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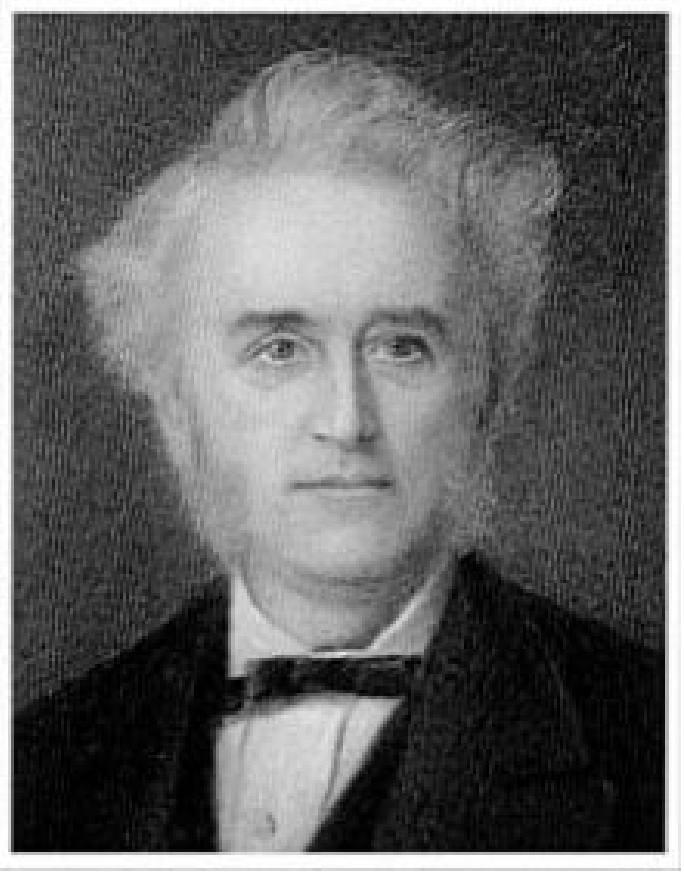

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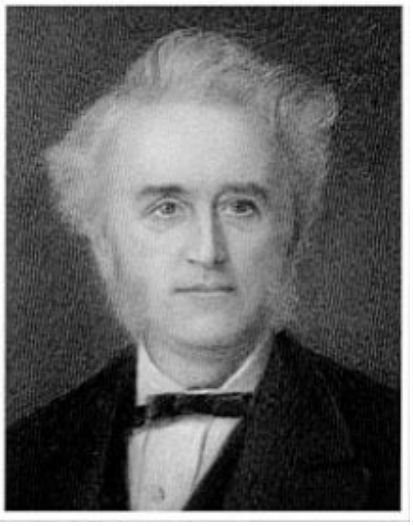

John Langdon Down (18 November, 1828 – 7 October, 1896), the British doctor who first fully described the syndrom, later named after him, that is one of the most common chromosome abnormalities in humans.
In December 2011, the General Assembly of the United Nations declared 21 March as the World Down Syndrome Day (WDSD). This year, the WDSD will be dedicated to the topic how people with Down syndrome can and do make meaningful contributions throughout their lives, whether in schools, workplaces, living in the community, public and political life, culture, media, recreation and sport.

Džon Langdon Daun (18.11.1828 – 7.10.1896), britanski lekar koji je prvi u potpunosti opisao sindrom, kasnije nazvan po njemu, koji je jedan od najčešćih hromosomskih abnormalosti kod čoveka.
U decembru 2011. godine, Generalna skupština Ujedinjenih nacija proglasila je 21. mart za Svetski dan Daunovog sindroma. Ove godine, taj Dan biće posvećen temi na koji način ljudi sa Daunovim sindromom mogu i daju značajan doprinos tokom svog života u školi, na radnom mestu, u društvu, javnom i političkom životu, kulturi, medijima, rekreaciji i sportu.

ORIGINAL ARTICLES

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The Böhler's angle in population of central Serbia – a radiological study

Vrednosti Böhler-ovog ugla u populaciji centralne Srbije – radiološka studija

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Abstract

Background/Aim. The values of the Böhler's angle (BA) are relevant parameters for diagnosis, management and prognosis of the calcaneal fracture and the outcome. Range of normal values of Böhler's angle (BA) in adults varies depending on the examined population, age, gender or ethnicity. The aim of this study was to determine the range of normal values of the Böhler's angle in the central part of Serbia. **Methods.** The lateral foot radiographs of 225 subjects (111 males and 114 females) without calcaneal fractures, divided into 6 age groups were observed to determine the normal values of the Böhler's angle by using the IMPAX 6.5.2.114 Enterprise software. Obtained values for Böhler's angle were compared among gender and groups using appropriate statistical tests. **Results.** The mean of Böhler's angle in observed population was 34.06°, ranging from 25.1° to 49.5° and was higher in males than in females included in our study. Gender difference was statistically significant. The distribution of the mean BA across the age groups showed tendency of decreasing with age and the highest BA was found in the youngest group. **Conclusion.** The findings presented in this paper confirmed the existence of wide range of BA values as well as its gender and age differences.

Key words:
calcaneus; anatomy; anthropology; gender identity; serbia; orthopedics.

Apstrakt

Uvod/Cilj. Određivanje Böhler-ovog ugla (BA) ima važnu ulogu u dijagnostici, odredjivanju načina lečenja, prognozi preloma kalkaneusa kao i proveri uspeha operativnog lečenja preloma. Raspon normalnih vrednosti BA kod odraslih varira u zavisnosti od ispitivane populacije, starosti, pola ili etničke pripadnosti. Cilj ovog istraživanja bio je da se utvrdi opseg normalnih vrednosti BA u centralnom delu Srbije. **Metode.** Böhler-ov ugao određivan je na profilnim radiografskim snimcima 225 ispitanika, oba pola (111 muških i 114 ženskih), podeljenjh u 6 starosnih grupa, bez uočenih fraktura, korišćenjem IMPAKS 6.5.2.114 Enterprise softvera. Korišćenjem statističkih testova upoređene su dobijene vrednosti BA u muškoj i ženskoj populaciji, kao i između različitih starosnih grupa. **Rezultati.** Prosečna vrednost BA u posmatranoj populaciji iznosila je 34,06°, u rasponu od 25,1°–49,5°. Srednja vrednost ovog ugla kod muškaraca bila je veća nego kod žena, a razlika vrednosti ugla između polova bila je statistički značajna. Srednja vrednost BA pokazuje tendenciju opadanja sa godinama, a najveća srednja vrednost BA uočena je u najmlađoj starosnoj grupi. **Zaključak**. Rezultati ovog istraživanja potvrdili su širok opseg normalnih vrednosti BA u ispitivanoj populaciji, kao i postojanje polnih i starosnih razlika.

Ključne reči:
kalkaneus; anatomija; antropologija; pol; srbija; ortopedija.

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Introduction

Calcaneus is the most common site of tarsal bones fractures [1]. These fractures have very variable patterns [2]; can be divided into intra- and extra-articular and they present the most common fractures of tarsal bones (up to 75%) and thus account for 2% of all fractures [3, 4]. The posterior articular surface of calcaneus is usually depressed as a result of the fracture. The Böhler's angle (BA) can be used for evaluation of the loss of calcaneal inclination when this angle is reduced and indicates the degree of proximal displacement of the calcaneal tuberosity. It is a relevant parameter for diagnosis, management and prognosis of the calcaneal fracture outcome [5]. Böhler's angle is named after surgeon Dr. Lorenz Böhler [6] (1885–1973), who introduced this angle in 1931 as a radiological method in the diagnosis of compression fractures of the calcaneus. It was noted in earlier studies that there was a reduction of this angle in intra-articular but also in the most of extra-articular fractures of the calcaneus [7]. Böhler's angle is otherwise called tuber joint angle, calcaneal angle or salient angle. The range of the normal values in adults, without presence of fractures, is from 25° to 40°, but this value varies depending on the examined population and is found to be in the range of 14° to 58.1° [1, 5]. In the first paper about BA, the angles of 30°–35° were mentioned as normal values. In some other textbooks, ranges from 20° to 45° were reported as normal values of this angle [8–14]. The range of normal BA varies depending on the gender, age and the ethnicity of the observed population. The assessment of the BA is important in the diagnosis, determining ways of treatment and prognosis of calcaneal fractures and it can be an indicator of operative treatment success [5]. The measurement is usually performed on lateral foot radiographs at the intersection of two lines or it can be determined using computed tomography (CT). The first line that is important in the construction of this angle is obtained by merging the highest points of the anterior and the posterior articular surface of the calcaneus. Another line connects the same point on the posterior articular surface and the most prominent (the most superior) point of the tuberosity of the calcaneus. Some earlier studies have reported difficulties in precise measurement of the BA on lateral foot radiographs and the possibility of variation of its value in increasing obliquity on the lateral fluoroscopic image [1]. The aim of this study was to determine the range of normal values of the Böhler's angle of the population in the central part of Serbia.

Methods

This study included 225 randomly taken subjects (111 males and 114 females) in order to determine the normal values of the BA in the population of central Serbia. The weight-bearing lateral foot and ankle joint radiographs were observed. The recordings were made with foot placed on solid surface. The subjects were without calcaneal fractures. The average age in the study sample was 43 years (ranging from 15 to 75). The subjects were divided into 6 age groups in order to examine the changes of the BA values with age and statistical significance of differences among the groups. The exclusion criterion was any congenital or acquired deformity of the foot or arthritic change. The study was conducted in the Clinical Centre "Kragujevac" from 1st January 2014 to 31st March 2016.

The computed radiographs were obtained on Digital x-ray system (Duo Diagnost, Philips Medical Systems, the Netherlands). Images were reviewed on a Picture Archiving and Communication System (PACS) and angles were obtained by using the IMPAX 6.5.2.114 Enterprise software (Agfa Healthcare, Belgium). The Böhler's angle was measured from the intersection of the line passing through the most prominent points of posterior and anterior articulating calcaneal facet and the line connecting posterior articulating calcaneal facet to the most prominent point of the calcaneal tuberosity (Figure 1). The precision of measurement was 0.1. All radiographs were analyzed by two independent observers. The intra-class correlation coefficient (ICC) was used for evaluation of inter-observer reliability and ICC > 0.8 was considered as excellent agreement.

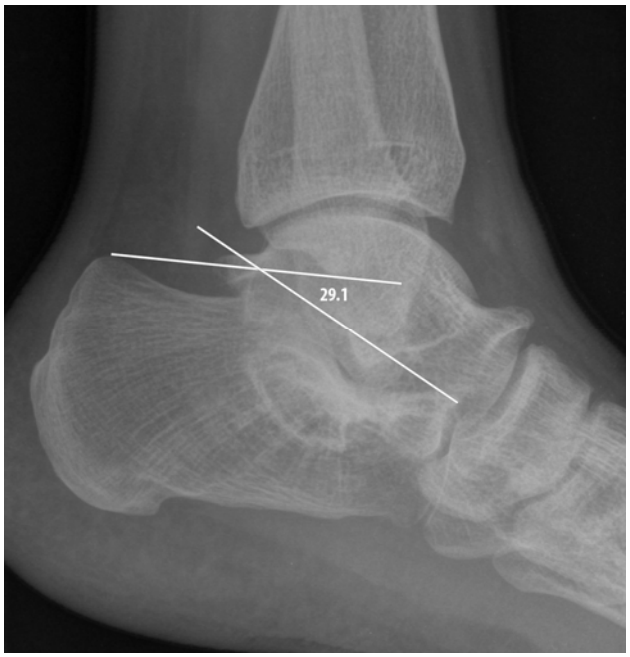

Fig. 1 – Measurement of Böhler's angle.

The results were analyzed using the statistical program (IBM SPSS Statistics 20). The analysis included descriptive and analytical statistical methods. Normality of data distribution was tested by Kolmogorov-Smirnov and Shapiro-Wilk test. Mann-Whitney was applied to compare significance of difference between genders, because variables in one of the individual groups (male group) were not normally distributed (Shapiro-Wilk test: $p = 0.014$). One way ANOVA test was used in comparing the different age groups. Pearson's coefficient of correlation was used for measuring the correlation between the age and the value of the BA. The level of statistical significance was set at 0.05.

