV dilatation with the ejection fraction decrease, clinical deterioration, and the presence of high percentage of ventricular pacing. In October 2015, the mentioned intervention was unsuccessful due to total left subclavian vein thrombosis on the side of the previously implanted pacemaker. Anticoagulation therapy was ordinated and the reevaluation was postponed. During this hospitalization, venography confirmed total left subclavian vein thrombosis despite the anticoagulation therapy. It was decided to implant a new LV lead on the right side and then subcutaneously shift it by pre-sternal tunneling to the previous left prepectoral pocket. The intervention was uneventful. The first controls have shown stable pacemaker parameters.

Conclusion This case report confirms that contralateral lead placement and subcutaneous pre-sternal tunnelling of the lead is feasible and safe in patients with an implanted pacemaker, an indication for system upgrade and ipsilateral vein obstruction.

Keywords: pacemaker system upgrade; vein obstruction; subcutaneous pre-sternal tunnelling

INTRODUCTION

Prolongation of the average human life span and extension of indications for pacemaker implantation have led to an increase in the number of implanted devices in the world and in our country [1]. Large randomized trials demonstrated the adverse effects of chronic right ventricular pacing associated with an increased risk of atrial fibrillation and heart failure [2, 3]. Therefore, it is not surprising that the number of system upgrades to implantable cardioverter defibrillators (ICDs) or cardiac resynchronization therapy (CRT) devices increases. The main reasons are a decrease in ejection fraction of the left ventricle (LV) and an increase in the New York Heart Association class in patients with implanted antibradycardia pacemakers, due to the consequences of chronic right ventricle pacing [3]. In the case of system upgrade, logical approach is to try a new lead implantation on the same side where the pacemaker system has already existed. In a certain percentage of patients, the presence of pacemaker leads can lead to venous thrombosis. It is estimated that in 5–26% of patients with chronically implanted devices there is a significantly obstructed or occluded respective vein [4, 5]. In these patients, it is possible to (1) implant an entire new pacemaker system on the opposite side; (2) implant an LV epicardial lead via lateral minithoracotomy; and (3) implant only a new lead on the opposite side, which will be transferred subcutaneously, by pre-sternal tunneling, to the pocket on the other side. While the first two solutions are often used in clinical practice, the third one is rarely described in the literature.

CASE REPORT

A 75-year-old male patient was admitted to the Pacemaker Center of the Clinical Center of Serbia in December 2015 for pacemaker upgrade to the CRT device. The dual-chamber pacemaker had been implanted due to sinus node dysfunction at our center in June 2011. The patient was feeling better after the pacemaker implantation; he tolerated physical effort well and didn't subsequently experience dizziness. Preoperatively,

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the LV ejection fraction was 50% (according to Simpson) with the LV end-diastolic volume of 110 cm^3. From July 2014, the patient had been complaining about low effort tolerance, peripheral edema and nocturnal shortness of breath. Echocardiography performed in August 2014 revealed dilatative cardiomyopathy with a significantly decreased LV ejection fraction (32% according to Simpson) and an increased LV end-diastolic volume (190 cm^3). Since then, he has been treated with optimal medical therapy for heart failure. Paroxysmal atrial fibrillation has been registered since October 2014. Stress echocardiography testing was negative. On February 2015, echocardiography was performed once again and it confirmed a low LV ejection fraction (34% according to Simpson) with the LV end-diastolic volume of 210 cm^3. During regular ambulatory pacemaker controls, normal function of the device was ascertained, with the percentage of ventricular pacing over 90%. The percentage of ventricular pacing could not be decreased because of the long PR interval. System upgrade of the CRT device was indicated but the patient postponed the intervention due to personal reasons.

In December 2015, the attempt to upgrade the pacemaker system to a CRT-P device was not successful due to venous thrombosis of the subclavian vein on the left side. It was decided to administer oral anticoagulation therapy and to try to implant a lead for coronary sinus on the left side again in two months. During the next hospitalization, before the re-intervention, digital subtraction angiography was done. The venous occlusion was verified (Figure 1), so an alternative solution was needed. We decided to try to implant the LV lead on the right side, than to shift it to the left and to connect it with the new CRT-P device in the previous left prepectoral pocket. Thus, we implanted the LV lead in the posterolateral coronary sinus tributary, using the technique of the right subclavian vein puncture. We proceeded to transfer the distal end of the lead subcutaneously, by pre-sternal tunneling, and to connect it with the new CRT device on the left side (Figure 2). To make the subcutaneous tunnel, a special chest tube was advanced from the contralateral side under the guidance of a trochar. Then, the trochar was removed and the lead was put into the chest tube. Finally, the tube was drawn out and the lead was left at the side of the pocket. The intervention was performed under general endotracheal anesthesia. Intraoperatively measured parameters of the pacemaker function were stable. The patient's recovery was uneventful, and he was discharged in good condition on the first postoperative day. After one-month and three-month follow-ups, the CRT control showed stable parameters, with no differences in relation to those obtained during the intervention.

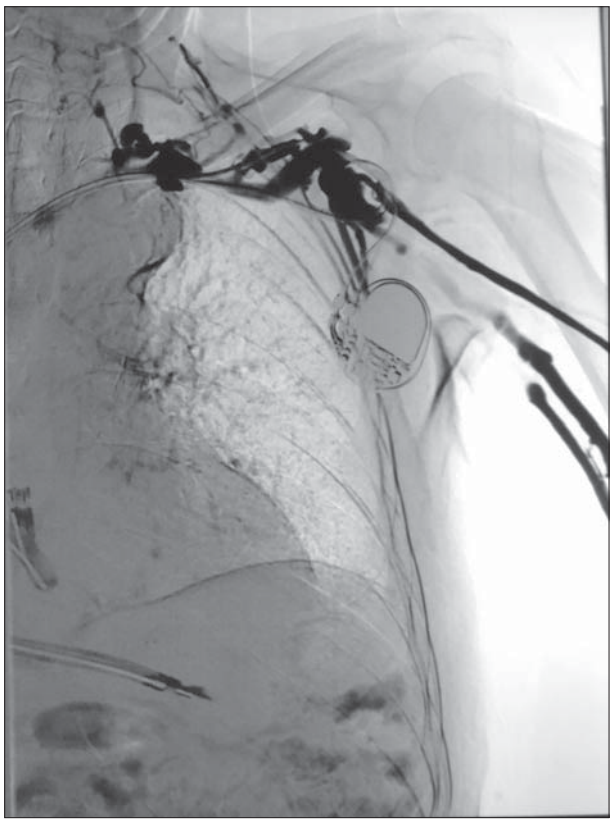

Figure 1. Digital subtraction angiography

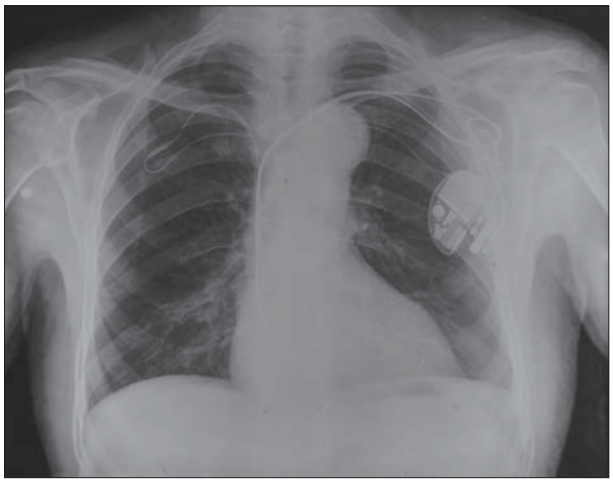

Figure 2. The new cardiac resynhronication therapy device

DISCUSSION

Many studies have confirmed the efficacy of CRT therapy in patients with symptomatic heart failure, left ventricular dysfunction and wide QRS complex [6, 7]. Therefore, it is important that every patient in whom the CRT is indicated achieves resynchronization. In order to reach this goal, it is valuable to have available alternative approaches. Contralateral lead placement and subcutaneous pre-sternal tunnelling of the lead to the device is an approach that was first described by Belott [8] in 1983. Since then, this technique has been sporadically described in the literature. The only retrospective study that evaluated the acute success, complication rates, long-term lead function, and subject tolerability of the contralateral pacemaker lead placement and subcutaneous, pre-sternal lead tunnelling in patients with chronically implanted rhythm devices, showed that this approach has high acute success and acceptable long-term outcome [5]. In this study, one of the twenty leads had to be replaced due to a structural defect and one patient reported discomfort related to the tunneled lead [5].

This approach has significant advantages over other methods described. Only one new lead needs to be implanted in this technique, in contrast to the approach that involves the implantation of a new system on the opposite side, which implies implanting three new leads through the venous system, thus significantly increasing the risk of further venous thrombosis and making the starting position of a possible new re-intervention significantly more difficult. On the other hand, this intervention takes less time than the LV lead implantation via lateral minithoracotomy, and is followed by a complete and quick recovery. Also, for an experienced operator, this intervention is not too demanding, but requires the use of specific tools.

It should be noted that subcutaneously implanted leads are more susceptible to damage, fracture. Also, unlike implanting a new pacemaker system on the opposite side, this intervention is more invasive, performed under general endotracheal anesthesia.

The presented case is specific due to the fact that the implantation of the LV lead into the coronary venous system was performed on the right side, which is a more complicated approach [9]. More common situation is that this technique is used when the device is on the right side and the upgrade procedure is done by adding the LV lead from the left side.

In summary, this case report confirms that contralateral lead placement and subcutaneous pre-sternal tunnelling of the lead is a feasible and safe approach in patients with a chronically implanted pacemaker, an indication for a system upgrade, and an ipsilateral vein obstruction.

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Уградња електроде венским путем и њено пребацивање на супротну страну престерналним тунелирањем као решење за болеснике са тромбозом поткључне вене и потребом за надоградњом пејсмејкер система

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САЖЕТАК

Увод Дуготрајни пејсинг десне коморе може бити повезан са појавом срчане слабости. Једна од наредних терапијских могућности је надоградња пејсмејкер система уградњом додатне електроде за стимулацију леве коморе (ЛК). Ова интервенција може бити отежана због тромбозе приступне вене. У литератури је описан врло мали број болесника код којих је овај проблем решен уградњом електроде за стимулацију ЛК са супротне стране од претходно уграђеног пејсмејкера и супкутаним пребацивањем до првобитне ложе пејсмејкера.

Приказ болесника Мушкарац стар 75 година хоспитализован је децембра 2015. године због надоградње пејсмејкера. Године 2011, због дисфункције синусног чвора, имплантиран је антибрадикардни пејсмејкер са леве стране. Јуна 2014. имао је прву манифестацију срчане слабости. Због дилатације и пада ејекционе фракције ЛК а присутног високог процента коморског пејсинга индикована је надоградња на ресинхронизациони пејсмејкер ситем. Октобра 2015. године покушана интервенција није успела због истостране потпуне тромбозе поткључне вене и започета је антикоагулантна терапија. Приликом последње хоспитализације урађена венографија је потврдила перзистирање тромбозе леве поткључне вене те је одлучено да се имплантира нова електрода за стимулацију леве коморе са контралатералне, десне стране, а да се она поткожно, престерналним тунелирањем, пребаци до претходне ложе пејсмејкера. Интервенција је протекла без компликација, а прве контроле показале су стабилне параметре пејсмејкер функције.

Закључак Овај приказ потврђује да је контралатерална уградња нове електроде и њено пребацивање до старе пејсмејкер ложе поткожним, престерналним тунелирањем изводљив и сигуран приступ код болесника са индикацијом за надоградњом пејсмејкер система и истостраном венском опструкцијом.

Кључне речи: надоградња пејсмејкер система; венска опструкција; поткожно престернално тунелирање

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Efficacy of infliximab in treatment of refractory panuveitis associated with Behçet disease

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SUMMARY

Introduction Behçet disease (BD) is a chronic multi-system disorder with manifestations in the ocular, urological, articular, and vascular systems. Tumor necrosis factor alpha is believed to play a pivotal role in BD. Therapeutic blockade of its activity by infliximab is a novel therapeutic approach and has successfully led to remission of the disease.

The aim is to report two cases of refractory BD-associated panuveitis (PU) treated with infliximab. The patients were followed for 12 months. The main therapy assessment parameters were the best corrected visual acuity (BCVA) in the better eye, slit lamp and fluorescein angiography (FAG) from baseline findings and from the final examination.

Case outline A male patient (45 years old, 25 years of BD history) and a female patient (45 years old, 15 years of BD history), both with posterior synechia, 3+ flare and complicated cataract, while the female also had hypopyon, were treated with infliximab administered at the dose of 5 mg/kg at weeks 0, 2, 6, and 14. The results for the male patient were as follows (baseline vs. the final examination): BCVA – 0.5 vs. 0.8; cellular reaction – 3+ vs. 1+; FAG – 1/2 vs. 0. The results for the female patient were as follows: BCVA – 0.1 vs. 0.3; FAG – 2/3 vs. 0. After 12 months, relapses or side-effects were not observed.