Results

This study included 225 participants of both gender who were classified into the different age groups. The mean Böhler's angle in total observed population was 34.1 ± 4.2°

and ranged from 25.1–49.5°. The mean of this angle in males included in our study was 35.3 ± 3.9° (ranging from 27.7° to 49.5°), while its mean value in female participants was 32.8 ± 4.1° (ranging from 25.1° to 43.5°). Gender difference was statistically significant (U = 4174.5; $p < 0.05$) (Table 1).

Analysis of the angle distribution showed that the highest frequency (41.33%), was in the range of angles between 30–34.9° as expected and it was according to results of other studies. The lowest frequency was (1.3%) in the range between 45–49.5°.

The values of the BA were compared among different age groups. As it was expected, the highest mean of the BA was in the youngest group (15–24 years) due to anatomical characteristics of calcaneus in the pre-adolescent ages (mean: 39.8° ± 4.9). The distribution of mean BA across the age groups showed tendency of decreasing with age and the lowest values were found in the group between 65 and 74 years, and the highest in the youngest age group. There was statistically significant difference among some of age groups regarding the mean BA (ANOVA; $p < 0.05$) (Table 2). The correlation between angle and age was significant (Pearson correlation; r = 0.581; $p < 0.01$).

There were several earlier studies of normal BA in different populations and the mean values and ranges of BA are given in Table 3.

Table 1

The mean value of the Böhler's angle in males and females

Gender	n (%)	Böhler's angle (°)				*p*
		Mean	SD	Range	Mann-Whitney U test	
Male	111 (49.33)	35.3	3.9	27.7–49.5		
Female	114 (50.67)	32.8	4.1	25.1–43.5		
Total	225 (100)	34.1	4.2	25.1–49.5		
Gender difference					4174.5	< 0.05

SD – standard deviation.

Table 2

The mean value and the range of the Böhler's (BA) angle in different age groups

Age groups (years) (range)	Böhler's angle (in degree)						
	Male (n)	Female (n)	Total (n)	Male mean ± SD	Female mean ± SD	Total mean ± SD	Range of BA (in degree)
65–74	13	15	28	33.1 ± 3.3	29.7 ± 3.1	31.3 ± 3.6 *a	25.1–40.9
55–64	21	22	43	33.4 ± 3.0	30.2 ± 2.6	31.7 ± 3.2 *a	27.6–34.1
45–54	18	21	39	33.0 ± 2.1	31.3 ± 3.6	32.1 ± 3.1 *a	25.1–34.1
35–44	33	30	63	35.4 ± 2.8	34.5 ± 3.1	35.0 ± 3.0 *b	26.5–40.8
25–34	15	17	32	38.2 ± 2.4	35.2 ± 3.2	36.6 ± 3.2 *c	31.3–42.7
15–24	11	09	20	41.5 ± 3.2	37.6 ± 5.2	39.8 ± 4.9 *d	28.9–49.5

*** $p < 0.01$ – statistically significant difference: a – compared to the age groups 35–44, 25–34 and 15–24; b – compared to the age groups: 65–74, 55–64, 45–54 and 15–24; c – compared to the age groups: 65–74, 55–64 and 45–54; d – compared to the age groups: 65–74, 55–64, 45–54 and 35–44.**
SD – standard deviation.

Table 3

The comparison of the mean calcaneal angles to the previous studies

Study	Population	Sample size	Age group (years) range	Böhler's angle (in degree) mean ± SD	Böhler's angle (in degree) range
Chen et al. [19]	USA	120	16–81	30 ± 6.0	14–50
Udoaka and Didia [18]	Nigerians	302	Not mentioned	32.8 ± 2.8	28–38
Igbigbi and Msamati [21]	Malawian	220	18–54	30.3 ± 7.2	14–45
Igbibi and Mutessaira [20]	Ugandans	206	20–40	36.4	20–50
Schepers et al. [25]	Dutch	33	18–65	32	25–40
Seyahil et al. [23]	Turkish	268	18–79	33.8 ± 4.8	20–46
Boyle et al. [26]	New Zeland	100	30–70	39.2	26.2–54.9
		763	0–14	35.2	14.3–58.1
Shoukry et al. [24]	Egyptian	220	20–40	30.1 ± 4.2	22–40
Willmott et al. [8]	British	127	16–92	36.4 ± 4.2	24.65–48.85
Isaacs et al. [7]	Australian	212	Not mentioned	29.4 ± 4.1	20–38
Khoshhal et al. [22]	Saudi Arabians	229	15–72	31.2 ± 5.6	16–47
Ramachandran et al. [5]	Indian	184	17–75	31.3 ± 5.0	18.7 – 46.2
Present study	Serbian	225	15–75	34.1 ± 4.2	25.1–49.5

SD – standard deviation.

Discussion

The assessment of the BA is of great importance in determining the indications for operative or non-operative treatment of the fractured calcaneus [15] and the surgical restoration with minimal anatomical and functional reduction [7]. According to the recommendation of AO Foundation, conservative treatment is indicated for the nondislocated calcaneal fractures with preserved values of BA [15]. Preoperative BA significantly correlated with the seriousness of injury and its postoperative value has a significant role in the prediction of functional recovery of the patient and the need for further surgery (e.g. subtalar fusion) [16]. It is an important prognostic factor for the outcomes of calcaneal fractures regardless of the treatment modality [17].

This angle, known as Böhler's, calcaneal-, tuber-joint- or salient angle, is also important for anthropometry and varies among the different populations [18]. Although some studies did not show any difference, the majority of evaluations of normal BA showed the gender, racial, territorial or the age differences of its values. This angle is usually measured using the lateral and axial radiographs. The variations of its normal values drew our attention to the assessment of BA in Serbian population, since the similar study has not yet been performed and this research may contribute to better knowledge of foot anatomy in this population. Taking this into consideration, findings of our study may be important in diagnosis and reconstructive surgery of calcaneal fractures and in anatomical and anthropometric studies.

Chen et al. [19] conducted the study in population of North Carolina [18]. There was no statistically significant difference between males and females, and it was not related to the side of the body. The reported mean BA and the lowest value of BA were lower than observed in this research.

Radiological study conducted in Nigerian population did not show significant gender dimorphism of BA [18]. The mean of the total population value of BA was lower than in our study.

Calcaneal angle in Ugandans was significantly sex dimorphic and it was similar to our findings. Authors also emphasized statistically significant difference between African populations of Nigeria and Uganda. There were no data about the age variations [20].

The reported values of BA in Malawian males and females were not statistically significant. The BA of the majority of examined Malawian subjects was in the 30–34° class. Statistically significant difference was found between Malawians and Nigerians, between Malawians and the Uganda population, but not between Malawians and Caucasians [21]. In agreement with this study, the majority of subjects from our study were in the 30–35° class, but the lowest value of BA was significantly higher.

The mean value of the Böhler's angle in Saudi population was not significantly related to age, gender or side of the body. The highest mean value of this angle was in the 15–20 years age group (33.1°), and the lowest one was in 21–30 age group (29.2°) [22]. In comparison to this population, Serbian subjects had higher mean and minimal BA, and the highest BA was in the youngest age group in both studies.

In Turkish population the highest mean value was in the 41–50 years age group (35.2°), and the lowest was in the group of 61–83 years (32.3°). There were no statistically significant gender differences and the significance was found neither among age groups nor between right and left foot. Comparing to the earlier studies, there was a significant difference among Turkish, Nigerian and Saudi populations. The value of the mean BA in Turkish population is in agreement with our findings, and the difference was not statistically significant. Opposite to findings of Seyahi et al.[23] statistically significant difference was found between mean BA of males and females as well as among age groups in our study. According to our results, the lowest mean BA was in the age group between 65–75 years and this is in agreement with the findings in Turkish population.

In the study conducted in Egyptians, it was concluded that the values of BA were reduced with aging. The sex dimorphism of BA was not statistically significant. The side of the body, occupation, residence and body mass index were not significantly related to the value of the BA [24].

The lower mean BA was also reported in Indian population. There was no report on the gender or the age variations [5].

The lower mean BA was also found in the study conducted in the Sydney Hospital among the patients with and without calcaneal fracture. The Böhler's angle in the group of patients with fracture of calcaneus was significantly reduced [7].

The Böhler's angle in British population was higher than in Serbians. Opposite to our findings, there were neither significant differences between the angles in males and females nor between the left and the right foot. Age was not a significant parameter for the value of the calcaneal angle [8].

According to Schepers et al. [25], the mean BA of the uninjured foot in the population of the Netherlands, was significantly higher than in the injured group. The mean BA in our study was higher and the lowest value of the BA, important for the fracture diagnosis, was equal.

The obtained results from the study conducted in New Zealand adult population showed that they were significantly different in comparison with our findings. The study also included children between 0–14 years and the mean BA was lower than in adults [26].

Previous studies showed that the BA in children is lower than in adults, but this is not of general importance. This angle rapidly increases with age until adolescence. This angle has its highest values in the age of six or seven, because of the rapid growth of the posterior articular facet of calcaneus and its disproportion in relation to calacaneal tuberosity [14]. The highest BA in our study was indeed found in the youngest age group.

Results of this study revealed the sex dimorphism of the BA in examined population, with the higher mean value in males. This was in agreement with the findings in Ugandan population [20], although the male Ugandan subjects had lower BA than female ones (opposite to our results). The other studies did not find the statistically significant gender differences, although the mean BA was higher in males [8, 18, 19, 21–24].

The mean values of BA were also significantly different between the age groups in Serbian population, with a negative correlation between the BA and age. This was also found in earlier studies in Egyptian and Ugandan population [20, 24]. Results reported in other studies, showed the same tendency, but the difference was not significant.

Considering the interpopulation differences, the mean BA in Serbians as well the range of this angle, our results were the most consistent with values reported for the Turkish population. In the observed population, the range of the BA value was from 24.1° to 49.5°.

The clinically important lowest value of the BA obtained from this study was similar to minimal BA in British, Dutch and Egyptian population and notably lower in the USA, Malawian and Indian population.

The limitation of this study may be the fact that measurements were not done on both feet of all the observed subjects. The reason is that the results of earlier studies as well as our small-sample test showed that difference was not statistically different.

Conclusion

The findings presented in this paper confirmed the existence of a wide range of gender and age differences in values of Böhler's angle. These findings about the Böhler's angle in Serbian population are important for the diagnostics and reconstructive surgery of the calacaneal fractures. Besides, results obtained in this study are important for anthropometric studies and forensic medicine.

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Health-related quality of life in patients undergoing hemodialysis

Kvalitet života povezan sa zdravljem bolesnika koji se leče hemodijalizom

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Abstract

Background/Aim. Chronic renal disease is one of the growing problems all over the world. Health-related quality of life (HRQoL) is an important indicator for those with a chronic disease, such as chronic renal disease, because it may serve as predictor of mortality and hospitalization. The aim of this study was to assess HRQoL in patients on chronic maintenance hemodialysis (HD), and compare it with patients suffering from hypertension (HTA), and normal controls of the same age and gender (C). **Methods**. The study enrolled 224 males and females older than 18 years: 67 in the HD group, 78 in the HTA group, and 79 in the C group. HRQoL was assessed in all groups using 15-D questionnaire. **Results**. Significantly higher level of education was recorded in the HD group compared to other two groups. In the HD group there were significantly less employed persons (9%) and significantly more retired (67.2%). All groups were similar regarding an average monthly income and marital status. We found significantly lower total HRQoL score in patients in the HD group, compared to normal controls (0.78 ± 0.16 vs. 0.89 ± 0.10 in the HTA and 0.95 ± 0.06 in the C group) as well as specific scores in almost all investigated domains, except in speech, eating and mental functions. Patients in the HD and HTA groups had similar self-reported quality of life in additional 3 domains: hearing, elimination and distress, while the HD group reported significantly lower scores in remaining 9 domains: mobility, vision, breathing, sleeping, usual activities, discomfort and symptoms, depression, vitality and sexual activity. Patients in the HTA group had significantly lower scores than normal controls in 8 domains (hearing, sleeping, elimination, usual activities, discomfort and symptoms, depression, distress and vitality) as well as in total quality of life, while in remaining 4 domains there was no significant difference (mobility, vision, breathing, sexual activity). **Conclusion**. Both investigated chronic diseases lead to impairment of HRQoL, which is substantially stronger in hemodialysis than in hypertension. Considering the relationship between depression and HRQoL measures, it may be useful to treat depression of HD patients in order to improve their quality of life.