Conclusion Infliximab is an effective and promising drug in treating refractory BD-associated PU. It promptly reduces acute symptoms of PU, but it still remains to be seen if a long-term remission in a great number of patients will be achieved.

Keywords: Behçet disease; TNF-*α*; infliximab; retinal vasculitis; panuveitis

INTRODUCTION

Behçet disease (BD) is a chronic, relapsing, multisystem inflammatory disorder characterized by recurrent oral and genital ulcerations and uveitis, with varying other manifestations associated with vascular inflammation [1, 2]. After the initial BD description by Hulusi Behçet, additional target organ involvements, including vascular, neurological, and gastrointestinal manifestations, have been recognized and added to the disease spectrum. BD is found most often in young, adult males between the ages of 20 and 40 of Mediterranean, Middle Eastern, or Japanese extraction [2]. The etiology of BD remains unknown, but it is accepted that genetic and environmental factors play a role in its pathogenesis. The ocular inflammation associated with BD represents one of the most challenging forms of uveitis to treat. Initial manifestations include recurrent attacks of anterior uveitis, with or without hypopyon, retinal vasculitis, retinal infiltrates and hemorrhage, disc hyperemia, and vitreous opacification. Late complications may include cataract, iris synechia, glaucoma, retinal vascular occlusion, retinal neovascularization, and optic atrophy [2, 3, 4].

BD is one of the most difficult forms of uveitis to treat. Variety in disease presentation and severity, as well as regional differences in the standard of care, demand a tailor-made approach [5–8]. The preferred treatment modality is combined drug therapy, which includes corticosteroids, non-steroid anti-inflammatory drugs, colchicine, immunosuppressive and cytotoxic agents. Anti-tumor necrosis factor (TNF) monoclonal antibodies have recently attracted attention as a novel therapeutic approach [5, 6, 8, 9].

Infliximab is a chimeric monoclonal antibody composed of mouse variable domains of monoclonal antibody cA2 and human constant domains. It is being used increasingly in refractory (to corticosteroids and immunosuppressive agents) inflammatory eye diseases [10]. Several short-term follow-up studies have demonstrated the efficacy and safety of TNF-*α* antagonist drugs in the treatment of refractory posterior uveitis [11, 12, 13].

The aim of this paper is to report our experience on using infliximab in treating two patients with refractory BD-associated posterior uveitis (PU) with a comprehensive literature review.

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CASE REPORTS

We present two patients with refractory PU associated with BD who received infliximab intravenously at the dose of 5 mg/kg of body mass at weeks 0, 2, 6. and 14.

The diagnosis of BD fulfilled the criteria of the International Study Group [14]. Both patients had had more than five recurrences yearly and had been treated with corticosteroids (10–20 mg of prednisone) and with immunosuppressive therapy (cyclosporine 5 mg/kg and methotrexate 15–20 mg/week).

Both patients had chronic, bilateral sight-threatening retinal vasculitis resistant to high doses of corticosteroids. At admission, they demonstrated acute retinal vasculitis and cystoid macular edema in both eyes.

The ophthalmological evaluation included the best corrected visual acuity (BCVA) measurement by Snellen, a slit lamp biomicroscopy evaluation, tonometry, ocular fundus ophthalmoscopy, and fundus fluorescein angiography (FAG) at baseline, at weeks 7 and 14, and after 12 months.

Both patients underwent an examination by a pulmonologist, including chest X-ray and purified protein derivate; they were also examined by a rheumatologist before the infliximab administration. Blood and urine analyses were performed as listed: complete blood count, erythrocyte sedimentation rate, kidney and liver function testing, C-reactive protein and autoimmune antibodies (monthly), and a check-up with the rheumatologist every three months.

After infliximab, no immunosuppressive agent was administered; prednisone with dose tapering was scheduled in the following manner: 10 mg/day over the first three months, followed by 5 mg/day in the next three months until withdrawal.

Before the therapy, the patients were fully informed and signed an informed consent regarding its possible side effects and the fact that the long-term risks of infliximab are unknown.

Complete remission was defined as the presence of less than 1+ cellular reaction (scale 0–4) and a score of 0 at FAG (score 0 – absence of active vasculitis; 1 – peripheral vasculitis; 2 – posterior pole vasculitis; 3 – vasculitis with retinal necrosis) [15].

Case 1

A 45-year-old man with a 25-year-long history of BD had complaints about blurred vision in the right eye (RE) starting two days before the admission. Due to retinal vasculitis and longstanding cystoid macular edema, a complete loss of vision occurred in the left eye (LE). At admission, BCVA of the RE was 0.5, while the LE exhibited no light perception. Slit lamp biomicroscopy reveled posterior synechia at 3, 4, and 7 o'clock positions, 3+ cellular reaction in the anterior chamber, and complicated cataract. At the retina, active vasculitis with infiltrates was observed; FAG demonstrated peripheral and posterior pole vasculitis (1–2). A dermatologist identified huge oral and genital ulcerations**.** Infliximab was administrated as stated above. After 24 hours, the retinal infiltrates decreased in number; seven days later, oral and genital ulcerations decreased and the patient gained one Snellen line. The infusions were repeated at weeks 2, 6 and 14. There were no signs of recurrences. Six months later, oral and genital ulceration appeared completely resorbed, BCVA of the RA was 0.8 Snellen with no signs of PU, 1+ cellular reaction and FAG 0 (absence of active vasculitis). By the end of the follow-up, at 12 months, there were no recurrences, nor adverse effects of the therapy.

Case 2

A 45-year-old female patient had a 15-year-long history of BD with complaints of redness and a decrease of visual acuity in both eyes. At admission, BCVA of the RE was 0.1; LE hand movement at 1 m. At slit lamp examination, on both eyes, hypopyon was demonstrated, 3+ flare in anterior chamber, complicated cataract, normal intraocular pressure. The FAG finding was defined as score 2–3. Just before administering infliximab, the patient presented acute swelling of the right knee joint and oral ulceration. Just 24 hours after the infusion, BCVA of the RE was 0.2 and the joint was less swollen. The infusions were repeated at weeks 2, 6, and 14. After the fourth infusion of Infliximab, BCVA of the RE was improved by two Snellen lines and BCVA of the LE was 0.1. At 12 months, no relapse was registered, flare was 1+, FAG score 0, BCVA remained stable (RE 0.3; LE 0.1). There were neither relapses of the disease, nor immediate side-effects of the therapy by the end of the follow-up.

DISCUSSION

The infliximab molecule is a chimeric antibody whose variable regions are monoclonal, derived from mouse cells, while the constant regions are of human origin. It is administered by intravenous infusion, and TNF-α binding and blocking are central to its mechanism of action. TNF-α is active in many places in the immune cascade, and is crucial in a number of immune diseases [16]. Infliximab therapy has been reported as being generally effective in anecdotal case series of BD patients with various refractory manifestations, including mucocutaneous lesions, uveoretinitis, arthritis, and gastrointestinal involvement [10, 13]. Sfikakis et al. [17, 18] were among the first to show that infliximab leads to remarkably rapid and effective suppression of almost all manifestations of Behçet's disease, at least in the short term, including acute sight-threatening PU. The recent studies have shown that remission is maintained in 75% of patients [11, 16, 19, 20]. However, there are different literature data on the number of infusions that would lead to disease remission. In one study, no patients received more than six infusions, and in another one, 75–78% of patients receiving nine infusions achieved disease remission in one year and 50% of subjects remained in remission for a further 12 months [15, 21]. Furthermore, in a small retrospective controlled case series, infliximab-treated patients maintained improved

visual acuity in the two-year follow-up after a course of six infusions over three months [22].

Lopez-Gonzalez et al. [12] described the use of Infliximab in patients with refractory posterior uveitis in a seven-year follow-up study, and used different numbers of infusions in patients' treatment to calm the disease down and to achieve remission. They concluded that a possible dosing interval could be three infliximab infusions of 5 mg/kg at weeks 0, 2, and 6, followed by every eight weeks for a year, along with other immunosuppressive agents such as methotrexate. It is significant in their investigation that all patients with posterior uveitis within BD had positive tolerance to the therapy, while no improvement was observed in chorioretinal lesions associated with multifocal choroiditis and birdshot retinochoroidopathy [12].

Of course, infliximab therapy should not be used as the initial therapy, nor in minor cases where the treatment of an acute attack and long-term remission could be achieved by conventional standard therapy. European League Against Rheumatism has published important guidelines based on expert consensus and systematic review of the literature [23, 24]. Arguably, azathioprine is recommended as the initial immunosuppressant of choice to prevent ocular complications. Additional therapy with cyclosporine and/or infliximab is indicated when there is severe eye disease [24]. Fresko and Yazici [8] suggest that if the patient has severe eye disease (defined as > 2 lines of drop in visual acuity on the 10/10 scale) and/or retinal disease (retinal vasculitis or macular edema), fast-acting drugs such as cyclosporine A or infliximab should be used in combination with azathioprine or corticosteroids. No other additional therapy with infliximab was administered to our patients – only prednisolone monotherapy over the first six months, although the literature data suggest the use of the therapy in combination with an immunosuppressive, like methotrexate, is more efficient [12, 16]. Fresko and Yazici emphasize rapid occurrence of relapsing if infliximab is used alone [8].

Infliximab has side effects. Patients treated with TNF-α blockers incur the risk of reactivation of latent tuberculosis and other infections, demyelinating disease, and congestive heart failure [25]. We did not find any adverse effects of this drug. Suhler et al. [20] described a broad range of side effects potentially attributable to infliximab, including lupus-like reaction, pulmonary embolus, and congestive heart failure. The most recent study from Sakai et al. [26] suggests that relief of uveitis attacks and extraocular manifestations by infliximab therapy significantly improved the health-related and vision-related quality of life in patients with BD.

Infliximab seems to be effective in treatment of refractory PU associated with BD. It promptly reduces acute visual symptoms, but it still remains to be seen whether it will produce long-term remission in a great number of patients. We did not observe any adverse effects. So, to answer all the raised questions, more trials are needed to be done. Yet, we do hope this new therapy will lead to a more effective treatment of BD, will reduce the incidence of relapses, and consequently, long-term therapy will be reduced as well.

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Ефикасност инфликсимаба у лечењу рефракторног панувеитиса удруженог са Бехчетовом болешћу

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САЖЕТАК

Увод Бехчетова болест (ББ) јесте хронични мултисистемски поремећај са очним, уролошким, зглобним и васкуларним манифестацијама. Фактор туморске некрозе – алфа има кључну улогу у патогенези ББ. Инфликсимаб блокира његову активности и то је нови терапијски приступ у лечењу ББ. Циљ овог рада је да прикаже исход лечења инфлуксимабом код два болесника са ББ који су имали рефракторни панувеитис (ПУ). Пацијенти су праћени у периоду од 12 месеци. Главни параметри праћења ефикасности лечења су били најбоље коригована оштрина вида на бољем оку, налаз на предњем сегменту и на флуоресцеинској ангиографији (ФАГ).

Приказ болесника Мушкарац (стар 45 година, болује од ББ 25 година, налаз: задње синехије, 3+ *flare* и компликована катаракта) и жена (стара 45 година, од ББ болује 15 година, налаз: хипопион, 3+ *flare* и компликована катаракта) лечени су инфликсимабом у дози од 5 *mg/kg* телесне масе у недељама 0, 2, 6 i 14. Резултати на почетку и крају лечења су били следећи: мушкарац са ББ – видна оштрина 0,5 *vs.* 0,8; *flare* 3+ *vs.* 1+; ФАГ 1/2 *vs.* 0; жена са ББ – видна оштрина 0.1 *vs.* 0.3; ФАГ 2/3 *vs.* 0. После 12 месеци рецидиви или нежељени ефекти нису уочени.

Закључак Инфликсимаб је ефикасан и обећавајући лек у лечењу ПУ код болесника са ББ. Њиме се постиже брзо смиривање акутних симптома ПУ.

Кључне речи: Бехчет; TNF-*α*; инфликсимаб; мрежњача; васкулитис; панувеитис

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Myoepithelioma originating from the floor of the mouth

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SUMMARY
Introduction Myoepithelioma primarily affects the parotid gland and usually presents as a slow-growing painless lump.
The aim of this paper is to report a case of myoepithelioma in the mouth floor.
Case outline A young man noticed a painless increased volume in the left side of the mouth floor region, which after one year of evolution presented as a sessile tumor with normal colored mucosa and the absence of secretion output. Computed tomography with contrast showed an image with slightly heterogeneous density, with well-defined limits. Incisional biopsy was performed under local anesthesia, and pathology examination of the sample revealed a myoepithelial neoplasm. Total excision of the lesion was performed under general anesthesia, and histopathological examination confirmed the diagnosis of the salivary gland myoepithelioma. The patient did not present signs of relapse after a year of follow up.
Conclusion Despite the fact that myoepithelioma originating in the salivary gland are considered rare, especially in the mouth floor, this tumor should be considered in the differential diagnosis of similar lesions. Proper treatment appears to be complete surgical excision and post-operative follow-ups shows should be carried out as long as possible, despite the fact that relapses are extremely rare.
Keywords: salivary gland; oral pathology; myoepithelioma

INTRODUCTION

Myoepithelioma was first described in 1943 [1]. However, it was only in 1991 that it was considered by the World Health Organization as a distinct pathological entity. Also known as myoepithelial adenoma, this tumor is composed entirely of myoepithelial cells, without duct formation in its interior and makes up about 1–1.5% of all salivary gland tumors [2, 3–14]. It affects both minor and major salivary glands, but is more commonly found in the parotid (about 50%), sublingual (33%), and submandibular glands (13%) [13, 15]. Patients between the fourth and sixth decades of life are the most often affected [4, 7, 11, 15], and there is no predilection for gender [11, 14]. It usually present as a painless nodule with slow growth [13, 14, 15].