Key words:
renal dialysis; hypertension; quality of life; surveys and questionnaires; health.

Apstrakt

Uvod/Cilj. Hronična bubrežna bolest danas je sve više zastupljena širom sveta. Kvalitet života povezan sa zdravljem (HRQoL) predstavlja koristan pokazatelj u populacijama obolelih od hroničnih bolesti kao što je hronična bubrežna bolest, pošto može poslužiti kao pouzdan prediktor smrtnog ishoda i hospitalizacije. Cilj ove studije bio je da se ispita kvalitet života povezan sa zdravljem populacije obolelih od terminalne bubrežne insuficijencije koji se leče hroničnom hemodijalizom (HD) i da se uporedi sa populacijom obolelih od hipertenzije (HTA) i populacijom naizgled zdravih osoba iste starosne dobi i polne strukture (C). **Metode**. Studijom je obuhvaćeno ukupno 224 ispitanika starijih od 18 godina, oba pola: 67 u HD grupi, 78 u HTA grupi i 79 u C grupi. HRQoL je procenjivan u svim grupama korišćenjem 15-D standardizovanog upitnika. **Rezultati**. Ispitanici iz HD grupe imali su značajno više obrazovanje od ostale dve grupe. U HD grupi bilo je značajno manje zaposlenih (9%), a značajno više penzionera (67,2%). Grupe se nisu razlikovale u pogledu prosečnog mesečnog prihoda i bračnog stanja. Bolesnici u HD grupi imali su značajno niži ukupni HRQoL skor u poređenju sa ostalim grupama (0,78 ± 0,16 vs. 0,89 ± 0,10 u HTA i 0,95 ± 0,06 u C grupi), a takođe i niže specifične skorove u skoro svim preostalim aspektima kvaliteta života, osim u domenu govora, jela i mentalne funkcije, gde nije bilo razlike između grupa. Bolesnici iz HD grupe su zabeležili značajno niže skorove u odnosu na HTA grupu u sledećim domenima: pokretljivost, vid, disanje, spavanje, uobičajene aktivnosti, nelagodnost i simptomi, depresija, vitalnost i seksualna aktivnost, a slične u domenima: sluh, pražnjenje i duševna patnja. U HTA grupi

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zabeleženi su značajno niži skorovi u odnosu na C grupu u osam domena (sluh, spavanje, pražnjenje, uobičajene aktivnosti, nelagodnost i simptomi, depresija, duševna patnja i vitalnost, a u četiri domena rezultati su bili slični (pokretljivost, vid, disanje, seksualna aktivnost). **Zaključak**. Obe ispitivane hronične bolesti dovode do smanjenja kvaliteta života povezanog sa zdravljem, s tim da je smanjenje značajno intenzivnije u slučaju hemodijalize nego u slučaju hipertenzije. S obzirom na povezanost depresije i ostalih merila kvaliteta života, lečenje depresije bi moglo biti korisno za poboljšanje kvaliteta života bolesnika na hemodijalizi.

Ključne reči:
bubreg, dijaliza; hipertenzija; kvalitet života; ankete i upitnici; zdravlje.

Introduction

Health-related quality of life (HRQoL) refers to physical, psychological and social domains of health, influenced by one's personal experience, beliefs, expectations and perceptions of health [1]. Because of these aspects, it is possible that two persons with similar health conditions, report different quality of life [2, 3]. However, transfer of various aspects and domains of health into particular quantitative value is not simple [4]. In past twenty years, several methods were used as measurements of HRQoL in healthy population [5], as well as in various categories of chronic diseases [6–8]. Health-related quality of life (HRQoL) is important diagnostic instrument in population with chronic diseases, such as chronic renal diseases. It may serve as predictor of mortality and hospitalization, according to results of the large international study with the total of 17,236 patients on hemodialysis [9].

Chronic renal disease (CRD) is a global health problem. The incidence of CRD is growing and is present in 11% of world population. This may be related to higher prevalence of elderly, but also with increased frequency of obesity, diabetes and hypertension which are well-known risk factors for CRD development [10]. According to the World Health Organization, CRD takes the 12th place in leading causes of death [11].

End-stage renal disease requires replacement of kidney function with the active therapy – kidney transplantation, chronic ambulatory peritoneal dialysis, or maintenance hemodialysis (HD). It is expected not only to replace the insufficient renal function, but also to improve HRQoL. However, the chronicity of disease and HD treatment impose major restrictions regarding intake of food and water. Patients undergoing HD lose their freedom to some extent and become dependent on a health facility, which often influence their marriage, family and social life. HD often results in lower income, which is also one of the aspects of quality of life [12].

The estimation of HRQoL is very important for chronically ill people, since it is possible to evaluate the burden of chronic disease.

There are very few studies of HRQoL regarding patients on HD in Serbia [13].The difference between the HD and other chronic diseases regarding influence on HRQoL has not been established so far, including the effect of specific treatment, simply by comparison with healthy population [14]. The estimation of HRQoL in patients on HD may be performed by various questionnaires [4, 15–18]. 15-D instrument is a generic, self-reported, standardized questionnaire covering 15 domains, which provides data about life quality through scores [18]. It is simple and multidimensional, hence suitable for population undergoing HD.

The aim of our study was to evaluate the HRQoL in population on HD, and to compare it not only to healthy controls of the same age, but also to population with hypertension as different chronic disease.

Methods

The study enrolled 224 males and females older than 18 years: 67 with the end-stage renal failure undergoing in-center HD, 78 with chronic hypertension on regular medicament treatment (HTA), and 79 apparently healthy normal controls (C). Patients in the HD and HTA group were recruited from the Clinic for Nephrology and Outpatient Clinic of the Military Medical Academy in Belgrade, respectively. Normal controls were healthy blood donors and people on regular preventive examinations in several Health Centers in Belgrade. At the moment of investigation, no one had an acute or chronic disease, or was on a medical therapy. Subjects in the HTA and C groups were matched for age and gender to the HD group. Patients with the active systemic disease, inflammatory bowel disease, malignant diseases, pregnancy, any acute disease at the moment of investigation, psychiatric or neurological disorder that might influence the usual activities, as well as patients without permanent vascular access for hemodialysis were not included. Patients in the HD group were on hemodialysis more than 6 months. All of them underwent dialysis three times a week for approximately 4 hours (between 180–270 min), with the single use of polysulfone membrane, surface area from 1.3–2.4 m^2. Blood flow was 230–350 mL/min, and the dialysate flow was 500 mL/min. Bicarbonat dialysis solution was used in all dialysis procedures and HD adequacy was measured by Kt/V index. The average value was 1.52 ± 0.27. More than 80% patients were on erythropoiesis stimulating agent. The health-related quality of life was measured by self-reported generic instrument 15-D [4, 17]. It is a 15-item questionnaire that measures functions in various domains as: mobility, vision, hearing, breathing, sleeping, eating, speech, excrete elimination, usual activities, mental functions, discomfort and symptoms, depression, distress, vitality, and sexual activity. It is rated on a 5-point scale, with a total score range between 0 and 1 (higher score indicates better HRQoL). Demographic and socioeconomic characteristics were investigated by self-reported questionnaire. Investigation was approved by local Ethical Committee and was conducted during 2015.

Obtained data were presented as means ± standard deviation (SD) or proportions (%). Normality of distribution was tested by Kolmogorov-Smirnov test. Differences betwe-

en groups were analyzed by Kruskall-Wallis test and χ^2 test for categories with *post hoc* Mann-Whitney test. Statistical significance was accepted at $p < 0.05$.

Results

Demographic and socio-economic characteristics of participants in all 3 groups are presented in Table 1. There were no significant differences between groups in age, gender, income and marital status ($p = 0.101$, 0.577, 0.166 and 0.052, respectively). Average duration of renal disease in the HD group was 13.04 ± 11.29 years, of which 6.21 ± 6.74 years on dialysis. Average duration of hypertension in the HTA group was 15.08 ± 13.90 years.

Post-hoc statistical analyses were performed for education and employment, since other 4 characteristics showed no difference between groups. The results are presented in Table 2.

Significantly more participants with college or university degree were recorded in the HD group, compared to other two groups, where high school level of education was predominant ($p < 0.001$). There was also statistically significant difference between groups regarding employment status compared to other two groups: in the HD group there were significantly less employed persons (9.0% vs. 34.6% in the HTA and 65.8% in the C group), and significantly more retired (67.2% vs. 55.1% and 24.1%), respectively.

Average scores of particular domains obtained from 15-D questionnaire are presented in Table 3, together with statistical analysis of differences among all three groups. Results indicated that the groups had similar scores of quality of life only in domains of speech, eating and mental functions. In all other domains as well as in total quality of life score, there were statistically significant differences among the groups. The lowest scores were recorded in the HD, and the highest scores in the C group.

In order to investigate further differences among the groups, *post-hoc* tests were performed for 12 domains and the total score. Since the differences among the groups in speech, eating and mental functions were not significant these 3 domains were excluded from further analysis. The results are presented in Table 4.

Table 1

Demographic and socio-economic characteristics of participants

Category	HD (n = 67)	HTA (n = 78)	C (n = 79)	χ^2	*p*
Participants, n (%)					
males	41 (61.2)	44 (56.4)	51 (64.6)	1.101 (df = 2)	0.577
females	26 (38.8)	34 (43.6)	28 (33.4)		
Age (yrs), range					
mean ± SD	58.6 ± 15.6	60.6 ± 13.7	56.2 ± 14.9	4.611 (df = 2)	0.101
	21–86	21–82	22–86		
Education, n (%)					
elementary school or less	11 (16.4)	9 (11.5)	2 (2.5)	34.906 (df = 4)	< 0.001
high school degree	27 (40.3)	60 (76.9)	63 (79.7)		
College/University degree	29 (43.3)	9 (11.5)	14 (17.7)		
Employment, n (%)					
employed	6 (9.0)	27 (34.6)	52 (65.8)	55.979 (df = 6)	< 0.001
unemployed	10 (14.9)	2 (2.6)	4 (5.1)		
retired	45 (67.2)	43 (55.1)	19 (24.1)		
other	6 (9.0)	6 (7.7)	4 (5.1)		
Income (per person, monthly) RSD					
< 20,000	15 (22.4)	21 (26.9)	11 (13.9)	6.480 (df = 4)	0.166
21–40,000	30 (44.8)	33 (42.3)	47 (59.5)		
> 40,000	22 (32.8)	24 (30.8)	21 (26.6)		
Marital status, n (%)					
married/with partner	48 (71.6)	63 (80.8)	53 (67.1)	12.620 (df = 6)	0.052
single	13 (19.4)	10 (12.8)	16 (20.3)		
widowed	5 (7.5)	1 (1.3)	0 (0)		
divorced	1 (1.5)	4 (5.1)	10 (12.7)		

HD – hemodialysis group; HTA – chronic hypertension group; C – normal control group.
SD – standard deviation.

Table 2

***Post-hoc* statistical analysis of difference between groups (Pearson χ^2 test, df = 3)**

Characteristic	HD:C		HD:HTA		HTA:C	
	χ^2	*p*	χ^2	*p*	χ^2	*p*
Education	49.364	< 0.001	18.012	< 0.001	18.263	< 0.001
Employment	25.046	< 0.001	22.539	< 0.001	5.609	0.061

HD – hemodialysis group; HTA – chronic hypertension group; C – normal control group.

Compared to normal controls, patients on hemodialysis had statistically lower scores in all 12 domains as well as in total 15-D score. When compared to the HTA group significantly lower scores remained in 9 domains and in total 15-D score, while the HD and HTA groups were similar regarding self-reported quality of hearing, elimination and distress. Patients in the HTA group had significantly lower scores than normal controls in 8 domains and total 15-D score, while in domains of mobility, vision, breathing and sexual activity there was no significant difference between HTA and apparently healthy persons of the same age.

hemodialysis were able to breathe normally, comparing with 73.4% of subjects in the C and 60.3% in the HTA group ($p < 0.001$). Only 34.3% of patients in the HD group were able to sleep normally, comparing with 73.4% in the C and 48.7% in the HTA group ($p < 0.001$). Also, 56% of patients on hemodialysis and 64.1% in the HTA group reported normal functions of bladder and bowel, which is significantly lower ($p < 0.001$) than in the C group (83.5%). Serious problems with bladder and/or bowel function were present only in the HD group (14.9%). Only 25.4% of HD patients were able to perform usual activities, comparing with 87.3% in the C and

Table 3

Average scores of 15-D questionnaire domains in all groups

	HD	HTA	C	Kruskall-Wallis (df = 2)	*p*
Mobility	0.78 ± 0.27	0.95 ± 0.12	0.97 ± 0.08	37.38	< 0.001
Vision	0.79 ± 0.28	0.91 ± 0.17	0.94 ± 0.11	11.90	0.003
Hearing	0.89 ± 0.21	0.92 ± 0.13	0.98 ± 0.08	11.46	0.003
Breathing	0.74 ± 0.26	0.86 ± 0.19	0.92 ± 0.14	22.72	< 0.001
Sleeping	0.71 ± 0.28	0.81 ± 0.22	0.93 ± 0.13	29.59	< 0.001
Eating	0.97 ± 0.11	0.99 ± 0.04	1.00 ± 0.00	6.46	0.059
Speech	0.98 ± 0.07	0.98 ± 0.08	0.99 ± 0.06	0.47	0.789
Elimination	0.74 ± 0.32	0.86 ± 0.19	0.95 ± 0.12	18.50	< 0.001
Usual activities	0.59 ± 0.33	0.87 ± 0.19	0.95 ± 0.14	67.52	< 0.001
Mental functions	0.92 ± 0.18	0.91 ± 0.17	0.96 ± 0.11	4.85	0.089
Discomfort	0.77 ± 0.27	0.90 ± 0.16	0.96 ± 0.10	26.75	0.000
Depression	0.73 ± 0.25	0.83 ± 0.19	0.92 ± 0.14	24.50	< 0.001
Distress	0.78 ± 0.27	0.83 ± 0.22	0.93 ± 0.14	15.74	< 0.001
Vitality	0.68 ± 0.23	0.83 ± 0.18	0.93 ± 0.13	50.28	< 0.001
Sexual activity	0.54 ± 0.35	0.83 ± 0.18	0.91 ± 0.18	50.18	< 0.001
Total 15-D score	0.78 ± 0.16	0.89 ± 0.10	0.95 ± 0.06	65.70	< 0.001

HD – hemodialysis group; HTA – chronic hypertension group; C – normal control group.

Table 4

***Post-hoc* statistical analysis of difference between groups (Mann-Whitney test, df = 3)**

	HD:C		HD:HTA		HTA:C	
	Mann-Whitney	*p*	Mann-Whitney	*p*	Mann-Whitney	*p*
Mobility	1,604.00	< 0.001	1,714.00	< 0.001	2,912.50	0.284
Vision	1,967.00	0.001	2,079.00	0.012	2,917.50	0.446
Hearing	2,195.50	0.004	2,585.00	0.885	2,451.00	0.001
Breathing	1,607.50	< 0.001	1,925.00	0.003	2,637.50	0.058
Sleeping	1,429.50	< 0.001	2,083.00	0.025	2,213.00	< 0.001
Elimination	1,806.50	< 0.001	2,197.00	0.059	2,443.00	0.003
Usual activities	924.00	< 0.001	1,295.00	< 0.001	2,447.00	0.002
Discomfort	1,611.50	< 0.001	1,942.00	0.002	2,624.50	0.023
Depression	1,536.00	< 0.001	2,097.5	0.030	2,292.50	0.002
Distress	1,864.50	< 0.001	2,408.50	0.371	2,314.50	0.001
Vitality	1,037.00	< 0.001	1,660.00	< 0.001	2,133.50	< 0.001
Sexual functions	1,107.00	< 0.001	1,410.00	< 0.001	2,684.50	0.082
Total 15-D score	707.00	< 0.001	1,428.50	< 0.001	1,828.50	< 0.001

HD – hemodialysis group; HTA – chronic hypertension group; C – normal control group.

When we analyzed distribution of particular categories in each domain separately, we found further important differences: 91.1% of participants in the C group and 85.9% in the HTA group self-reported normal mobility, comparing with 53.7% in the HD group ($p < 0.001$); in the C and HTA groups 77.2% and 73.1% of subjects self-reported normal visual function, while in the HD group only 56.7% were in this category ($p = 0.002$); 92.4% of normal controls had normal hearing functions, which is significantly higher percentage comparing with the HD and HTA groups (76.1 and 71.8%, respectively; $p < 0.001$). Only 40.3% of patients on

66.7% in HTA group ($p < 0.001$). Moreover, 10% of HD patients were unable to manage any of previously usual activities, while this category was reported neither in the C, nor in the HTA group. In the HD group 49.3% patients were free of physical discomfort comparing with 86.1% in the C and 71.8% in the HTA group ($p < 0.001$). One patient in the HD group reported unbearable physical discomfort, and additional 7 (10.4%) severe discomfort. These categories were absent in other two groups. Totally, 69.6% in the C and 46.2% in the HTA group reported absence of sadness, melancholy or depression comparing with 34.3% patients in the HD gro-

up ($p < 0.001$). In the HD group 11.9% of patients described themselves as very said or extremely depressed. 53.7% in the HD and 55.1% in the HTA group had not have symptoms of distress, which was significantly lower than 78.5% in the C group ($p < 0.001$). Only 20.9% of patients in the HD group scored their vitality into highest category, comparing with 72.2% in the C and 43.6% in the HTA group ($p < 0.001$), while 11.9% in the HD group found themselves in category with lowest score. Finally, even 25.4% of patients in the HD group reported that their state of health makes sexual activity impossible, comparing with 1.3% in the C and 5.1% in the HTA group ($p < 0.001$), while only 28.4% in HD group stated that their health had no adverse effects on sexual life (comparing to 75.9% in the C and 65.4% in the HTA group).

Discussion

The health-related quality of life assessment is very important in patients with chronic diseases, because it provides an unique subjective measure of patient's perception of self well-being. Although subjective in nature, this perception may strongly influence the severity of disease, mortality rate and hospitalization [9]. Increasing proportion of elderly people in general population leads to increased incidence and prolonged duration of chronic diseases. Decrease in HRQoL in patients on HD is related to higher death rate [19, 20], depression and cognitive impairments [21–23] and malnutrition [24]. Depression is particularly strongly related to low HRQoL [21–23].

Several studies reported that HRQoL is particularly compromised in patients on hemodialysis [15, 25–28], which is confirmed with our results. Large study of HRQoL in 570 patients who underwent hemodialysis in 24 different centers revealed that, although dialysis is considered as a highly standardized procedure, there are clinically relevant differences in HRQoL among centers [29]. Taking that into account, we carried out our survey in one dialysis centre. Investigation conducted in Serbia by Stojanović and Stefanović [30] marked that poor income substantially reduce HRQoL in the HD patients. Socio-economic status in the HD patients in our study, however, was relatively maintained: their marital status and income did not differ from other two groups of the same age and gender. Notable differences were found in employment status (in the HD group there were more retired and less employed persons than in the HTA and C group) and education level (in the HD group there were more patients with the highest education level than in other two groups where high school levels were predominant). Higher education level is usually present in population with higher HRQoLs, but our results indicate that severity of disease and complexity of replacement therapy in the patients on HD are more important factors that influence HRQoL than the education level.

Early retirement may be the consequence of the major impairments in the physical aspect of HRQoL. When we analyzed specific scores, we found that only two domains of physical health were neither influenced by hemodialysis, nor by hypertension – eating and speech. In all 3 groups we recorded very high scores in these domains. The ability to eat normally is important in patients on hemodialysis, hence in this population malnutrition markedly influences mortality [24]. Patients in the HD group showed particularly low scores in other domains of physical health: mobility, vision, breathing and sexual activity. Only half of the HD patients were able to move indoors and outdoors and on the stairs. Moreover, 2 patients reported themselves as completely bed-ridden and unable to move about, while in the C and HTA group there was no one falling in this category. Similarly, only half of the HD patients reported normal visual function, i.e. that they can read without difficulties (with or without glasses). In this group we found 1 patient who was almost completely blind. Only 40% of the patients on hemodialysis were able to breathe normally, while every tenth reported shortness of breath, even after light activity. The lowest average score in the HD group was found in domain of sexual activity – as low as 0.54 ± 0.35. For one-quarter of these patients, state of health makes their sexual activity impossible. Hypertensive patients, on the other hand, reported scores in these physical domains as high as normal controls, but in domains of hearing, elimination and physical discomfort their scores were similar to the ones of the HD group, indicating that hypertension also influenced these aspects.

All subjects reported that their overall mental functions were not impaired (average score varied from 0.91 in the HD to 0.96 in the C group). However, when specific domains of mental health were analyzed, we found that depression was common in the HD group: only one-third of the patients were not melancholic or depressed. At the same time, every tenth of them reported being very sad, and 1 as extremely depressed. Symptoms of distress (anxiety, nervousness) were present in substantial percentage both in the patients on hemodialysis and those with hypertension. Hemodialysis had major influence on sleeping, too. Only one-third of the patients were able to sleep normally. Persons who suffered severe sleeplessness were recorded only in the HD group. They reported that sleeping was almost impossible even with full use of sleeping pills, so they stayed awake most of the night. Anxiety and insomnia were also often present in a study conducted on the population of 84 patients on hemodialysis in Greece (of similar age and social characteristics as in our study) [24]. Hypertensive patients in our study had less sleeping problems, but still not achieved the quality of sleeping reported in the control group.

Patients on hemodialysis had particularly low average score in the domain of vitality (0.68 ± 0.23). Only 20% reported themselves as healthy and energetic, while more than 10% categorized themselves as very weary and 1 patient as extremely weary, and totally exhausted. Hypertension also influences vitality, although to less extent.

Having usual activities imposed extreme difficulties to patients on hemodialysis. Only one-quarter of them managed to keep their jobs, or to study, perform usual housework and participate in free-time activities. Hypertensive patients were more successful in keeping such activities, but still less successful than the normal controls of the same age.

Health-related quality of life in patients on hemodialysis is markedly lower than in healthy population of the same age and socio-demographic characteristics, which

was proved in several studies [26, 27]. However, the difference between patients on hemodialysis and patients who suffer from other chronic long-lasting disease such as hypertension has not been investigated so far. Nevertheless, results we obtained from the hypertensive group may be compared to a study conducted on 121 hypertensive patients in Serbia [31]. The author evaluated their HRQoL using 15-D instrument and reported lower average 15-D score (0.76 ± 0.15) than in our study (0.89 ± 0.10). The differences may be explained by older age in later study (69.3 years compared to 58.1 in our study), since the same author observed that quality of life in all domains decreased with age. Similar to our study, speech and eating were not affected by hypertension (the results were in the range of basic levels).

Conclusion

Both investigated chronic diseases lead to impairment of HRQoL, which is substantially stronger in hemodialysis than in hypertension. Considering the relationship between depression and HRQoL measures, it may be useful to treat depression in population of the HD patients, in order to improve their quality of life.