Myoepithelial cells are part of the normal composition of the salivary glands and are important components of many types of salivary gland tumors such as pleomorphic adenoma, adenoid cystic carcinoma, and terminal duct carcinoma [16, 17]. These cells are located between the basal lamina and the acinar and ductal cells. They have structural characteristics similar to epithelial and smooth muscle cells [3, 18].

Myoepithelioma is rarely found, with more than 200 cases reported [18]. Thus, this paper aims to report what we believe to be the second case of myoepithelioma in the mouth floor described in the English language literature in the past 20 years, highlighting its clinical and pathologic characteristics and appropriate treatment.

CASE REPORT

A 28-year-old black male attended the Oral and Maxillofacial Surgery and Traumatology Clinic at the Baiano's Center for Dental Studies, Salvador, Brazil, complaining of a painless swelling in the left mouth floor region which lasted for one year. Regarding its previous medical history, there was nothing to consider. At physical examination, a swelling, firm to palpation and lined by normal mucosa, could be noticed. It was located in the floor of the mouth, in the left anterior region (Figure 1A).

Computed tomography imaging with contrast showed a hyperdense lesion in a region close to the left base of the tongue, with contours well-defined and of slightly heterogeneous density, measuring about 4 × 2.5 × 1.5 cm in its greatest diameter (Figure 1B). At the ultrasound examination it was possible to observe epithelial, subcutaneous, and muscle tissues within normal limits, and the presence of fluid collection within the lesion was not detected.

An incisional biopsy under local anesthesia was performed and histopathological examination revealed a well-circumscribed neoplasm characterized by the presence of plasmacytoid myoepithelial, epithelioid, and eventually cuboid cells in a fibrous or hyaline matrix (Figure 1E).

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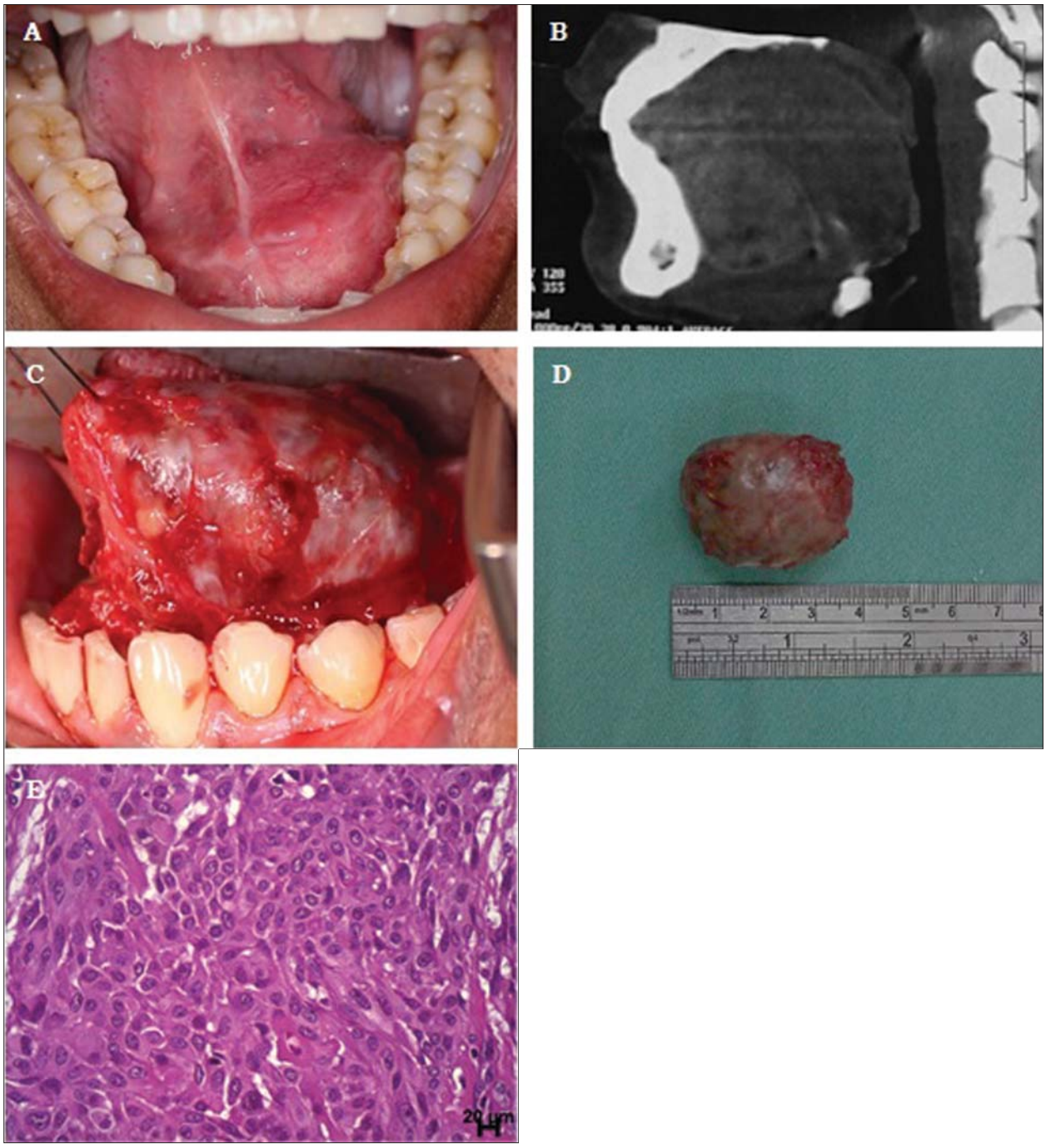

Figure 1. A) Clinical image showing a swelling located in the floor of the mouth; B) tomographic image (sagittal multiplanar reconstruction) presenting a well located lesion; C) nodular and well-delimited lesion within the floor of the mouth; D) nodular lesion measuring 4 × 2.5 × 1.5 cm; E) a solid area showing proliferation of plasmacytoid, epithelioid, and, eventually, spindle-shaped cells

The patient thereafter underwent excisional biopsy under general anesthesia through intraoral access in the left anterior floor of the mouth region. During the surgery we could notice that the lesion had well-defined boundaries, easy identification and cleavage, with rubber consistency and predominantly yellowish color with purplish spots (Figure 1 C and D).

The surgical specimen was stored in 10% formaldehyde and sent for histopathological examination, and a diagnosis of myoepithelioma was established. The patients recovery was uneventful and after two years of follow-up he showed no signs of recurrence.

DISCUSSION

The occurrence of myoepithelioma in the head and neck area is rare, while the involvement of the oral cavity is extremely rare, representing about 1–1.5% of all salivary gland tumors [5, 18, 19, 20]. According to Table 1, only one article was published about myoepithelioma located in the floor of the mouth, and maxilla was the most frequent site. There was no predilection for gender. In regard to the age group predilection, the most affected were persons in the third and fifth decades of life.

Table 1. Summarization of clinical cases of face myoepitheliomas reported in the last 20 years

Autors	Year	Age	Sex	Color	Site	Treatment	Follow-up	Recurrence
Kanazawa et al. [3]	1999	42	Female	Yellow	Hard palate	Local excision	2 years	No
Piatelli et al. [4]	1999	47	-	-	Jugal mucosa	Excisional biopsy	3 years	No
Carinci et al. [5]	2001	30	Male	-	Tongue base	Local resection + chemotherapy	4 years and 4 months	No
Isogai et al. [6]	2003	47	Female	Yellow	Buccal mucosa	-	6 months	No
Nair et al. [14]	2004	58	Male	Brown	Hard palate	Local excision	6 months	No
Onbas et al. [7]	2005	65	Female	-	Hemiface	-	-	-
Woo et al. [22]	2005	22	Female	-	Dorsal tongue	Excisional biopsy	1 year and 2 months	No
Cuesta Gil et al. [20]	2008	54	Female	White	Maxilla	Hemimaxillectomy	3 years	No
Patrocinio et al. [8]	2009	38	Male	-	Maxilla	Local resection	9 years	No
Nikitakis et al. [19]	2010	45	Male	White	Dorsal tongue	Excisional biopsy	2 years	No
Hunt et al. [18]	2011	21	Male	White	Mouth floor	Excision of the	-	-
Park and Seo [9]	2011	23	Male	Yellow	Buccal mucosa	Submandibular gland local excision	2 years	No
Rishabh et al. [10]	2011	22	Male	Brown	Orbit	Local excision	5 months	No
Sperandio et al. [2]	2011	42	Female	Black	Soft palate	Local excision	1 year	No
Badal et al. [11]	2013	55	Male	-	Maxilla	Hemimaxillectomy	-	-
Gore et al. [12]	2013	70	Female	-	Maxilla	-	-	-
Gore et al. [12]	2013	62	Female	-	Maxilla	-	-	-
Gore et al. [12]	2013	30	Female	-	Maxilla	-	-	-
Mochizuki et al. [13]	2013	40	Female	White	Parotid gland	Enucleation	1 year	No
Yadav et al. [17]	2013	40	Male	-	Soft palate	Local excision	6 months	No
Present case	2016	28	Male	Black	Mouth floor	Local excision	2 years	No

Clinically, myoepithelioma presents itself as a slow-growing, circumscribed, and painless swelling [4, 10, 12, 13, 18, 19, 21]. The presented case showed an evolution period of two years, without painful symptoms associated, and imaging examinations revealed a circumscribed lesion in the floor of the mouth in the left anterior region. Myoepithelioma shows no predilection for gender and affects a wide age range but some authors claim that the fifth decade of life is the most affected age group [13, 14, 18, 19, 20, 21].

Most myoepitheliomas of salivary glands occur in parotid glands (50%), sublingual (33%) and submandibular gland (13%) [2, 6, 13, 15]. Rarely, it affects locations such as the maxillary sinus, lacrimal gland, nasal cavity, larynx or dermis [6]. The origin of the tumor described in this study appears to be a minor salivary gland and its site is extremely rare, with only one case of the mouth floor myoepithelioma documented in the researched English language literature [20].

The reported case fulfills the criteria for myoepithelioma. Myoepithelial cells are similar to smooth muscle cells, probably of ectodermal origin, but they perform functions of mesodermal cells [22]. Usually, myoepithelioma presents multiple cellular patterns as fusiform, plasmacytoid, epithelioid, clear cell, mixed pattern, and abundant presence of mucoid acellular stroma [3, 4, 6, 9, 12, 18, 19, 20]. The plasmacytoid type tends to occur more often in the oral cavity, especially in the palate, when compared with other types of myoepithelioma, although the fusiform pattern is the most common and often primarily affects the parotid gland [3, 4, 18]. Patterns containing epithelioid cells and clear cells develop in the parotid glands and often suffer malignant transformation [6]. Histological pattern does not influence the biological behavior of the lesion [18].

Myoepithelioma is often confused with pleomorphic adenomas due to the large amount of myoepithelial cells present in these two tumors [3, 9, 19, 20]. Myoepitheliomas were once considered a variant of pleomorphic adenoma [13]. However, since 1991, the World Health Organization has clearly differentiated myoepithelioma from pleomorphic adenoma, showing that myoepithelioma presents epithelial cells, but it has no duct differentiation or presence of chondroid or myxochondroid matrix.

The differential diagnosis includes pleomorphic adenoma and other salivary gland tumors, including cancer. The first suspect in the presented case was pleomorphic adenoma, followed by plunging ranula. However, in the floor of the mouth, other tumors such as lipomas and neurofibromas can also be found.

Myoepitheliomas are less likely to recur than pleomorphic adenoma. However, they can undergo malignant transformation, especially when there are recurrent relapses or tumor existence for a long time without treatment [9]. The prognosis is based on histopathology, being favorable for the benign form, which does not eliminate the need for regular monitoring to detect local recurrence, though it is rare when the lesion is completely removed [9, 18, 20].

According to Table 1 and the current literature, the treatment usually consists of complete removal of the lesion, with no reports of recurrence after an average time of 25 months following surgery [2, 9, 12, 13, 18]. Recurrence rates of 10% and 18% are reported, probably due to incomplete removal of the lesion. The prognosis is favorable [12, 14]. In the present case, after two years of postoperative follow-up, there were no signs of recurrence. However, it is wise to carry out follow-ups as long as possible, despite the fact that relapses are extremely rare.

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Миоепителиом пода уста

Винисијус Рио Верде Мело Муниз, Паулине Магаљаис Кардозо, Рафаел Фернандес де Алмеида Нери, Леонардо де Араужо Мело, Браулио Карнеиро Жуниор, Жеан Нунес дос Сантос

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САЖЕТАК

Увод Миоепителиоми се првенствено налазе на паротидној жлезди, обично као безболни израштај са спорим растом. Циљ овог рада је да опише случај миоепителиома у поду уста.