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Importance of early ventilation tubes insertion in chronic otitis media with effusion in children with congenital cleft palate

Značaj rane insercije ventilacionih cevčica kod hroničnog sekretornog otitisa kod dece sa urođenim rascepom nepca

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Abstract

Background/Aim. Otitis media with effusion (OME) is almost universal in children with cleft palate with an incidence of more than 90%, but the approach to managing this problem varies significantly among authors. The Eustachian tube dysfunction is the main factor that leads to the presence of the middle ear effusion. This is especially prominent in children with congenital cleft palate and explains the prolonged course of this process. The objective of this study was to determine the effectiveness of early ventilation tubes insertion in children with cleft palate at the time of palatoplasty by monitoring the course and duration of the disease as well as development of complications. **Methods**. In the prospective study with predefined regular follow-up intervals and parameters, the two groups of children were observed. The group one (E) included 45 children with congenital cleft palate who underwent the early insertion of ventilation tubes during palatoplasty, and the group two (C) had the same number of children with cleft palate who were treated conservatively on an as-needed basis. Assessment parameters were findings of otomicroscopy, tympanometry, play and pure tone audiometry. Each child was followed-up for 5 full years at total of nine follow-up examinations. **Results**. Result analysis showed that there were no statistically important differences between the two study groups in terms of the course and duration of the presence of the middle ear effusion, or in terms of complications and speech development. **Conclusion**. Based on the results obtained, we can conclude that there is no significant benefit in early ventilation tubes insertion in children with cleft palate, therefore our recommendation is watchful waiting and a conservative treatment on an as-needed basis, with the ventilation tubes insertion when a surgeon, based on his or her experience and individual findings considers it necessary.

Key words:
otitis media with effusion; cleft palate; middle ear ventilation; conservative tretment; otologic surgical procedures; child; serbia.

Apstrakt

Uvod/Cilj. Otitis media sa efuzijom (OME) je gotovo univerzalna pojava kod dece sa rascepom nepca sa učestalošću većom od 90%, ali se pristup rešavanju ovog problema veoma razlikuje između autora. Disfunkcija Eustahijeve tube je glavni faktor za nastajanje sekreta u srednjem uvu, što je naročito izraženo kod dece sa urođenim rascepom nepca i objašnjava dugotrajnost ovog procesa. Cilj istraživanja bio je da se utvrdi efektivnost rane insercije ventilacionih cevčica kod dece sa rascepom nepca prilikom palatoplastike, posmatrajući tok i dugotrajnost oboljenja, kao i razvoj komplikacija. **Metode**. U prospektivnoj studiji sa unapred određenim pravilnim intervalima i obeležjima posmatranja praćene su dve grupe dece. U prvoj grupi (E) bilo je 45 dece sa urođenim rascepom nepca kojima je urađena rana insecija ventilacionih cevčica prilikom palatoplastike, a u drugoj (K) isti broj dece sa rascepom nepca koja su po potrebi lečena konzervativnim tretmanima. Obeležja posmatranja bila su nalazi otomikroskopije, timpanometrije i tonalne liminarne audiometrije. Svako dete pojedinačno je praćeno punih pet godina na ukupno devet kontrola. **Rezultati**. Analiza rezultata pokazala je da ne postoje statistički značajne razlike između dve posmatrane grupe u odnosu na tok i dugotrajnost prisustva sekreta u srednjem uvu, kao ni na razvoj komplikacija i govora. **Zaključak**. Na osnovu rezultata koje smo dobili možemo da zaključimo da ne postoji veliki benefit u ranoj inserciji ventilacionih cevčica kod dece sa rascepom nepca, te je naša preporuka redovno praćenje deteta i konzervativna terapija po potrebi, a insercija ventilacionih cevčica onda kada hirurg na osnovu svog iskustva i individualnog nalaza ispitanika to smatra neophodnim.

Ključne reči:
otitis medija, serozni; nepce, rascep; uvo, srednje, aeracija; lečenje, konzervativno; hirurgija, otološka, procedure; deca; srbija.

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Introduction

Otitis media with effusion (OME) is very common in children with congenital cleft palate. Cleft lip and palate belong to a group of common congenital malformations of the head with an incidence of around 1 in 700 individuals [1]. The connection between cleft palate and OME was first described more than a century ago [2, 3]. Paradise and Bluestone [4] first described that all children with cleft palate had effusion in the middle ear. Since then, numerous studies have been published showing that the incidence of OME in children with cleft palate is higher than 90% [5–9]. Muntz [10] reported that 96% of children with cleft palate needs tympanostomy tube placement, and around 50% of them required repeated tympanostomy tube placement. The Eustachian tube dysfunction, recurrent infections of the upper respiratory tract and allergies have all been stated as causes for OME in children with cleft palate [11, 12]. Most authors agree that the Eustachian tube dysfunction with relapsed or prolonged subclinical inflammation components is the main etiopathogenetic factor in the development of chronic OME [13–16] which is particularly prevalent in children with congenital cleft palate. The abnormal insertion or function of the tensor veli palatini muscle and/or levator veli palatini muscle can cause insufficient dilation of the Eustachian tube. Studies have shown that the functional integrity of the tensor and/or levator veli palatini muscles plays the main role in the Eustachian tube function, and consequently in the development of the disease in the middle ear as well [2, 17–28]. According to one group of authors, palatoplasty has been shown to be beneficial in reducing the incidence of middle ear diseases, improving hearing and the Eustachian tube function compared to the patients who did not undergo palatoplasty [21, 22, 28], but a definite and unified approach to managing this problem is still lacking.

The objective of this study was to determine the effectiveness of the early ventilation tubes insertion in children with cleft palate by monitoring the course and duration of the disease as well as the development of possible complications.

This was a prospective study with predefined follow-up intervals at 6 months for each patient as well as assessment parameters: otomicroscopic evaluation of the appearance of the tympanic membrane, tympanometric findings and audiometric findings (pure tone audiometry).

Methods

A prospective study was conducted in ten-year period from 2005 until the end of 2014 and included 90 children of both sexes diagnosed with congenital cleft palate, divided into 2 equal groups. In the experimental group (E) there were 45 children with congenital cleft palate who underwent the early routine ventilation tubes insertion during palatoplasty. We opted for Shepard ventilation tubes of 1.1 mm in diameter. All the interventions were performed under general endotracheal anesthesia and with the use of the surgical microscope (Leica F40), and the tubes were placed in the anteroinferior quadrant of the eardrum. The ventilation tubes were in function for 6–12 months on average, and only the children with minimum 6 months of tube functioning were included in the statistical analysis. In the control group (C), there were 45 children with congenital cleft palate who did not undergo the early routine ventilation tubes insertion, and during the follow-up period the usual conservative treatments with antibiotics, mucolytics, antihistamines and decongestants were administered, depending on their problems and individual needs.

The patients with congenital cleft palate in the groups E and C were reviewed at the age of 2 to 6 months, and then evaluated at the regular intervals of 6 months according to the above-mentioned assessment parameters. The minimum follow-up period per patient was 5 years.

Results

A total of 90 participants divided into two groups of 45 participants each were enrolled in our study. There were 52 (57.7%) male participants, and 38 (42.3%) female participants. The patients were initially reviewed at the time of their first visit to our institution for congenital cleft palate which on average corresponded to the age of 6 months, whereas the final assessment was done at the age 5 or 6.

Only the children with bilateral OME were enrolled in the study because of the more objective and easier data processing, even though in the process of participant selection we encountered rare cases of unilateral middle ear effusion. The children with cleft palate within the scope of malformations associated with the head and neck syndrome were also excluded. There were no significant differences between the experimental and control group in terms of their age at the beginning of the study, their sexes and bilaterality of the process.

Medical history data did not indicate any significant family load in terms of OME or congenital cleft palate. In 12 out of 90 (13.3%) participants, according to the data obtained, one of the parents or a close relative had hearing problems or problems with the middle ear infections, and 21 (23.3%) positive medical history data were in relation to congenital cleft palate in the family.

Otomicroscopy

One out of two parameters introduced at the beginning of the evaluation of the participants was that of otomicroscopy. Table 1 and Figure 1 show otomicroscopic findings that were obtained at different points throughout the entire length of the study, so that each of the participants had a total of 9 otomicroscopic evaluations. The evaluation at the age of 18 months was omitted because the experimental group had ventilation tubes in the eardrum. For the purposes of easier statistical analysis, the otomicroscopic findings were divided into 3 groups: NE – normal eardrum (normal findings), OE – opaque eardrum with indistinct landmarks, with light reflex shortened or smeared, and CE – complicated eardrum (eardrum with detectable complications in terms of atrophy, retractions, perforations or cholesteatoma pockets). According to the otomicroscopic findings there were no sig-

Table 1

Prevalence rate of the middle ear effusion (otomicroscopic findings)

Age (months)	Groups						Statistical Significance
	Experimental, n (%)			Control, n (%)			
	NE	OE	CE	NE	OE	CE	
6	2 (4)	43 (96)	0 (-)	3 (7)	42 (93)	0 (-)	$\chi^2 = 0.04$ $p = 0.9780$
12	3 (7)	42 (93)	0 (-)	3 (7)	42 (93)	0 (-)	$\chi^2 = 0.00$ $p = 1.0000$
24	2 (4)	42 (93)	1 (18)	5 (11)	39 (87)	1 (2)	χ^2=0.40 $p = 0.8187$
30	3 (7)	41 (91)	1 (22)	5 (11)	38 (84)	2 (4)	$\chi^2 = 0.18$ $p = 0.9149$
36	5 (11)	39 (87)	1 (18)	7 (16)	35 (78)	3 (7)	$\chi^2 = 0.18$ $p = 0.9148$
42	9 (20)	34 (76)	2 (4)	9 (20)	33 (73)	3 (7)	$\chi^2 = 0.18$ $p = 0.9149$
48	9 (20)	33 (73)	3 (7)	10 (22)	31 (69)	4 (9)	$\chi^2 = 0.04$ $p = 0.9780$
54	10 (22)	30 (67)	5 (11)	11 (24)	29 (64)	5 (11)	$\chi^2 = 0.04$ $p = 0.9780$
60	12 (27)	27 (60)	6 (13)	11 (24)	29 (64)	5 (11)	$\chi^2 = 0.04$ $p = 0.9780$

NE – normal eardrum; OE – opaque eardrum; CE – complicated eardrum.

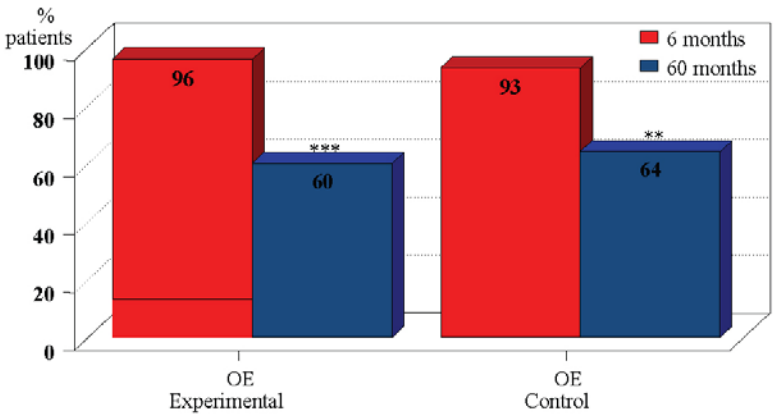

Fig. 1 – Otomicroscopic findings in opaque eardrum (OE) at the beginning and the end of the study.

nificant differences between the control and experimental group during the entire evaluation period. When the otomicroscopic findings of the control and experimental group were compared at the end of the study, a statistically significant difference ($p < 0.01$; 0.001) in OE findings was registered in comparison to the beginning of the study, and the identical trend was observed in both groups.

Tympanometric findings

In establishing the diagnosis of chronic OME the tympanometric findings are most important. Table 2 shows prevalence rate of the middle ear effusion. The testing at the age of 18 months was omitted because the experimental group had ventilation tubes, which rendered tympanometry impossible. A statistically significant difference between the two groups was observed at the evaluation at 24 months of age ($\chi^2 = 14.40$, $p = 0.007$), while at later evaluations this significance was slowly reduced. Figure 2 shows the tympanometric findings in participants of both the experimental and control group. At the final testing after 60 months of age, a statistically significant decrease in the percentage of the participants with tympanometric findings B was registered as well as a considerable increase in the percentage of the participants with the C findings, compared to the results at the beginning of the study in both groups.

Audiometry findings

Pure tone audiometry was done at 48 months of age when adequate cooperation of the participants was possible, and the testing was repeated at the age of 54 and 60 months (Table 3). Hearing levels, as in play audiometry, were divided into 4 groups with the average hearing thresholds ranging from 20 to 50 dB, showing that there were no significant statistical deviations between the experimental and control groups.

As the average age of our study participants at the first exam was about 6 months when otoscopic findings could be unclear even in children without OME, it is not surprising

Table 2

Prevalence rate of the middle ear effusion (tympanometric findings)

Age (months)	Groups				Statistical Significance
	Experimental (n = 45)		Control (n = 45)		
	n	%	n	%	
6	42	93.3	41	91.1	$\chi^2 = 0.04$ $p = 0.9780$
12	41	91.1	43	95.6	$\chi^2 = 0.18$ $p = 0.9149$
24	20	44.4	38	84.4	$\chi^2 = 14.40$ $p = 0.0007$
30	30	66.7	32	71.1	$\chi^2 = 0.18$ $p = 0.9149$
36	28	62.2	29	64.4	$\chi^2 = 0.04$ $p = 0.9780$
42	29	64.4	27	60.0	$\chi^2 = 0.18$ $p = 0.9149$
48	25	55.5	28	62.2	$\chi^2 = 0.40$ $p = 0.8187$
54	26	57.8	29	64.4	$\chi^2 = 0.40$ $p = 0.8157$
60	24	53.3	26	57.8	$\chi^2 = 0.18$ $p = 0.9149$

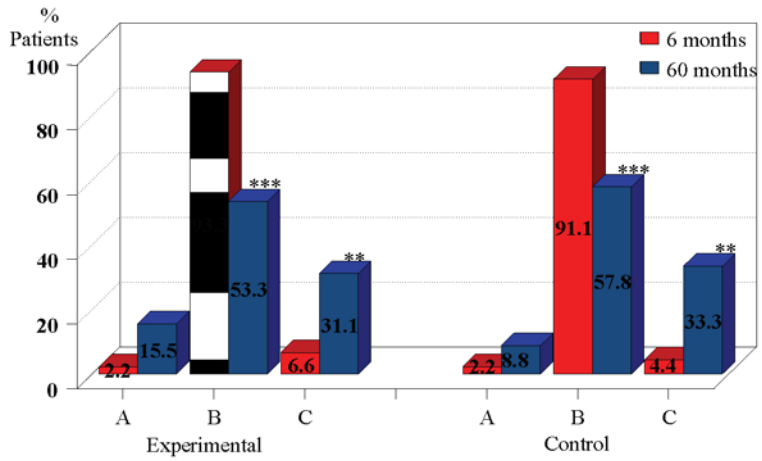

Fig. 2 – Prevalence rate of the middle ear effusion (tympanometric findings)
****, *** $p < 0.01$; 0.001 at the beginning and the end of the study.**

Table 3

Hearing threshold levels (Pure tone audiometry)

Age (months)	Groups								Statistical Significance
	Experimental, n (%)				Control, n (%)				
	20 dB	30 dB	40 dB	50 dB	20 dB	30 dB	40 dB	50 dB	
48	17 (38)	19 (42)	5 (11)	4 (9)	16 (31)	20 (44)	4 (9)	5 (11)	$\chi^2 = 0.04$ $p = 0.9780$
54	16 (36)	18 (40)	6 (13)	5 (11)	15 (29)	20 (44)	5 (11)	5 (11)	$\chi^2 = 0.04$ $p = 0.9780$
60	16 (36)	17 (38)	7 (16)	5 (11)	14 (29)	21 (47)	5 (11)	5 (11)	$\chi^2 = 0.18$ $p = 0.9149$

that in only 5 (5.6%) participants otoscopic findings were normal (NE), and in 85 (94.4%) the eardrum was opaque and with indistinct landmarks (OE). At the beginning of the study, the eardrum complications (CE) were not observed. Normal otomicroscopic findings (NE), which were very rare in both groups at the beginning of the study, were encountered more often over the course of time, so that at 36 months of age there were 5 (11%) in the experimental group, and 7 (16%) in the control group. On the other hand, the opaque eardrum with indistinct landmarks findings (OE), which

were, at the beginning of the study, in a very high percentage, came to 33 (73%) in the experimental and 3 (69%) in the control group at 48 months of age. Otomicroscopic findings with the eardrum complications, which did not exist at the beginning, started to show at the testing at 24 months of age in one case each in both groups (2.2%). Later on, this percentage slowly increased, without significant deviations between the experimental and control groups (Table 2). Normal otomicroscopic findings were considerably higher at the final exam at 60 months of age in both groups compared to the beginning of the study, so that there were 12 (27%) in the experimental group, and 11 (24%) in the control group, while the majority of both group participants, 27 (60%) in the group E, and 29 (64%) in the group C, were in the category of the opaque eardrum findings OE. Otomicroscopic findings indicating complications (CE) were detected in a small number of participants, 6 (13%) in the group E and 5 (11%) in the group C. The reason behind this is that smaller changes in the eardrum like atrophy or tympanosclerotic plaques were included in the opaque eardrum findings (OE).

At the beginning of the study, a total of 83 (92.2%) participants had tympanometric curve (type B), while 5 (5.5%) participants showed negative pressure values (type C), and only 2 (2.2%) participants had normal findings.

The findings in the control and experimental group were very similar. There were 42 (93.3%) participants in the experimental group and 41 (91.1%) participants in the control group with the tympanometric findings B (Figure 3). Significantly large number of the flat tympanometric curve findings (type B) at the beginning of the study in both groups (44.4%) participants which is a statistically significant difference in relation to the control group with 38 (84.4%) participants with the same findings. Such statistically significant difference appears only at this one evaluation, directly following the removal of the ventilation tubes in the participants of the experimental group. Already at the subsequent testing at 30 months of age the number of tympanograms B in the experimental group increased to 30 (66.7%) at the expense of the tympanogram C, which dropped to 7 (15.5%). In the control group, the number of participants with the tympanogram B dropped to 32 (71%), while the number of participants with the tympanogram C increased to 11 (24.4%). The number of normal tympa-nograms (A) was unchanged in both groups. The following period was characterized by a statistically significant symmetrical and gradual decrease in the number of participants with tympanograms B in both groups, and by an increase in the number of participants with tympanograms A and C, without statistically significant differences between the experimental and control groups, and this trend was continued until the end of the study.

After the completion of the study, a statistically significant decrease was seen in the percentage of the participants with the tympanometric findings B in both groups along with a statistically significant increase in the percentage of the participants with the tympanometric findings C, but there were no statistically significant differences between the experimental and control group.

Audiological assessment, which began with play audiometry at 36 months of age of the participants, was completed at 60 months of age, at the age when the findings

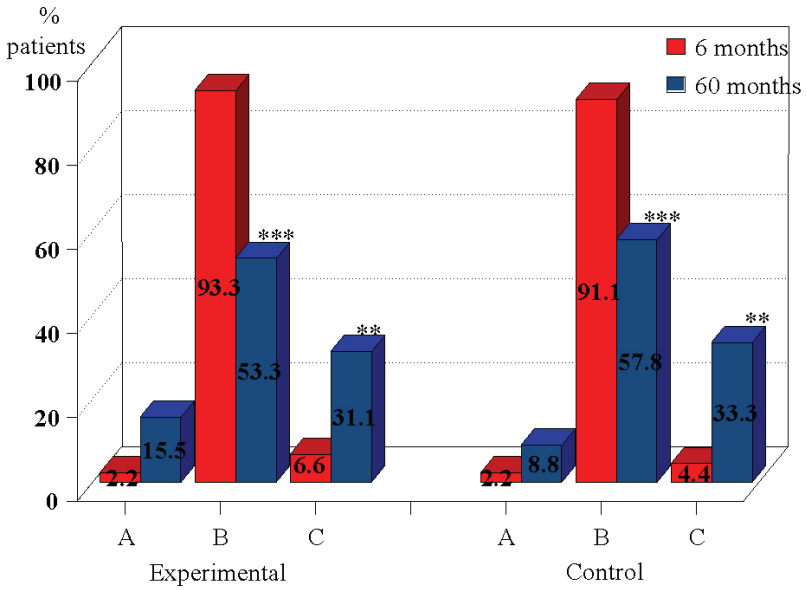

Fig. 3 – Tympanometric findings at the beginning and the end of the study.

decreased considerably over time. This decrease was particularly noticeable in the experimental group at 24 months of age evaluation performed after ventilation tubes removal, when tympanogram B was found in only 20 of pure tone audiometry can be interpreted as accurate. According to the final audiological findings there was no significant statistical difference between the experimental and control group, and the majority of participants in both groups

were within the normal field of hearing of 20 and 30 dB. (Table 3).

Discussion

Regarding chronic OME in children with congenital cleft palate, differences among authors are even more pronounced. The one thing all authors agree on is that OME in children with congenital cleft palate is almost universal and, depending on the author, the incidence varies between 85% and 97% [5–9]. This corresponds to the 92.2% of the tympanometric findings B in 90 participants of the 2 groups in our study. In addition, it is a common opinion that management of this disease is much more difficult in children with congenital cleft palate than in children without cleft. However, as there is no doctrinal approach to this disease, numerous differences in opinion on its treatment, depending on the age of patients, stage of the disease and clinical-audiological findings, still exist.

According to current trends, palatoplasty should be performed between 6 and 12 months of age [21, 22, 29], depending on the type of cleft, and early ventilation tubes insertion means their placement before or during palatoplasty.

Although objective parameters (tympanometry) undeniably demonstrate that the presence of effusion in the middle ear in children with cleft palate is pretty much universal, approach to management of this problem among the authors worldwide is often inconsistent. A group of authors consider that it is necessary to perform early routine placement of ventilation tubes in all cases of congenital cleft palate [30, 31]. Many authors favor the early placement of ventilation tubes in children with cleft palate as a way to prevent hearing loss and ensure speech development [32–34]. It is, also, stated that early ventilation tubes insertion in children with cleft palate is beneficial in short-term hearing loss prevention and long-term speech improvement [35]. Another group of authors emphasize a conservative treatment while a third group advocate for early unilateral insertion of the ventilation tube [30–36].

The arguments of the authors who recommend early routine insertion of the ventilation tubes are prevention of complications of chronic OME and enabling correct speech development and mastoid pneumatization. The advocates of the conservative treatment believe that the insertion of ventilation tubes, and especially potential reinsertions due to recurrence of the disease may result in a considerable damage to the eardrum as well as other problems, and that the complications of OME may develop independently of early ventilation tubes insertion since they are more related to the pathoanatomic substrate of cleft palate.

Conclusion

We can be fairly certain that children with congenital cleft palate will also present OME at birth and therefore instead of waiting for the onset of symptoms, the inclusion of otorhinolaryngologist care from birth is necessary.

A detailed analysis of the results of this multiyear study in which each child was observed for 5 full years at 6 month-time intervals, reveals that there were no statistically significant differences in the duration of the disease or in the development of complications between the two observed groups. Directly following the removal of the ventilation tubes, the experimental group demonstrated a temporary statistically significant improvement in the tympanometric findings, but the effusion was present again in the middle ear so the findings equalized with the control group. However, after several years, both groups showed a significant decrease in the presence of effusion in the middle ear as a result of the soft palate musculature strengthening and improved function of the Eustachian tube. Each child was also monitored by a speech pathologist and no significant differences in the speech development among the subjects were observed.