Приказ болесника Младић је приметио безболну отеклину на левој страни пода уста, са једногодишњом еволуцијом у сесилан тумор, нормално пребојен, без секреције. Компјутеризована томографија са контрастом приказала је добро ограничену промену мале хетерогене густине. Биопсија је урађена у локалној анестезији, а хистопатолошки преглед указао је на миоепителну неоплазму. Промена је у целости одстрањена у општој анестезији, а патохистолошки налаз потврдио дијагнозу миоепителиома пљувачне жлезде. Болесник је праћен годину дана и није испољио знаке рецидива болести.

Закључак Миоепителиоми пљувачних жлезда су ретки, посебно у поду уста, али овај тумор треба размотрити у диференцијалној дијагнози сличних лезија. Неопходна је потпуна хируршка ексцизија, а време постоперативног праћења би требало да је што је могуће дуже иако су рецидиви изузетно ретки.

Кључне речи: пљувачна жлезда; орална патологија; миоепителиом

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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Surgical treatment of a carotid artery aneurysm associated with kinking – A case report and review of literature

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SUMMARY

Introduction An extracranial carotid artery aneurysm is a rare clinical entity with potentially debilitating consequences. Our aim is to present a case of a large internal carotid artery aneurysm combined with medial internal carotid artery (ICA) kinking successfully treated by resection with an end-to-end anastomosis.

Case outline A 34-year-old female patient was admitted to our hospital due to dizziness and frequent non-specific headaches. On admission, routine echocardiography showed an aneurysm of the atrial septum. Multislice computed tomography of the supraaortic branches showed medial kinking of the right ICA with a 15 mm aneurysm localized on the vertex of the angulation. Kinking was present on the left ICA as well, with a small aneurysm of 5 mm in diameter. The right ICA aneurysm was resected and the artery was reconstructed with an end-to-end anastomosis. The postoperative course was uneventful and the patient was symptom-free after a one-year follow-up.

Conclusion We showed that surgery of an aneurysm and kinking of the carotid artery in the medial segment of the ICA is possible and safe to perform. Detailed preoperative preparation, precise surgical technique, and short clamping time all contributed to a good final outcome.

Keywords: carotid artery aneurysm; kinking; surgical treatment

INTRODUCTION

An extracranial carotid artery aneurysm is a rare clinical entity with potentially debilitating consequences [1]. According to major referral centers, they account for 0.4–0.9% of all repaired aortic and peripheral artery aneurysms [1, 2]. Therefore, only a small number of reports in the literature describes an internal carotid artery (ICA) aneurysm associated with kinking [3–7]. Our aim is to present a case of a large ICA aneurysm combined with medial ICA kinking successfully treated with resection with an end-to-end anastomosis.

CASE REPORT

A 34-year-old female patient was admitted to our hospital due to dizziness and frequent non-specific headaches. Arterial hypertension, hyperlipidemia, smoking, and positive family history were identified as risk factors for atherosclerosis. The patient denied any other chronic illnesses, previous surgery, or trauma.

On admission, routine echocardiography showed an aneurysm of the atrial septum and a potentially patent foramen ovale. Subsequent transesophageal echocardiography confirmed the presence of the aneurysm, but the presence of a shunt between the atria was excluded.

Multislice computed tomography of the supraaortic branches showed medial kinking of the right ICA with a 15 mm aneurysm localized on the vertex of the angulation (Figure 1). Kinking was also present on the left ICA with a small aneurysm of 5 mm in diameter. Other supraaortic branches and intracranial arterial network had no significant lesions. In addition, computed tomography of the brain without contrast did not reveal any pathological findings.

The patient underwent surgery in general anesthesia. Carotid arteries were exposed

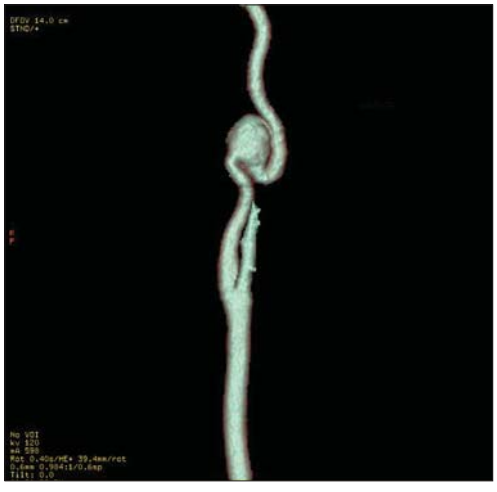

Figure 1. Multislice computed tomography angiography; the right internal carotid artery aneurysm associated with medial kinking

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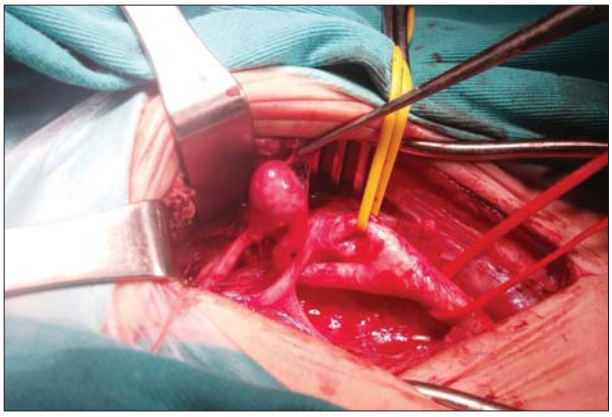

Figure 2. Intraoperative findings; the right internal carotid artery aneurysm associated with kinking, positioned cranial to the hypoglossal nerve

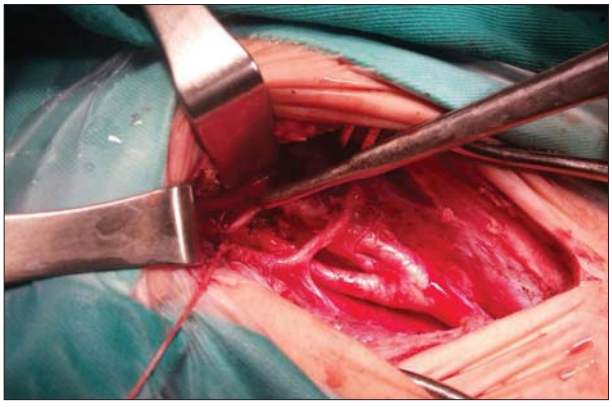

Figure 3. Intraoperative findings; the right internal carotid artery reconstructed with end-to-end anastomosis

through a typical longitudinal incision on the right side of the neck. The aneurysm and the kinked segment of the ICA were dissected. The aneurysm was located approximately 5 cm from the carotid bifurcation, and about 1.5 cm distally from the hypoglossal nerve (Figure 2). After systemic heparin administration, carotid arteries were clamped (without shunt insertion), the aneurysm was resected and the ICA was reconstructed with an end-to-end anastomosis (Figure 3). Clamping time was 7 minutes.

The resected aneurysm was sent for pathohistology, which showed that the arterial wall was irregularly thinned, with a discrete intimal layer and congestion in the adventitial layer.

On the second postoperative day, the patient had a mild edema of the right hypopharynx, which was successfully treated with corticosteroids. There were no other complications in the immediate postoperative period. She was discharged from the hospital in good condition on the fourth postoperative day. After the one-year follow-up the patient was symptom-free and Doppler ultrasound revealed normal findings on the right carotid artery.

DISCUSSION

Carotid artery aneurysm treatment accounts for only 1–1.5% of all surgeries performed in treatment of extracranial cerebrovascular disease [1, 8]. The patients' age varies from 26 to 82 years throughout the studies, and is typically related to the etiology of the disease [1].

Most authors report atherosclerosis as the most common cause of true extracranial ICA aneurysms. On the other hand, pseudoaneurysms can be a result of trauma or infection, especially in younger population. There is also a subgroup of patients with pseudoaneurysms related to previous carotid endarterectomy with patch angioplasty [1, 2, 9, 10].

Carotid aneurysms are often identified by the presence of a pulsatile mass on the lateral side of the neck. Symptomatic ICA aneurysms usually give neurological symptoms, global in more cases than hemispheric. In addition, a significant number of patients with larger aneurysms also have symptoms due to the compression of the surrounding structures. However, prevention of complications like rupture, complete thrombosis of the aneurysm, and brain embolisation resulting in an acute ischemic event is the main goal of treatment.

Treatment of carotid artery aneurysm comprises of surgical and endovascular approaches. In distant past, ligation of the common carotid artery was the treatment of choice, but had high rates of morbidity and mortality [11]. Later, various surgical techniques were developed, including aneurysmectomy with primary/patch closure, resection of the aneurysm with primary anastomosis or grafting (both venous and synthetic) [12].

A recent systematic review identified 281 articles reporting carotid artery aneurysms from 1900 to July 2014 [10]. Although natural history of this disease is not well understood, aneurysms seem to rupture rarely. Consequently, the focus of treatment was mainly the prevention of thromboembolic events. Most authors conducted surgical treatment with good long-term results, but with considerable incidence of cranial nerve damage. Endovascular approach also showed satisfying results, but with no mid- or long-term follow-up.

True prevalence of ICA kinking in the general population is unknown. Several reports show that this condition is bilateral in 25–50% of cases and that it is more common in women [13, 14]. The relationship between the degree of ICA kinking and neurologic symptoms is still unclear. Patients with tortuous carotid arteries are rarely symptomatic, but if so, they usually present with global neurological symptomatology. In a randomized controlled trial, including patients with ICA kinks and coils with hemispheric neurological symptoms, the authors showed significantly better results with surgical than with best medical treatment [13]. Changes in hemodynamics of the blood flow through the kinked ICA segment can mimic stenosis and can also influence changes in the intimal layer of the arterial wall, leading to ulcerations and predisposition for thrombosis.

We identified just a few cases in the literature concerning ICA aneurysms secondary to carotid artery kinks and coils, and, to our knowledge, none of them presented a case of such a young female patient [3, 4, 6, 7]. In our case, a saccular aneurysm of the ICA was formed secondary to hemodynamically significant kinking of the vessel.

According to Welleweerd et al. [14], carotid artery aneurysms can be histologically classified as degenerative

and dissective. Although our sample was not identically processed, it could be categorized as degenerative due to the variable thickness of the arterial wall and the absence of any intimal disruptions. However, there were no inflammatory cells found in the sample, which differs from the majority of findings in the abovementioned study.

The incidental finding of atrial septal aneurysm without patent foramen ovale could have been important for our patient. Several studies linked this condition to cerebrovascular symptoms and recent strokes in patients with normal carotid arteries [15, 16]. Considering the age of the patient, the presence of the ICA kinking bilaterally, and the two separate entities resulting from the weakness of the cardiovascular wall structure, our opinion is that these conditions might have embryological background.

In our case, the kinking and aneurysm were located well above the mandible angle and cranial to hypoglossal nerve. Meticulous surgical technique and high approach to ICA were performed with the resection of the posterior belly of the digastric muscle. According to our previous experience with treatment of carotid artery aneurysms, the presence of kinking facilitates the resection of the aneurysm with the reconstruction of the ICA with the end-to-end anastomosis [17].

We showed that surgery of an aneurysm and kinking of carotid artery in the medial segment of the ICA is possible and safe to perform. Detailed preoperative preparation, precise surgical technique, and short clamping time all contributed to a good final outcome.

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Хируршко лечење анеуризме каротидне артерије удружене са кинкингом – приказ болесника и преглед литературе

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САЖЕТАК

Увод Екстракранијална анеуризма каротидних артерија је редак клинички ентитет са могућим онеспособљавајућим последицама. Циљ рада је да прикажемо случај велике анеуризме унутрашње каротидне артерије (УКА) удружене са кинкингом, која је успешно хируршки третирана ресекцијом анеуризме са термино-терминалном реконструкцијом артерије.

Приказ болесника Жена стара 34 године примљена је у болницу због вртоглавица и учесталих неспецифичних главобоља. На ехокардиографском прегледу уочена је анеуризма атријалног септума. Мултислајсна компјутеризована томографија супрааорталних грана показала је медијални кинкинг десне УКА са анеуризмом промера 15 *mm* на врху ангулације. Кинкинг је уочен и на левој УКА са анеуризмом промера 5 *mm*. Анеуризма десне УКА је ресецирана, а артерија је реконструисана термино-терминалном анастомозом. Постоперативни ток је био уредан, као и годину дана после операције.

Закључак Хируршко лечење анеуризме УКА удружене са медијалним кинкингом је ефикасно и безбедно.