Based on all the tests that we performed, our conclusion as well as our recommendation is that early routine ventilation tubes insertion in children with cleft palate is not needed. However, it is absolutely necessary for those children to be closely monitored since their birth by an otorhinolaryngologist who will, based on his/her expertise and experience, reach a decision on optimal timing for the potential placement of the ventilation tubes in each particular case.

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Change in the incidence and anatomic distribution of colorectal adenoma and cancer over a period of 20 years – A single center experience

Promene u incidenci i anatomskoj distribuciji kolorektalnih adenoma i karcinoma u periodu od 20 godina – iskustvo jednog centra

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Abstract

Background/Aim. In recent years, many studies have demonstrated a proximal shift in the distribution of adenomas and colorectal cancers. The aim of this study was to investigate whether there are differences in the incidence and anatomical distribution of adenomas and colorectal cancers spanning a 20 year time gap. **Methods.** We performed a retrospective observational study of colorectal adenomas and cancers diagnosed during total colonoscopy in a high volume tertiary care facility in two 1-year periods of time – 1990 and 2010. **Results.** During the analyzed period, 4,048 colonoscopies were performed, 1,148 were performed in 1990 and 2,900 were done in 2010. The study included 466 patients with adenomas and 121 patients with colorectal cancers. Frequency of proximal adenoma changed from 16.5% to 32.7% ($p < 0.001$). By analyzing colonoscopies in 2010, an increase in the incidence of adenomas compared to 1990 was noticed. The number of adenomas sized 0–5 mm rose from 32.8% to 56.9% ($p < 0.001$). Frequency of colon carcinoma changed from 5.3% to 2.0% ($p < 0.001$). Incidence of cancers in the proximal colon rose from 21.3% to 48.4% ($p = 0.002$). A higher incidence of cancers in the proximal colon and a lower incidence of distal cancers were observed, while no difference was observed in the incidence of rectal cancers. **Conclusion.** Presence of proximal colon adenoma and cancer is higher, while the overall incidence of colon cancer is lower. This finding should be taken into account when planning the screening for colorectal cancer.

Key words:
colorectal neoplasms; adenoma; carcinoma; diagnosis; incidence.

Apstrakt

Uvod/Cilj. Poslednjih godina mnoge studije su ukazale da je došlo do promene u distribuciji adenoma i karcinoma debelog creva, odnosno da se povećava zastupljenost proksimalnih lezija. Cilj ove studije je bio da se utvrdi postoji li razlika u zastupljenosti i distribuciji adenoma i karcinoma debelog creva u dva vremenska perioda sa razlikom od 20 godina. **Metode.** Sprovedena je retrospektivna opservaciona studija o kolorektalnim adenomima i karcinomima koji su dijagnostikovani kolonoskopski u tercijarnom zdravstvenom centru tokom 1990. i 2010. godine. **Rezultati.** Od ukupno 4,048 kolonoskopija izvedenih tokom dva analizirana perioda 1,148 je urađeno tokom 1990. a 2,900 je urađeno tokom 2010. godine. Studijom je obuhvaćeno 466 bolesnika sa adenomima i 121 bolesnik sa karcinomom debelog creva. Zastupljenost proksimalnih adenoma se promenila sa 16.5% na 32.7% ($p < 0.001$). Analizirajući kolonoskopije iz 2010. godine, uočen je porast incidencije adenoma u poređenju sa nalazom iz 1990. godine. Broj adenoma veličine 0–5 mm je porastao sa 32.8% na 56.9% ($p < 0.001$). Učestalost karcinoma kolona je promenjena sa 5.3% na 2.0% ($p < 0.001$). Zastupljenost karcinoma u proksimalnim partijama debelog creva je porasla sa 21.3% na 48.4% ($p = 0.002$). Uočena je veća incidenca karcinoma u proksimalnom kolonu i manja incidenca distalih karcinoma kolona, ali ne i razlika u incidenci kod rektalnog karcinoma. **Zaključak.** Pokazana je veća učestalost proksimalnih adenoma i kancera, dok je ukupna učestalost karcinoma kolona manja. Ovaj zaključak je značajan radi sprovođenja skrininga za kolorektalni karcinom.

Ključne reči:
kolorektalne neoplazme; adenom; karcinom; dijagnoza; incidenca.

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Introduction

Colorectal cancer (CRC) is the second most common cancer in women and the third in men worldwide. According to the World Health Organization GLOBOCAN database in 2012, approximately 1.4 million new cases of CRC were diagnosed and 694,000 people died as a result of CRC [1]. Cancer development most commonly begins with adenoma formation [2, 3] and therefore adenoma detection and removal is paramount [4]. Previous studies have shown that adenomas larger than 11 mm have a higher malignant potential [5, 6]. The incidence of CRC increases with age [7]. In recent years, many studies have indicated that there has been a change in the distribution of adenomas and CRC, with a proximal shift of the lesions [8–19]. This knowledge significantly affects colonic screening programs.

The current screening options for bowel cancer include fecal occult blood test (FOBT) and endoscopic assessments of the colon, including flexible sigmoidoscopy and total colonoscopy [4]. FOBT is primarily a non-specific method, while flexible sigmoidoscopy allows one to visualize only the distal parts of the colon, thus potentially leaving proximal lesions undiscovered [20]. The combination of FOBT with flexible sigmoidoscopy will diagnose 25% of CRCs and advanced neoplasia (adenomas over 1 cm, at least 25% villous, high-grade dysplasia, or invasive cancer) [21]. Consequently, total colonoscopy is favored as a method of choice for screening [22].

The aim of this study was to determine whether there are differences in the incidence and distribution of adenomas and CRC comparing the years 1990 and 2010.

Methods

We performed a retrospective observational study of colorectal adenomas and cancers diagnosed during total colonoscopy in the Clinic for Gastroenterology and Hepatology, Clinical Center of Serbia, Belgrade, Serbia, during two one-year periods of time: 1990 and 2010.

Two different databases were created during the study. The adenoma database included personal data, localization, number and size. According to size, adenomas were categorized into 0–5 mm, 6–10 mm, 11–20 mm and > 20 mm. The cancer database included personal data, localization and indication for examination. The data was collected from procedure reports.

Only colonoscopies reaching the cecum were included. Incomplete colonoscopies for any reason, namely inadequate patient preparation, intolerance, or tortuous colon, were excluded. Patients who met the criteria for hereditary nonpolyposis CRC syndrome and familial adenomatous polyposis, or those with a past medical history of CRC, ulcerative colitis and Crohn's disease, were excluded from the study.

Lesions located between the cecum and the splenic flexure, were classified as proximal, while lesions arising in the descending colon, sigmoid and rectum were classified as distal.

Certified gastroenterologists using standard endoscopic equipment performed all examinations. Colonoscopes used in 1990 were CF-20HI, and in 2010 were CF-Q180AL Olympus Optical Co., Tokyo, Japan. Additional technologies such as narrow band imaging were not used.

The bowel preparation regimen, four liters of polyethylene glycol (PEG) solution, was similar in the two periods. Sedation using intravenous midazolam or intravenous propofol was administered on a case-to-case basis and was performed by an anesthesiologist.

For continuous variables, we employed the Kolmogorov-Smirnov test to assess normality. For normal variables, means and standard deviations were reported. For non-normal data, medians and interquartile ranges were determined. χ^2 test was used to assess the differences between the two periods. Independent-sample *t*-test was used to assess differences between the means in the two periods. *P* values less than 0.05 were considered as statistically significant.

Results

During the analyzed period, 4,048 colonoscopies were performed, 1,148 were performed in 1990 (first period) and 2,900 were done in 2010 (second period). The study included 466 patients with adenomas (Table 1) and 121 patients with colorectal cancers (Table 2).

Table 1

Demographic and clinical characteristics of patients diagnosed with adenomas

Characteristics of patients	1990	2010	*p*
Number of patients	100	366	
male, n (%)	62 (62)	206 (56.3)	0.143
female, n (%)	38 (38)	160 (43.7)	
Female-to-male ratio ≥ 70 years	1	0.52	
Female-to-male ratio < 70 years	0.57	0.88	
Age (years), mean (range)	58 (34–82)	61 (19–88)	0.113
Adenomas detected by size, %			
0–5 mm	32.8	56.9	< 0.001
6–10 mm	39.5	28.8	0.063
11–20 mm	14.3	9.6	0.194
> 20 mm	13.4	4.7	0.001
Adenomas detected, %			
adenoma detection rate	14.02	14.69	
total number of adenomas	127	678	
proximal adenomas	16.5	32.7	< 0.001

Table 2

Demographic and clinical characteristics of patients diagnosed with cancers

Characteristics of patients with cancers	1990	2010	*p*
Number of patients, n	61	60	
male, n (%)	37 (60.7)	33 (55)	0.529
female, n (%)	24 (39.3)	27 (45)	
Female-to-male ratio ≥ 70 years	0.71	0.56	
Female-to-male ratio < 70 years	0.63	1.05	
Age (years), mean (range)	61 (21–84)	66 (19-83)	0.626
Indication for examination, n (%)			
positive FOBT	0 (0)	3 (5)	0.77
rectal bleeding	35 (57.4)	18 (30)	0.002
positive family history	0 (0)	5 (3)	0.021
colopathy	25 (41)	18 (30)	0.207
other	21 (34.4)	25 (41.6)	0.412
Cancers detected			
total number of cancers, n	61	60	< 0.001
proximal cancers, %	21.3	48.4	0.002

FOBT – fecal occult blood test.

In 1990, 100 patients were found to have an adenoma, in contrast to 366 in 2010. In men, adenomas were more common than in women, but without a statistically significant difference in the two observed time periods (Table 1). Median age of the patients was higher in the second than in the first period (58 compared to 61) but it was not statistically significant ($p = 0.113$). Female-to-male ratio is also shown in Table 1. The number of male and female patients by age intervals for 1990 and 2010 is shown in Figure 1.

By analyzing colonoscopy reports in 2010, an increase in adenomas was observed when compared to 1990 (Figure 2). The number of adenomas sized 0–5 mm rose from 32.8% to 56.9%, which was highly statistically significant ($p < 0.001$). A decline in the number of adenomas sized 6–10 mm (from 39.5% to 28.8%), 11–20 mm (from 14.3% to 9.6%) and > 20 mm (from 13.4% to 4.7%) was also noticed (Table 1). The frequency of proximal adenomas changed from 16.5% to 32.7%, which proved to be highly statistically significant ($p < 0.001$).

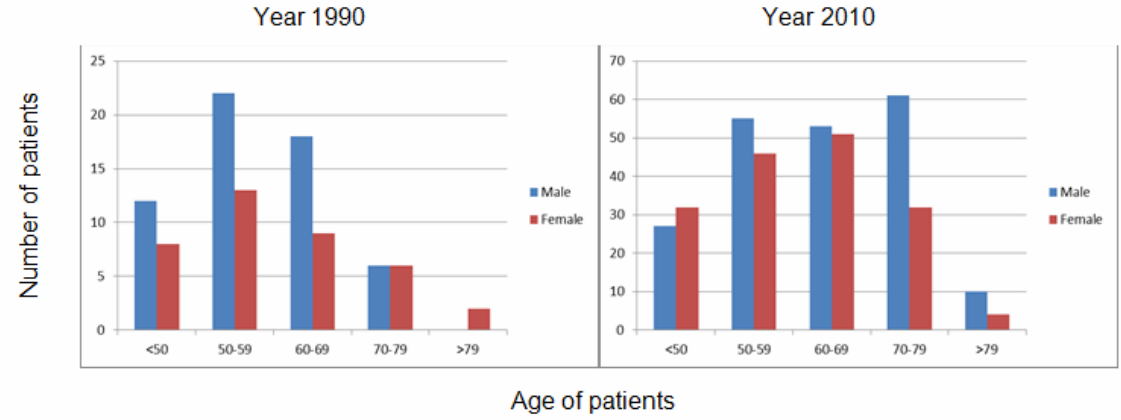

Fig. 1 – Adenomas – Number of male and female patients in age groups.