Кључне речи: анеуризма каротидне артерије; кинкинг; хируршко лечење

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REWIEV ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

The impact of currently used oral antihyperglycemic drugs on dysfunctional adipose tissue

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SUMMARY
Obesity is a disease with pandemic frequency, often accompanied by chronic metabolic and organic complications. Type 2 diabetes mellitus (T2DM) is among the most common metabolic complications of obesity. The first step in the treatment of T2DM is medical nutrition therapy combined with moderate physical activity and with advice to patients to reduce their body weight. Pharmacotherapy starts with metformin, and in the case of inadequate therapeutic response, another antihyperglycemic agent should be added. The most clinical experience exists with sulfonylurea agents, but their use is limited due to high incidence of hypoglycemia and increase in body weight. Based on the fact that dysfunction of adipose tissue can lead to the development of chronic degenerative complications, precise use of drugs with a favorable effect on the functionality of adipose tissue represents an imperative of modern T2DM treatment. Antihyperglycemic drugs of choice in obese individuals are those which cause maturation of adipocytes, improvement of secretion of protective adipokines, and redistribution of fat mass from visceral to subcutaneous depots. Oral antihyperglycemic agents that can affect the functionality of adipose tissue are metformin, SGLT-2 inhibitors, DPP-4 inhibitors, and thiazolidinediones.
Keywords: adipose tissue; adipokines; type 2 diabetes mellitus; treatment

INTRODUCTION

Obesity is a disease characterized by the excessive accumulation and storage of adipose tissue in the body, which presents a risk to health and can lead to many complications [1, 2, 3]. Adipose tissue is a metabolically active organ with both endocrine and paraendocrine effects [3]. Dysfunction of this tissue is clearly associated with more frequent occurrence of visceral obesity, type 2 diabetes mellitus (T2DM), insulin resistance (IR), and chronic subclinical inflammation [3, 4, 5]. Namely, fat tissue makes up approximately 10–20% of the total body mass, while that percentage in obese persons can be four to five times greater [6, 7]. Reduction in adenosine monophosphate-activated protein kinase α (AMPKα), peroxisome proliferator-activated receptor gamma, coactivator 1 α (PPARGC1A, PGCα), and peroxisome proliferator-activated receptor α (PPARα) genes' expression decreases the oxidative capacity of adipocytes, and thereby inhibits the possibility of energetic metabolism turnover in the adipose tissue, which represents the main pathophysiological model that causes obesity [8]. Knowing this fact, current therapy of T2DM and the development of modern antihyperglycemic drugs are based on the stimulation of those impaired pathways in the adipose tissue.

It is known that in the presence of excessive obesity the possibility of prediabetes development increases, which can, in the later course, lead to the onset of T2DM, which imposes the need for implementation of the active screening procedures among populations with a great propensity to develop diabetes, like among obese individuals, but also a need to intensify their treatment [9]. Populations with greater susceptibility for T2DM development include subjects with prediabetes, obese and overweight individuals, subjects with established cardiovascular diseases, and persons older than 45 years [9]. In these cases, it is indicated to perform the two-hour oral glucose tolerance test with 75 g of glucose [9, 10].

The consequence of dysfunctional adipose tissue is sustained lipid toxicity, followed by IR and associated metabolic complications. These metabolic alterations negatively affect global metabolic homeostasis. The adipose tissue distribution optimization and its functional metabolic flexibility are promoting insulin sensitivity and metabolic control in patients with T2DM. These therapeutic approaches require a deep understanding of adipose tissue in all broad aspects. In this article, we will discuss the influence of the different glucose-lowering agents on adipose tissue depots with respect to adipokines' production, plasticity, cellular composition, as well as metabolic signatures of pharmacotherapy of T2DM [9, 10].

Randomized controlled studies showed that in persons with the higher risk of developing T2DM, lifestyle changes and/or drug therapy can prevent progression of the disease [11]. Considering that at the moment of diabetes

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diagnosis 80–90% of patients are overweight or obese, the American Diabetes Association guidelines recommend the introduction of antihyperglycemic drugs with weight-reducing or at least weight-neutral properties in patients with body mass index (BMI) ≥ 27 kg/m^2, whenever other circumstances allow it [10]. Antihyperglycemic drugs that stimulate weight reduction are metformin, α-glycosidase inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonist, amylin mimetics, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. Dipeptidyl peptidase-4 inhibitor (DPP-4) inhibitors are weight-neutral to weight-reducing, while secretagogues, thiazolidinediones, and insulin are related to a significant increase in body weight [9, 10].

Therapy

Initial therapy for T2DM surely includes lifestyle changes such as intensification of physical activity to minimum of 150 min./week and changes in dietary habits [9, 10, 11]. Metformin is the first line of drug therapy, according to current recommendations [9, 10]. If this treatment fails to give expected results in a period of three months, combination therapy should be introduced [9, 10]. While choosing the right additional antihyperglycemic drug, it is necessary to bear in mind its effect on the body weight [9, 10, 12].

The list of available glucose-lowering agents is shown in Table 1.

Sulfonylureas are drugs that have been used for several decades. They show high efficiency in HbA1c reduction, and the evidence from earlier landmark studies indicates their positive effect on the delay of chronic microvascular complication development. However, nowadays, at least in developed countries, they are replaced with other drugs, because they cause high rates of hypoglycemia, tend to increase body weight, and have a negative effect on spontaneous vasodilatation of coronary arteries [12].

α-Glucosidase inhibitors have limited use, considering their modest efficiency in HbA1c reduction accompanied

Table 1. Properties of available glucose-lowering agents that may tailor the individualized treatment choice in patients with T2DM

Class	Compound(s)	Cellular mechanism(s)	Primary physiological action(s)
Biguanides	Metformin	activates AMP-kinase	↓ hepatic glucose production
Sulfonylureas	2nd generation: Glyburide Glipizide Gliclazide Glimepiride	closes KATP channels on β-cell plasma membranes	↑ insulin secretion
Meglitinides	Repaglinide Nateglinide	closes KATP channels on β-cell plasma membranes	↑ insulin secretion
Thiazolidinediones	Pioglitazone Rosiglitazone	activates the nuclear transcription factor PPARγ	↑ insulin sensitivity
α-Glucosidase inhibitors	Acarbose Miglitol	inhibits intestinal α-glucosidase	slows intestinal carbohydrate digestion/absorption
DPP-4 inhibitors	Sitagliptin Vildagliptin Saxagliptin Linagliptin Alogliptin	inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1) concentrations	↑ insulin secretion ↓ secretion of glucagon
Bile acid sequestrants	Colesevelam	binds bile acids in intestinal tract, increasing hepatic bile acid production	?↓ hepatic glucose production ?↑ incretin levels
Dopamine-2 agonists	Bromocriptine	activates dopaminergic receptors	modulates hypothalamic regulation of metabolism ↑ insulin sensitivity
SGLT-2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin	inhibits SGLT-2 receptors in the proximal nephron	blocks glucose reabsorption by the kidney, increasing glucosuria
GLP-1 receptor agonists	Exenatide Liraglutide Albiglutide Lixisenatide Dulaglutide	activates GLP-1 receptors	↑ insulin secretion ↓ glucagon secretion slows gastric emptying ↑ satiety
Amylin mimetics	Pramlintide	activates amylin receptors	↓ glucagon secretion slows gastric emptying ↑ satiety
Insulins	Lispro Aspart Glulisine Human regular Human NPH Glargine Detemir Degludec	activates insulin receptors	↑ glucose disposal ↓ hepatic glucose production

AMP-kinase – adenosine monophosphate-kinase; KATP channels – adenosine triphosphate-sensitive potassium channels; PPARγ – peroxisome proliferator-activated receptor gamma; DPP-4 – dipeptidyl peptidase-4; GLP-1 – glucagon-like peptide-1; SGLT-2 – sodium-glucose cotransporter-2; NPH – neutral protamine Hagedorn

by gastrointestinal side effects (diarrhea, flatulence) [12]. However these drugs found their place in the treatment of obese patients after the bariatric surgery. A number of patients treated with bariatric surgery procedures report the so-called "dumping syndrome," and the use of acarbose showed a decrease in incidence of this complication, thus leading to an improvement in the quality of life in these patients [13].

Bile acid sequestrants are used mainly in treating hypercholesterolemia, since their main effect is low-density lipoprotein (LDL) cholesterol lowering [14]. However, they demonstrate satisfying glucose-lowering effect (HbA1c reduction in the 0.3–1.1% range is reported), in particular colesevelam [14]. Their physiological actions remain unknown, with the assumption that they are based on the incretin effect through the stimulation of incretin secretion (GLP-1 and others) and on the impact on the hepatic glucose production [14].

Bromocriptine is one of the newer antihyperglycemic agents, with a unique central mechanism of action. Normal weight individuals have maximum prolactin secretion during the night, because of the low dopaminergic activity, while after waking up prolactin level decreases [15]. Obese individuals with IR have prolactin levels two times higher during the day compared to healthy persons [15]. The main mechanism of the bromocriptine antihyperglycemic action is an increase in the daily dopaminergic activity and lowering of the prolactin level [15]. Previous experiences show that bromocriptine monotherapy or its combination with other oral antihyperglycemic agents leads to the reduction of HbA1c ranging from 0.4% to 0.7% [15]. Even though it shows low/mild HbA1c reduction effect, benefits of bromocriptine use are weight reduction combined with low incidence of hypoglycemia [12, 15]. The side effects of bromocriptine (orthostatic hypotension, nausea, vertigo, and possible interactions with other plasma protein-binding drugs) limit its use [12, 15]. Since postprandial glycemia is an equally important indicator of glycoregulation and of HbA1c and fasting glycemia, large efforts have been made recently in the therapeutic targeting of this particular aspect of diabetes management. Efficiency in reduction of postprandial glycemia are shown by meglitinides, GLP-1 receptor agonists (mainly short-acting ones), DPP-4 inhibitors, SGLT-2 inhibitors, and amylin mimetics [16].

ORAL ANTIHYPERGLYCEMIC AGENTS AND DYSFUNCTIONAL ADIPOSE TISSUE

Metformin

Metformin has been used in the treatment of T2DM since the 1950s. It is already known that metformin reduces body weight [9, 10]. However, the greatest reduction of fat mass has actually been detected in subcutaneous abdominal depots [17]. Also, it is shown that metformin causes the highest insulin stimulated glucose uptake in the visceral adipose tissue [17]. Fujita et al. [17] have questioned the positive effect of this drug on dysfunctional adipose tissue, showing that in an in vitro model metformin actually blocks the differentiation of visceral tissue preadipocytes into mature adipocytes and that it does not reduce the size or the number of adipocytes, which could be expected as the positive effect [17]. This way, the maturation of preadipocytes and the secretion of adipocyte final maturation indicators, such as adiponectin, which demonstrates a strong anti-inflammatory and antidiabetic effect, are suppressed [17]. On the other hand, positive effects of metformin are shown among women with polycystic ovary syndrome. Tan et al. [18] published that metformin use significantly lowers the level of chemerine, an adipocytokine involved in the pathogenesis of IR and hypertriglyceridemia [18]. Metformin's main mechanism of action in adipose tissue is the activation of adenosine monophosphate (AMP)-kinase and lipogenesis suppression in preadipocytes, and the greatest antihyperglycemic effect is achieved through lowering the hepatic glucose production [19].

DPP-4 inhibitors

DPP-4 inhibitors are among newer antihyperglycemic agents, and according to the current diabetes guidelines are referred to as weight-neutral [9, 10]. DPP-4 are proteases located on the cell surface, but there is also a soluble fraction of this proteases in plasma [20]. Recently, this enzyme was recognized as an adipocytokine, responsible for the development of the metabolic syndrome and T2DM [20]. DPP-4 interfere with insulin signalization through paracrine and endocrine ways [20].

Although until now they were referred to as weight-neutral, recent studies on a DPP-4 inhibitor, evogliptin, in an animal model, indicate possible beneficial effects in term of body weight reduction. Namely, this drug shows the possibility of changing energy balance within the white adipose tissue [21]. Evogliptin in an animal model does not increase thermogenesis in white adipose tissue, but, contrary, reduces uncoupling protein-1(UCP-1) level in mitochondria of adipocytes [21]. It is shown in an animal model that evogliptin induces energy consumption with the help of increased expression of cytochrome c oxidase subunit 4 isoform 1(Cox4I1), which correlates with an increased concentration of protein molecule PPARGC1A [21]. This protein is directly involved in the transcription processes that stimulate production of enzymes necessary for mitochondrial biogenesis and energy consumption [21]. Also, PPARGC1A stimulates the differentiation of muscle fibers, and has protective effect in terms of obesity development [20, 21]. Evogliptin use led to a decrease in leptin level, which can be a result of weight reduction or a possible consequence of a decrease in the level of leptin resistance [21]. The effect of decreasing leptin resistance is just a hypothetical one, since authors did not measure the expression of leptin receptor [21]. Similar effect in humans is caused by vildagliptin [21].

SGLT-2 inhibitors

In the last 10 years, a new therapeutic approach has been developed, which does not include the use of insulin in

the treatment of T2DM. Under physiological conditions, glucose that is excreted in primary urine is entirely reabsorbed back to plasma in renal tubules, so less than 1% of glucose is excreted by urine [21]. Under SGLT-2 receptor inhibition conditions, a major part of excreted glucose does not go through the reabsorption process – it stays in the urine and is eliminated from the body in this way [21].

Until now there have been some concerns over the fact that the use of SGLT-2 inhibitors increases the LDL-cholesterol levels. However, this group of agents demonstrates a positive effect on the lipid profile through decreasing the levels of triglycerides and increasing the levels of C2 sub-fraction of high-density lipoprotein cholesterol, thus reducing the overall atherogenic risk. One of the explanations for their antiatherogenic effect lays in the fact that SGLT-2 inhibitors suppress the transformation of large LDL particles into small dense LDL particles, which carry great atherogenic potential but are difficult to detect in everyday routine laboratory diagnostics [22]. Additionally, the use of dapagliflozin reduces the BMI level, hepatic transaminases level, and increases the adiponectin level [22]. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of elevated liver enzymes in obese people. It is known that subjects with high level of small dense LDL particles, NAFLD, and low adiponectin level have additionally increased cardiovascular risk [21, 22]. Considering positive effects of dapagliflozin on all mentioned risk factors and also an impact on decreasing the levels of triglycerides, it is clear why it should be used in people with cardiometabolic complications of dysfunctional adipose tissue. Lundkvist et al. [19] conducted a trial among 50 obese individuals with prediabetes, based on previous favorable experiences in body weight management among obese patients with T2DM. The results showed the possibility of dapagliflozin use in this population, due to significant weight reduction, reduction of systolic blood pressure, and improved glucose tolerance that have been achieved [19].

Out of SGLT-2 inhibitors, empagliflozin emerged as the most significant agent. The results of the recently completed Empagliflozin Removal of Excess of Glucose Outcome (EMPA-REG OUTCOME) study indicate that empagliflozin significantly reduces cardiovascular mortality and hospitalization rate because of heart failure in patients with T2DM [23]. This is due to the antihyperglycemic effect of SGLT-2 inhibitors but also because of their effect on natriuresis, body weight reduction, blood pressure, and lipid profile. Even though protective effect of empagliflozin in diabetic patients is established, the effects of SGLT-2 inhibitors on this specter of cardiovascular risk factors under prediabetes conditions is known only from animal models [23]. A study by Kusaka et al. [24] was conducted on rats with prediabetes, and it clearly showed that after seven weeks of treatment with empagliflozin, weight reduction was gained despite the increased food intake when compared to the control group. Regarding the fact that there was no difference in the amount of fat mass between the study group and the control group, and that the size of subcutaneous fat mass was smaller in the study group, a question on the protective role of empagliflozin has imposed itself. This study has demonstrated that there is a significant difference in the size of adipocytes [24]. Empagliflozin use leads to the histological changes in the structure of adipose tissue, in the sense of reducing the diameter of adipocytes, which have more favorable metabolic impact than insufficiently differentiated adipocytes with large diameter [24]. In relation to metabolic parameters, reduction of HbA1c, lowering of postprandial glycemia, and decrease in insulin level were observed [24]. Although it was noted that empagliflozin does not lower the level of total cholesterol and free fatty acids (FFA), it certainly reduces the rate of lipid peroxidation [24]. On the other hand, people with prediabetes have a high risk of developing cardiovascular diseases [1–5]. Taking into account the favorable effect of empagliflozin on preventing hypertrophy and fibrosis of the left ventricle, SGLT-2 inhibitors could also be used in the treatment of individuals with prediabetes [23, 24].

Thiazolidinediones

It has been clearly proven by now that there is a correlation between IR, T2DM, and adipose tissue dysfunction [1, 2, 4, 5]. One of the key genes responsible for function of adipose tissue is PPARγ [25]. Previous studies have shown that PPARγ plays a role in numerous functions of adipose tissue, such as preadipocytes differentiation and secretion of adipocytokines, as well as controlling the level of inflammation and insulin sensitivity within adipose tissue [25]. As mentioned earlier, important markers of dysfunction and inadequate differentiation of adipose tissue are the larger diameter of adipocytes, reduced expression and low level of circulating adiponectin, and reduced expression of PPARGC1A [25, 26].Thiazolidinediones are PPARγ agonists, and by that they increase glucose uptake in adipocytes, and prevent FFA release and possible subsequent lipotoxicity, which represents one of the key physiopathogenetic mechanisms in T2DM development [27].

In individuals with IR there is a reduction in several key molecules responsible for insulin activity, such as glucose transporter type 4, PPARGC1A, markers of terminal differentiation of adipose tissue, and insulin receptor substrate [27, 28]. The use of pioglitazone leads to an improvement in insulin sensitivity in non-obese subjects with IR, regardless of its impact on the change in levels of circulating FFA and other lipid and lipoprotein parameters [28]. The explanation of this effect of thiazolidinediones lays in their positive activity on adipose tissue remodeling. The use of this agent leads to the replacement of large adipocytes with well-differentiated and more insulin-sensitive adipocytes with smaller diameter [28]. This kind of adipose tissue remodeling has a positive effect on inflammation, which is one of the leading physiopathogenetic mechanisms of IR and T2DM. In fact, there is a clear correlation between the adipocyte size and the level of circulating interleukin-6 (IL-6). The reduction in size of adipocytes reduces the level of IL-6 in the serum [28]. On the other hand, thiazolidinediones stimulate the production of adiponectin [27, 28]. It was noted that the level of

adiponectin in individuals treated by pioglitazone is the result of increased contribution of high-molecular-weight adiponectin fraction (HMW) adiponectin [28]. HMW adiponectin is highly protective regarding atherosclerosis and T2DM development [1, 2, 3]. PPARγ demonstrates high expression in the adipose tissue. Although the role of thiazolidinediones on PPARγ stimulation is well documented, its role in the expression of this nuclear receptor is still debated [28]. The beneficial effect of pioglitazone is reflected through the redistribution of fat mass in the body. The use of pioglitazone increases body weight and fat mass. However, beneficial metabolic effect of pioglitazone is a result of adipose tissue redistribution, reflected through the reduction in visceral adipose tissue amount and the increase in the amount of subcutaneous fat depots [28, 29].

PARENTERAL PHARMACOTHERAPY

Among the currently available parenteral therapies for obese patients with T2DM, two classes also promote weight loss. Pramlintide, a synthetic form of amylin, induces short-term satiety and may be useful in combination with other agents. A recent study pointed out an improvement in glucose tolerance in diabetic patients in dose-dependent manner, as well as a promotion of insulin secretion [30].

On the other hand, GLP-1 receptor agonist-associated effects are visceral fat specific. Liraglutide stimulated white adipose tissue browning and thermogenesis independently of nutrient intake [31]. Exenatide reduced epicardial, subcutaneous, and liver fat in diabetic patients, in a similar way as liraglutide, activating brown adipose tissue and generating clearance of triglycerides and glucose [32]. Treatments of patients with GLP-1 receptor agonists promote weight loss and increase circulating adiponectin levels. Also, expression of adiponectin receptors in visceral adipose tissue is increased by exenatide administration [32]. Chronic low-grade inflammation has been reported as a connection between obesity and T2DM. Studies suggest that treatment of obese patients with GLP-1 receptor agonists decreases circulating cytokines including monocyte chemoattractant protein-1 plasma concentration and inhibits the expression of inflammatory cytokines in 3T3-L1 adipocytes [32].

Most patients with T2DM require insulin and/or insulin-analog therapy. Despite the presence of various insulin and/or insulin-analog regiments, it is very difficult to achieve an optimal glycemic control in obese patients. The risk of severe hypoglycemia and weight gain have a major impact on metabolic control during the insulin therapy. Less weight gain and reduced risk of hypoglycemia are benefits offered by using long-acting insulin analogs [33].

HOW MIGHT TREATMENT OPTIONS LOOK LIKE IN THE FUTURE?

Today, we have a wide range of options, so that treatment could be tailored for each patient, in most cases combining two or more drugs to achieve recommended HbA1c targets [10]. In the future, there will be likely 50 or more available oral or parenteral drugs to choose from, for pharmacotherapy of diabetic patients. Because of that, the choice of therapy will be strongly personalized and based on the patient's genetic profile. We could expect that genetic testing will be used to distinguish different types of adipose tissue, different cytokine receptor expression and to diagnose subtypes of adipose tissue maturation disorder and dysfunction, in order to cope with the direct cause of T2DM.

CONCLUSION

Among variety of oral antihyperglycemic agents, during the tailoring of appropriate individual therapy for overweight and obese patients with T2DM, it is necessary to bear in mind their impact on the function of adipose tissue. Priority should be given to those groups of agents that stimulate the differentiation and maturation of preadipocytes, have a positive effect on the secretion of adipokines, and exert a protective effect on the redistribution of fat mass, through reduction of the amount of visceral adipose tissue depots and increase in the amount of subcutaneous adipose tissue departments.

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Утицај савремених оралних антихипергликемијских лекова на дисфункционално масно ткиво

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САЖЕТАК

Гојазност је болест са пандемијском учесталошћу, коју прате хроничне метаболичке и органске компликације. Међу најчешће метаболичке компликације гојазности спада тип 2 шећерне болести, а први корак у њеном лечењу је нутритивна терапија уз дозирану физичку активност и редукцију телесне масе. Медикаментно лечење се започиње метформином, а у случају неадекватног успеха додају се и други антихипергликемијски лекови. Са дериватима сулфонилуреје постоји највеће клиничко искуство, али је њихова употреба ограничена јер изазивају учестале хипогликемије и пораст телесне масе. У светлу сазнања да је масно ткиво ендокрини орган и да управо дисфункција овог ткива доводи до хроничних компликација, императив у савременој терапији је употреба лекова са снажним ефектом на функционалност овог ткива. Антихипергликемијски лекови избора код гојазних особа су они који доводе до матурације адипоцита, лучења протективних адипоцитокина и редистрибуције масне масе из висцералних у субкутане депое. Орални хипогликемијски агенси који утичу на функционалност масног ткива су метформин, СГЛТ-2 инхибитори, ДПП-4 инхибитори и тиазолидиндиони.

Кључне речи: масно ткиво; адипоцитокини; тип 2 дијабетеса; терапија

UDC: 355.415.6-055.2(497.11)"1914/1918"(049.32); 364.65-054.73(497.11)"1914/1918"(049.32)

ПРИКАЗ КЊИГЕ / BOOK REVIEW

Сведочанства из Првог светског рата (The Great War Revisited)

Аутор: Славица Поповић-Филиповић
Издавач: Историјски архив, Ваљево, 2017
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Славица Поповић-Филиповић, реномирани аутор у области српске историје медицине, годинама се бави и историјом медицинских мисија у Србији у време Првог светског рата. Књига „Сведочанства из Првог светског рата“ (*The Great War Revisited*) настала је истраживањем страних медицинских мисија и бројних појединаца, који су дошли у помоћ српском народу 1914–1915. На апел српске владе и српског Црвеног крста стигле су медицинске мисије и санитетска помоћ из Русије, Велике Британије, Француске, Америке, Швајцарске, Холандије, Грчке и Данске, а појединци из Пољске, Канаде, Аустралије, Новог Зеланда, Чешке, Словачке, Ирске, Норвешке, Белгије, Италије и Шпаније. Санитетска и материјална помоћ стигла је из Јужне Америке и Јапана.

Током рата и по ослобођењу, стране медицинске мисије, биле оне војне или добровољачке, мењале су своје циљеве зависно од потреба у Србији – од првих хируршких болница, до болница за лечење инфективних болести и медицинских екипа за организовано спровођење превенције, сузбијања и лечења велике епидемије пегавог тифуса. Епидемија пегавог тифуса је сузбијена у лето 1915, али је велики број медицинских мисија остао, па су тако у Србији формирали диспанзере и амбуланте за лечење локалног становништва. У време великог повлачења један број чланова медицинских мисија је одбио да напусти земљу и остао је да брине о српским рањеницима и болесницима у време окупације. Стране болнице у великом повлачењу пружале су медицинску помоћ на путу, у време искрцавања, евакуације и смештаја српских војника и избеглица, у заштити ратних заробљеника и интернираних цивила у логорима, у обнављању здравственог система у ослобођеној земљи. Бројни хуманисти су подржали деловање српског Црвеног крста у Србији и у избеглиштву. Један број медицинских мисија које су радиле у Србији у периоду 1914–1915 пратио је српску војску на свим фронтовима: у Србији, на Солунском фронту, на Корзици и у Француској, у Тунису и Алжиру, на руском фронту и Добруџи. Велики број медицинских радника који су радили у Србији у време Великог рата вратили су се да помажу Србима у избеглиштву и остали им верни и у послератном периоду.

Мала Србија је преко ноћи постала космополитска раскрсница. О томе говоре

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бројна сведочанства домаћих и страних хроничара, њихови драгоцени историјски записи из тог периода. У Србији у то време није се борила само елита српских и европских лекара и хуманиста већ и медицинског особља из прекоокеанских земаља.

Књига „Сведочанства из Првог светског рата" састоји се из два дела: први је посвећен страним медицинским мисијама, док у другом делу аутор наводи писма, записе, дневнике и друга сведочанства учесника.

Књига уједно обележава стогодишњицу од смрти др Елси Мод Инглис (*Elsie Maud Inglis*) (1864–1917), хирурга из Шкотске, оснивача и руководиоца Болнице шкотских жена за службу у иностранству (*The Scottish Women's Hospitals for foreign service*). Од десет болница шкотских жена намењених српском народу, четири су деловале у Србији (у Крагујевцу, Ваљеву, Младеновцу и Лазаревцу, у време велике епидемије пегавог тифуса), три болнице су радиле на Солунском фронту, а по једна болница на Корзици, у Француској и на Руском фронту и Добруџи. У време окупације Србије Болница шкотских жена радила је у Крушевцу, а по ослобођењу у Врању и Београду. Овим поводом у Србију из Шкотске долази делегација потомака др Елси Инглис, који ће обићи градове у којима су деловале болнице шкотских жена.

По речима рецензента Велибора Видића, историчара из Ваљева: „Ово је свакако једна од књига од које ћемо кретати као појединци и народ и којој ћемо се увек радо враћати".

Поводом стогодишњице Великог рата и поплаве пригодних радова, ово дело не спада у ту групу. Оно није ни дескриптивна историографија, ни анализа већ публикованих радова. Ово дело је резултат упорног и многогодишњег истраживања које је ауторка урадила од Аустралије и Новог Зеланда, преко Србије, до Шкотске и Канаде. Обилазећи архиве, музеје, библиотеке и потомке учесника у свим овим земљама, она је била прави представник српског националног бића које брине о свом историјском искуству, а до сазнања о њему долази на једини прави начин – истраживањем, а не анализом полуистина и спекулацијама. То је посебна вредност овог дела. Чињенице су ту. Само треба извући поуке. Због тога би се требало овом делу радо враћати.

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Пре подношења рукописа Уредништву часописа „Српски архив за целокупно лекарство“ (СА) сви аутори треба да прочитају Упутство за ауторе (*Instructions for Authors*), где ће пронаћи све потребне информације о писању и припреми рада у складу са стандардима часописа. Веома је важно да аутори припреме рад према датим пропозицијама, јер уколико рукопис не буде усклађен с овим захтевима, Уредништво ће одложити или одбити његово публиковање. Радови објављени у СА се не хонорашу. За чланке који ће се објавити у СА, самом понудом рада Српском архиву сви аутори рада преносе своја ауторска права на издавача часописа – Српско лекарско друштво.

ОПШТА УПУТСТВА. СА објављује радове који до сада нису нигде објављени, у целости или делом, нити прихваћени за објављивање. СА објављује радове на енглеском и српском језику. Због боље доступности и веће цитираности препоручује се ауторима да радове свих облика предају на енглеском језику. У СА се објављују следеће категорије радова: уводници, оригинални (научни и стручни) радови, метаанализе, прегледни радови, претходна и кратка саопштења, прикази болесника и случајева, слике из клиничке медицине, видео-чланци, радови за праксу, актуелне теме, радови из историје медицине и језика медицине, лични ставови, наручени коментари, писма уреднику, прикази књига и други прилози. Оригинални радови, претходна и кратка саопштења и прикази болесника и случајева публикују се искључиво на енглеском језику, а остале врсте радова се могу публиковати и на српском језику само по одлуци Уредништва. Радови се увек достављају са сажетком на енглеском и српском језику (у склопу самог рукописа). Текст рада куцати у програму за обраду текста *Word*, фонтом *Times New Roman* и величином слова 12 тачака (12 *pt*). Све четири маргине подесити на 25 *mm*, величину странице на формат А4, а текст куцати с двоструким проредом, левим поравнањем и увлачењем сваког пасуса за 10 *mm*, без дељења речи (хифенације). Не користити табулаторе и узастопне празне карактере (спејсове) ради поравнања текста, већ алатке за контролу поравнања на лењиру и *Toolbars*. За прелазак на нову страну документа не користити низ „ентера“, већ искључиво опцију *Page Break*. После сваког знака интерпункције ставити само један празан карактер. Ако се у тексту користе специјални знаци (симболи), користити фонт *Symbol*. Подаци о коришћеној литератури у тексту означавају се арапским бројевима у угластим заградама – нпр. [1, 2], и то редоследом којим се појављују у тексту. Странице нумерисати редом у доњем десном углу, почев од насловне стране.

При писању текста на енглеском језику треба се придржавати језичког стандарда *American English* и користити кратке и јасне реченице. За називе лекова користити искључиво генеричка имена. Уређаји (апарати) се означавају фабричким називима, а име и место произвођача треба навести у облим заградама. Уколико се у тексту користе ознаке које су спој слова и бројева, прецизно написати број који се јавља у суперскрипту или супскрипту (нпр. ^{99}*Tc*, *IL*-6, O_2, $Б_{12}$, *CD*8). Уколико се нешто уобичајено пише курзивом (*italic*), тако се и наводи, нпр. гени (*BRCA1*).

Уколико је рад део магистарске тезе, односно докторске дисертације, или је урађен у оквиру научног пројекта, то треба посебно назначити у Напомени на крају текста. Такође, уколико је рад претходно саопштен на неком стручном састанку, навести званичан назив скупа, место и време одржавања, да ли је рад и како публикован (нпр. исти или другачији наслов или сажетак).

КЛИНИЧКА ИСТРАЖИВАЊА. Клиничка истраживања се дефинишу као истраживања утицаја једног или више средстава или мера на исход здравља. Регистарски број истраживања се наводи у последњем реду сажетка.

ЕТИЧКА САГЛАСНОСТ. Рукописи о истраживањима на људима треба да садрже изјаву у виду писаног пристанка испитиваних особа у складу с Хелсиншком декларацијом и одобрење надлежног етичког одбора да се истраживање може извести и да је оно у складу с правним стандардима. Експериментална истраживања на хуманом материјалу и испитивања вршена на животињама треба да садрже изјаву етичког одбора установе и треба да су у сагласности с правним стандардима.

ИЗЈАВА О СУКОБУ ИНТЕРЕСА. Уз рукопис се прилаже потписана изјава у оквиру обрасца *Submission Letter* којом се аутори изјашњавају о сваком могућем сукобу интереса или његовом одсуству. За додатне информације о различитим врстама сукоба интереса посетити интернет-страницу Светског удружења уредника медицинских часописа (*World Association of Medical Editors – WAME; http://www.wame.org*) под називом „Политика изјаве о сукобу интереса“.

АУТОРСТВО. Све особе које су наведене као аутори рада треба да се квалификују за ауторство. Сваки аутор треба да је учествовао довољно у раду на рукопису како би могао да преузме одговорност за целокупан текст и резултате изнесене у раду. Ауторство се заснива само на: битном доприносу концепцији рада, добијању резултата или анализи и тумачењу резултата; планирању рукописа или његовој критичкој ревизији од знатног интелектуалног значаја; завршном дотеривању верзије рукописа који се припрема за штампање.

Аутори треба да приложе опис доприноса појединачно за сваког коаутора у оквиру обрасца *Submission Letter*. Финансирање, сакупљање података или генерално надгледање истраживачке групе сами по себи не могу оправдати ауторство. Сви други који су допринели изради рада, а који нису аутори рукописа, требало

би да буду наведени у Захвалници с описом њиховог доприноса раду, наравно, уз писани пристанак.

НАСЛОВНА СТРАНА. На првој страници рукописа треба навести следеће: наслов рада без скраћеница; предлог кратког наслова рада, пуна имена и презимена аутора (без титула) индексирана бројевима; званичан назив установа у којима аутори раде, место и државу (редоследом који одговара индексираним бројевима аутора); на дну странице навести име и презиме, адресу за контакт, број телефона, факса и имејл адресу аутора задуженог за кореспонденцију.

САЖЕТАК. Уз оригинални рад, претходно и кратко саопштење, метаанализу, преглед литературе, приказ случаја (болесника), рад из историје медицине, актуелну тему, рад за рубрику језик медицине и рад за праксу, на другој по реду страници документа треба приложити сажетак рада обима 100–250 речи. За оригиналне радове, претходна и кратка саопштења и метаанализе сажетак треба да има следећу структуру: Увод/Циљ, Методе, Резултати, Закључак; сваки од наведених сегмената писати као посебан пасус који почиње болдованом речи. Навести најважније резултате (нумеричке вредности) статистичке анализе и ниво значајности. Закључак не сме бити уопштен, већ мора бити директно повезан са резултатима рада. За приказе болесника сажетак треба да има следеће делове: Увод (у последњој реченици навести циљ), Приказ болесника, Закључак; сегменте такође писати као посебан пасус који почиње болдованом речи. За остале типове радова сажетак нема посебну структуру.

КЉУЧНЕ РЕЧИ. Испод Сажетка навести од три до шест кључних речи или израза. Не треба да се понављају речи из наслова, а кључне речи треба да буду релевантне или описне. У избору кључних речи користити *Medical Subject Headings – MeSH (http://www.nlm.nih.gov/mesh)*.

ПРЕВОД НА СРПСКИ ЈЕЗИК. На трећој по реду страници документа приложити наслов рада на српском језику, пуна имена и презимена аутора (без титула) индексирана бројевима, званичан назив установа у којима аутори раде, место и државу. На следећој – четвртој по реду – страници документа приложити сажетак (100–250 речи) с кључним речима (3–6), и то за радове у којима је обавезан сажетак на енглеском језику. Превод појмова из стране литературе треба да буде у духу српског језика. Све стране речи или синтагме за које постоји одговарајуће име у нашем језику заменити тим називом.

Уколико је рад у целости на српском језику (нпр. рад из историје медицине, језика медицине и др.), потребно је превести називе прилога (табела, графикона, слика, схема) уколико их има, целокупни текст у њима и легенду на енглески језик. Сажетке и радове који су у целости на српском језику аутори из Србије треба да пишу ћирилицом.

СТРУКТУРА РАДА. Сви поднаслови се пишу великим масним словима (болд). Оригинални рад, метаанализа, претходно и кратко саопштење обавезно треба да имају следеће поднаслове: Увод (Циљ рада навести као последњи пасус Увода), Методе рада, Резултати, Дискусија, Закључак, Литература. Преглед литературе чине: Увод, одговарајући поднаслови, Закључак, Литература. Првоименовани аутор метаанализе и прегледног рада мора да наведе бар пет аутоцитата (као аутор или коаутор) радова публикованих у часописима с рецензијом. Коаутори, уколико их има, морају да наведу бар један аутоцитат радова такође публикованих у часописима с рецензијом. Приказ случаја или болесника чине: Увод (Циљ рада навести као последњи пасус Увода), Приказ болесника, Дискусија, Литература. Не треба користити имена болесника, иницијале, нити бројеве историја болести, нарочито у илустрацијама. Прикази болесника не смеју имати више од пет аутора.

Прилоге (табеле, графиконе, слике итд.) поставити на крај рукописа, а у самом телу текста јасно назначити место које се односи на дати прилог. Крајња позиција прилога биће одређена у току припреме рада за публиковање.

СКРАЋЕНИЦЕ. Користити само када је неопходно, и то за веома дугачке називе хемијских једињења, односно називе који су као скраћенице већ препознатљиви (стандардне скраћенице, као нпр. ДНК, сида, ХИВ, АТП). За сваку скраћеницу пун термин треба навести при првом навођењу у тексту, сем ако није стандардна јединица мере. Не користити скраћенице у наслову. Избегавати коришћење скраћеница у сажетку, али ако су неопходне, сваку скраћеницу објаснити при првом навођењу у тексту.

ДЕЦИМАЛНИ БРОЈЕВИ. У тексту рада на енглеском језику, у табелама, на графиконима и другим прилозима децималне бројеве писати са тачком (нпр. 12.5 ± 3.8), а у тексту на српском језику са зарезом (нпр. 12,5 ± 3,8). Кад год је то могуће, број заокружити на једну децималу.

ЈЕДИНИЦЕ МЕРА. Дужину, висину, тежину и запремину изражавати у метричким јединицама (метар – *m*, килограм (грам) – *kg* (*g*), литар – *l*) или њиховим деловима. Температуру изражавати у степенима Целзијуса (°C), количину супстанце у молима (*mol*), а притисак крви у милиметрима живиног стуба (*mm Hg*). Све резултате хематолошких, клиничких и биохемијских мерења наводити у метричком систему према Међународном систему јединица (*SI*).

ОБИМ РАДОВА. Целокупни рукопис рада – који чине насловна страна, сажетак, текст рада, списак литературе, сви прилози, односно потписи за њих и легенда (табеле, слике, графикони, схеме, цртежи), насловна страна и сажетак на српском језику – мора износити за оригинални рад, претходно и кратко саопштење, рад из

историје медицине и преглед литературе до 5.000 речи, а за приказ болесника, рад за праксу, едукативни чланак и рад за рубрику „Језик медицине“ до 3.000 речи; радови за остале рубрике могу имати највише 1.500 речи.
Видео-радови могу трајати 5–7 минута и бити у формату avi, *mp4 (flv)*. У првом кадру филма мора се навести: у наднаслову Српски архив за целокупно лекарство, наслов рада, презимена и иницијали имена и средњег слова свих аутора рада (не филма), година израде. У другом кадру мора бити уснимљен текст рада у виду апстракта до 350 речи. У последњем кадру филма могу се навести имена техничког особља (режија, сниматељ, светло, тон, фотографија и сл.). Уз видео-радове доставити: посебно текст у виду апстракта (до 350 речи), једну фотографију као илустрацију приказа, изјаву потписану од свег техничког особља да се одричу ауторских права у корист аутора рада.

ПРИЛОЗИ РАДУ су табеле, слике (фотографије, цртежи, схеме, графикони) и видео-прилози.

ТАБЕЛЕ. Свака табела треба да буде сама по себи лако разумљива. Наслов треба откуцати изнад табеле, а објашњења испод ње. Табеле се означавају арапским бројевима према редоследу навођења у тексту. Табеле цртати искључиво у програму *Word*, кроз мени *Table–Insert–Table*, уз дефинисање тачног броја колона и редова који ће чинити мрежу табеле. Десним кликом на мишу – помоћу опција *Merge Cells* и *Split Cells* – спајати, односно делити ћелије. Куцати фонтом *Times New Roman*, величином слова 12 *pt*, с једноструким проредом и без увлачења текста. Коришћене скраћенице у табели треба објаснити у легенди испод табеле.

Уколико је рукопис на српском језику, приложити називе табела и легенду на оба језика. Такође, у једну табелу, у оквиру исте ћелије, унети и текст на српском и текст на енглеском језику (никако не правити две табеле са два језика!).

СЛИКЕ. Слике су сви облици графичких прилога и као „слике“ у CA се објављују фотографије, цртежи, схеме и графикони. Слике означавају се арапским бројевима према редоследу навођења у тексту. Примају се искључиво дигиталне фотографије (црно-беле или у боји) резолуције најмање 300 *dpi* и формата записа *tiff* или *jpg* (мале, мутне и слике лошег квалитета неће се прихватати за штампање!). Уколико аутори не поседују или нису у могућности да доставе дигиталне фотографије, онда оригиналне слике треба скенирати у резолуцији 300 *dpi* и у оригиналној величини. Уколико је рад неопходно илустровати са више слика, у раду ће их бити објављено неколико, а остале ће бити у е-верзији чланка као *PowerPoint* презентација (свака слика мора бити нумерисана и имати легенду).
Видео-прилози (илустрације рада) могу трајати 1–3 минута и бити у формату *avi, mp4*(*flv*). Уз видео доставити посебно слику која би била илустрација видеоприказа у *e*-издању и објављена у штампаном издању.
Уколико је рукопис на српском језику, приложити називе слика и легенду на оба језика.

Слике се у свесци могу штампати у боји, али додатне трошкове штампе сносе аутори.

ГРАФИКОНИ. Графикони треба да буду урађени и достављени у програму *Excel*, да би се виделе пратеће вредности распоређене по ћелијама. Исте графиконе прекопирати и у *Word*-ов документ, где се графикони означавају арапским бројевима према редоследу навођења у тексту. Сви подаци на графикону куцају се у фонту *Times New Roman*. Коришћене скраћенице на графикону треба објаснити у легенди испод графикона. У штампаној верзији чланка вероватније је да графикон неће бити штампан у боји, те је боље избегавати коришћење боја у графиконима, или их користити различитог интензитета.

Уколико је рукопис на српском језику, приложити називе графикона и легенду на оба језика.

СХЕМЕ (ЦРТЕЖИ). Цртежи и схеме се достављају у *jpg* или *tiff* формату. Схеме се могу цртати и у програму *CorelDraw* или *Adobe Illustrator* (програми за рад са векторима, кривама). Сви подаци на схеми куцају се у фонту *Times New Roman*, величина слова 10 *pt*. Коришћене скраћенице на схеми треба објаснити у легенди испод схеме.

Уколико је рукопис на српском језику, приложити називе схема и легенду на оба језика.

ЗАХВАЛНИЦА. Навести све сараднике који су допринели стварању рада а не испуњавају мерила за ауторство, као што су особе које обезбеђују техничку помоћ, помоћ у писању рада или руководе одељењем које обезбеђује општу подршку. Финансијска и материјална помоћ, у облику спонзорства, стипендија, поклона, опреме, лекова и друго, треба такође да буде наведена.

ЛИТЕРАТУРА. Списак референци је одговорност аутора, а цитирани чланци треба да буду лако приступачни читаоцима часописа. Стога уз сваку референцу обавезно треба навести *DOI* број чланка (јединствену ниску карактера која му је додељена) и *PMID* број уколико је чланак индексиран у бази *PubMed/MEDLINE*.

Референце нумерисати редним арапским бројевима према редоследу навођења у тексту. Број референци не би требало да буде већи од 30, осим у прегледу литературе, у којем је дозвољено да их буде до 50, а у метаанализи до 100. Број цитираних оригиналних радова мора бити најмање 80% од укупног броја референци, односно број цитираних књига, поглавља у књигама и прегледних чланака мањи од 20%. Уколико се домаће монографске публикације и чланци могу уврстити у референце, аутори су дужни да их цитирају. Већина цитираних научних чланака не би требало да

буде старија од пет година. Није дозвољено цитирање апстраката. Уколико је битно коментарисати резултате који су публиковани само у виду апстракта, неопходно је то навести у самом тексту рада. Референце чланака који су прихваћени за штампу, али још нису објављени, треба означити са *in press* и приложити доказ о прихватању рада за објављивање.

Референце се цитирају према Ванкуверском стилу (униформисаним захтевима за рукописе који се предају биомедицинским часописима), који је успоставио Међународни комитет уредника медицинских часописа (*http://www.icmje.org*), чији формат користе *U.S. National Library of Medicine* и базе научних публикација. Примери навођења публикација (чланака, књига и других монографија, електронског, необјављеног и другог објављеног материјала) могу се пронаћи на интернет-страници *http://www.nlm.nih.gov/bsd/uniform_requirements.html*. Приликом навођења литературе веома је важно придржавати се поменутог стандарда, јер је то један од најбитнијих фактора за индексирање приликом класификације научних часописа.

ПРОПРАТНО ПИСМО (*SUBMISSION LETTER*). Уз рукопис обавезно приложити образац који су потписали сви аутори, а који садржи: 1) изјаву да рад претходно није публикован и да није истовремено поднет за објављивање у неком другом часопису, 2) изјаву да су рукопис прочитали и одобрили сви аутори који испуњавају мерила ауторства, и 3) контакт податке свих аутора у раду (адресе, имејл адресе, телефоне итд.). Бланко образац треба преузети са интернет-странице часописа (*http://www.srpskiarhiv.rs*).

Такође је потребно доставити копије свих дозвола за: репродуковање претходно објављеног материјала, употребу илустрација и објављивање информација о познатим људима или именовање људи који су допринели изради рада.

ЧЛАНАРИНА, ПРЕТПЛАТА И НАКНАДА ЗА ОБРАДУ ЧЛАНКА. Да би рад био објављен у часопису *Српски архив за целокупно лекарство*, сви аутори који су лекари или стоматолози из Србије морају бити чланови Српског лекарског друштва (у складу са чланом 6. Статута Друштва) за годину у којој се рад предаје Уредништву. Сви домаћи аутори такође морају бити претплаћени на часопис или измирити накнаду за обраду чланака (*article processing charge*) за годину у којој се рад предаје Уредништву, у износу од 3.000 динара. Аутори и коаутори из иностранства су у обавези да плате накнаду за обраду чланака (*article processing charge*) у износу од 35 евра. Уплата у једној календарској години обухвата и све наредне, евентуалне чланке, послате на разматрање у тој години. Сви аутори који плате ову накнаду могу, уколико то желе, да примају штампано издање часописа. Треба напоменути да ова уплата није гаранција да ће рад бити прихваћен и објављен у *Српском архиву за целокупно лекарство*. Обавеза плаћања накнаде за обраду чланка не односи се на студенте основних студија и на претплатнике на часопис.

Установе (правна лица) не могу преко своје претплате да испуне овај услов аутора (физичког лица). Уз рукопис рада треба доставити копије уплатница за чланарину и претплату / накнаду за обраду чланка, као доказ о уплатама, уколико издавач нема евиденцију о томе. Часопис прихвата донације од спонзора који сносе део трошкова или трошкове у целини оних аутора који нису у могућности да измире накнаду за обраду чланка (у таквим случајевима потребно је часопису ставити на увид оправданост таквог спонзорства).

Додатне информације о чланарини и претплати могу се добити путем имејла (*office@srpskiarhiv.rs*) и на интернет-страници часописа *http://srpskiarhiv.rs/en/subscription/).*

СЛАЊЕ РУКОПИСА. Рукопис рада и сви прилози уз рад могу се доставити имејлом (*office@srpskiarhiv.rs*), електронски преко система за пријављивање на интернет-страници часописа (*http://www.srpskiarhiv.rs*), препорученом пошиљком или лично, доласком у Уредништво. Уколико се рад шаље поштом или доноси у Уредништво, рукопис се доставља одштампан у три примерка и нарезан на *CD* (снимљени материјал треба да је истоветан оном на папиру).

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За све додатне информације, молимо да се обратите на доленаведене адресе и број телефона.

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When writing text in English, linguistic standard American English should be observed. Write short and clear sentences. Generic names should be exclusively used for the names of drugs. Devices (apparatuses, instruments) are termed by trade names, while their name and place of production should be indicated in the brackets. If a letter-number combination is used, the number should be precisely designated in superscript or subscript (i.e., ^{99}Tc, IL-6, O_2, B_{12}, CD8). If something is commonly written in italics, such as genes (e.g. *BRCA1*), it should be written in this manner in the paper as well.

If a paper is a part of a master's or doctoral thesis, or a research project, that should be designated in a separate note at the end of the text. Also, if the article was previously presented at any scientific meeting, the name, venue and time of the meeting should be stated, as well as the manner in which the paper had been published (e.g. changed title or abstract).

CLINICAL TRIALS. Clinical trial is defined as any research related to one or more health related interventions in order to evaluate the effects on health outcomes. The trial registration number should be included as the last line of the Summary.

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The authors should enclose the description of contribution to the article of every co-author individually (within the Submission Letter). Funding, collection of data or general supervision of the research group alone cannot justify authorship. All other individuals having contributed to the preparation of the article should be mentioned in the *Acknowledgment* section, with description of their contribution to the paper, with their written consent.

TITLE PAGE. The first page of the manuscript (cover sheet) should include the following: title of the paper without any abbreviations; suggested running title; each author's full names and family names (no titles), indexed by numbers; official name, place and country of the institu-

tion in which authors work (in order corresponding to the indexed numbers of the authors); at the bottom of the page: name and family name, address, phone and fax number, and e-mail address of a corresponding author.

SUMMARY. Along with the original article, preliminary and short communication, meta-analysis, review article, case report, article on history of medicine, current topic article, article for language of medicine and article for practitioners, the summary not exceeding 100–250 words should be typed on the second page of the manuscript. In original articles, preliminary communications, and meta-analyses, the summary should have the following structure: Introduction/Objective, Methods, Results, Conclusion. Each segment should be typed in a separate paragraph using boldface. The most significant results (numerical values), statistical analysis and level of significance are to be included. The conclusion must not be generalized, it needs to point directly to the results of the study. In case reports, the summary should consist of the following: Introduction (final sentence is to state the objective), Case Outline (Outline of Cases), Conclusion. Each segment should be typed in a separate paragraph using boldface. In other types of papers, the summary has no special outline.

KEYWORDS. Below the summary, 3 to 6 keywords or phrases should be typed. The keywords need not repeat words in the title and should be relevant or descriptive. *Medical Subject Headings – MeSH* (*http://www.nlm.nih.gov/mesh*) are to be used for selection of the keywords.

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If an article is entirely in Serbian (e.g. article on history of medicine, article for "Language of medicine", etc.), captions and legends of all enclosures (tables, graphs, photographs, schemes) – if any – should be translated into English as well.

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LENGTH OF PAPER. The entire text of the manuscript – title page, summary, the whole text, list of references, all enclosures including captions and legends (tables, photographs, graphs, schemes, sketches), title page and summary in Serbian – must not exceed 5,000 words for original articles, preliminary and short communications, review articles and articles on history of medicine, and 3,000 words for case reports, articles for practitioners, educational articles and articles for "Language of medicine"; for any other section maximum is 1,500 words.

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If the manuscript is entirely in the Serbian language, tables and corresponding legend should be both in Serbian and English. Also, the table cells should contain text in both languages (do not create two separate tables with a single language!).

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ACKNOWLEDGMENT. List all those individuals having contributed to preparation of the article but having not met the criteria of authorship, such as individuals providing technical assistance, assistance in writing the paper or running the department securing general support. Financial aid and all other support in the form of sponsorship, grants, donations of equipment and medications, etc., should be mentioned too.

REFERENCES. The reference list is the responsibility of the authors. Cited articles should be readily accessible to the journals readership. Therefore, following each reference, its DOI number and PMID number (if the article is indexed for MEDLINE/PubMed) should be typed.

References should be numbered in Arabic numerals in order of citation in the text. The overall number of references should not exceed 30, except in review articles, where maximum of 50 is acceptable, and in meta-analysis, where up to 100 referenceas are allowed. The number of citations of original articles must be at least 80% of the total number of references, and the number of citations of books, chapters and literature reviews less than 20%. If monographs and articles written by Serbian authors could be included

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