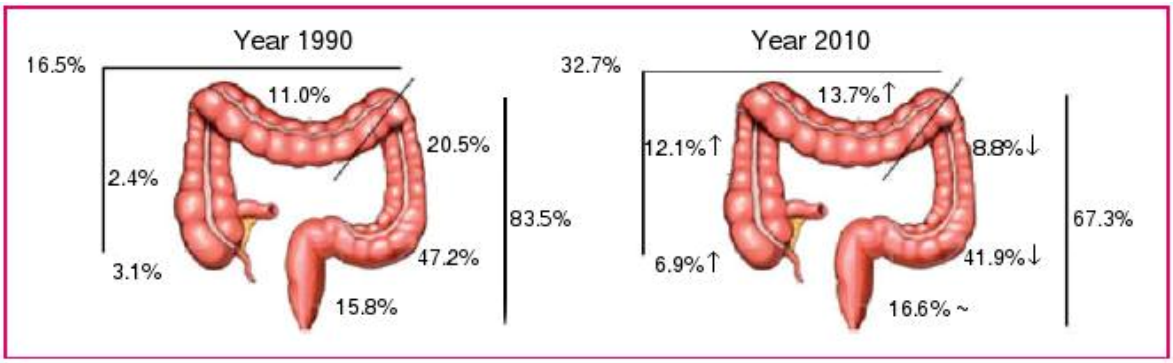

Fig. 2 – Distribution of adenomas according to colon segment.

In 1990, 61 cancers where diagnosed, and in 2010, 60 were discovered, which was statistically significant ($p < 0.001$). Males were diagnosed more often, but with no significant difference between the two time periods (Table 2). Median age of the patients was higher in the second period (61 compared to 69), which was not statistically significant ($p = 0.626$). Female-to-male ratio is shown in Table 2. The number of male and female patients by age intervals for 1990 and 2010 is shown in Figure 3. Analyzing the underlining indications for colonoscopy in 2010, colonoscopies were performed more often because of positive FOB test and family history, which is in contrast to 1990, where colonoscopies were mostly performed due to rectal bleeding (Table 2). The incidence of cancers in the proximal colon rose from 21.3% to 48.4%, which proved to be statistically significant ($p = 0.002$).

In 2010, there was a higher incidence of cancers in the proximal colon and a lower incidence of distal cancers observed, while no difference was observed in incidence of rectal cancers (Figure 4).

Discussion

Colorectal cancer is the fourth most common cause of cancer-related death [1]. According to epidemiological data, the World Health Organization Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) database, in 2012 there is a tenfold variation in the incidence of colorectal cancer worldwide, with the highest values seen in Australia and New Zealand and the lowest values observed in West Africa [1]. Mortality, according to the same study, was highest in Central and Eastern Europe and lowest in West Africa [1]. In recent decades screening techniques for the diagnosis and removal of adenomas (precancerous lesions) as well as for detection of colon cancer in early stages have been developed. Despite the rapid development of these screening programs, by comparing the epidemiological data from 2008 and 2012, an increase in number of new cases, as well as increased mortality rates from colorectal cancer were observed [1, 23]. The current screening options are: analysis of stool for occult blood and endoscopic assessment of the colon, including flexible sigmoidoscopy and total colonoscopy [4].

In this retrospective study, we looked at the incidence and anatomical distribution of adenomas and cancers in various segments of the colon during two 1-year periods (in 1990 and 2010) in our center.

We found a noticeable increase in the occurrence of proximal adenomas during 2010, when compared to 1990. Our results are consistent with studies conducted by de Oliveira et al. [8] who analyzed the topographic distribution of

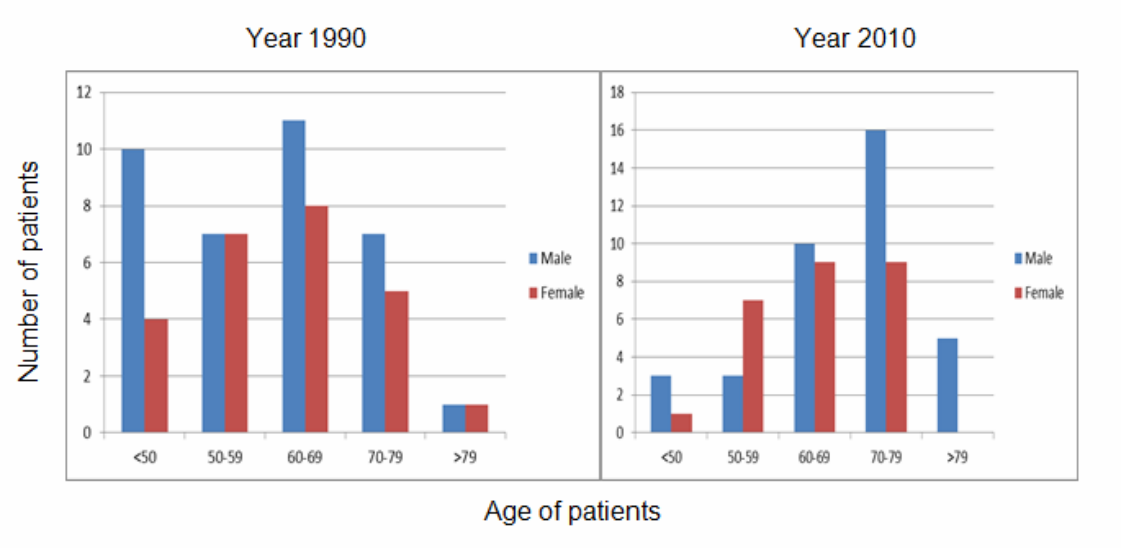

Fig. 3 – Carcinomas – Number of male and female patients in age groups.

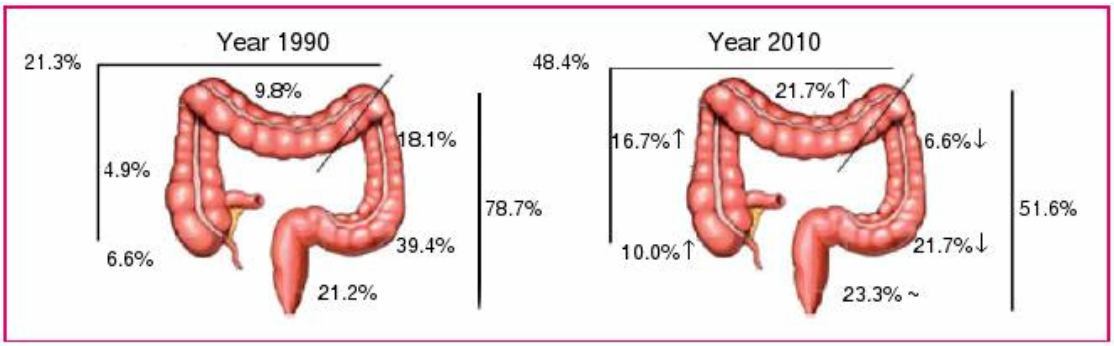

Fig. 4 – Distribution of cancers according to colon segment.

adenomas during two annual periods (2003 and 2012). Their results showed an increase in the presentation of proximal adenomas from 30.6% to 38.8%. By analyzing colonoscopies done in the fifteen-year period from 1996 to 2011, a Romanian study by Visovan et al. [10] presented similar results (from 9.36% to 17.12%). Comparable results were shown by a study conducted in Italy by Fenoglio et al. [15] who analyzed colonoscopies performed in the period 1997–2006 (from 19.2% to 26%). Chen et al. [14] from China also found a proximal shift in adenoma location in the period of 1990–2009 in the population under the age of 50 years (from 15.01% to 20.99%). A study conducted in Italy by Parente et al. [12] showed that in the population aged 60 years and over, the presence of proximal adenomas was higher (37%) when compared to patients aged 50–59 years (29%). In Korea, Kim et al. [19] demonstrated that with the increasing age there was an increase in the incidence of proximally localized adenomas.

Increasing incidence of colorectal cancers in the proximal parts of colon was also been presented in many previously published studies, and is supported in our study. A study carried out in Japan by Iida et al. [9] analyzed patients with colorectal cancers in the period 2005–2012, and found that aging increases the number of proximal cancers and that this difference was most pronounced among women. Seydaoğlu et al. [11] showed that in the period of 1993–2008 the incidence of proximal cancers changed (from 19.8% to 25.6%). In an Italian study conducted by Caldarella et al. [13] the incidence of proximal cancers increased during the observed period of 1985–2005. In the Netherlands, Mensink et al. [16] examined patients from 1981 and 1996 and found that the incidence of proximal cancer changed from 25% to 37%. In Japan, Takada et al. [17] showed that in the period of 1974–1994 there was an increase in proximal cancer in women (up from 44.2% to 49.7%). In the USA, Cucino et al. [18] observed distributions of colorectal cancer in African Americans and Caucasians in the period of 1970–2000. The results showed that there was an increased incidence of proximal cancers in both racial groups.

An explanation for this shift to proximal adenoma and colon cancer is not entirely clear. The reason for the reduction in the incidence of advanced polyps and carcinomas, as well as proximal shift of adenomas and carcinomas may be explained by an increase in the availability of the colonoscopy. Namely, the colonoscopy is more indicated, and polypectomy is more frequently carried out in the early stages of the evolution of polyps. Another reason might be the fact that the flexible rectosygmoidoscopy is accessible examination than colonoscopy, and provides examination of the distal colon. Examination of the proximal colon can be difficult due to technical difficulties or insufficient bowel preparation. Lieberman et al. [24] described that endoscopist more often overlooked proximal than distal lesion.

Recently published studies have shown that the physiological microflora of the colon have an impact, too. In fact, several studies have shown that there is a difference in microflora of healthy people and those with adenomas or colorectal cancers. In patients with adenomas an increased abundance of *Bacteroidetes* [25, 26], *Firmicutes*, *Proteobacteria* [27] and *Fusobacterium* [26, 28] was observed, while *Lactobacillus* and *Eubacterium* were associated with having a protective role [26]. In patients with colorectal cancers, previous studies showed an increase in the number of bacteria from the genera: *Bacteroides-Prevotella*, *Enterococcus*, *Escherichia*, *Shigella*, *Klebsiella*, *Streptococcus*, *Peptostreptococcus*, *Fusobacterium* [27], along with *Microbacterium* and *Anoxybacillus* [29]. Zeller et al. [30] have shown that in patients with colorectal cancers there was an increase in number of *Proteobacteria* and a decrease in number of *Actinobacteria*.

It is believed that through certain receptors and activation of certain signaling pathways microflora participate in the formation of adenomas and colorectal cancers [26, 27, 31]. The best evaluated of these is the route via toll-like receptors (TLR) that recognize microbial signal molecules-pathogen-associated molecular patterns (PAMPs). TLR activation initiates a sequence of intracellular signals leading to the formation of pro-inflammatory cytokines, the collapse of apoptosis regulation and uncontrolled cell proliferation, which together leads to cancer formation [27, 31].

Dietary habits also influence colorectal cancer development. Gut bacteria metabolize proteins and form nitrosamines, thereby promoting carcinogenesis, leading to the conclusion that an increased dietary intake of protein in the form of red meat presents a risk factor for the development of adenomas and cancers of the colon [26, 32].

Genetic studies showed that proximal cancers are most commonly associated with microsatellite instability (MSI), and that distal cancers are associated with chromosomal instability (CIN) and chromosome 5q, 17p and 18q [33].

Dejea et al. [34] showed that tumors in the ascending colon and hepatic flexure were biofilm-positive in 87% of cases whereas tumors located in the transverse and descending colon displayed biofilm-positivity in only 13%. Biofilms are defined as aggregations of microbial communities encased in a polymeric matrix that adhere to either biological or non-biological surfaces. The authors concluded that principal coordinates analysis revealed that biofilm communities on paired normal mucosa, distant from the tumor itself, cluster with tumor microbiomes as opposed to biofilm-negative normal mucosa bacterial communities also from the tumor host. Therefore, colon mucosal biofilm detection may predict increased risk for the development of sporadic CRC.

Comparing the female-to-male ratio in patients with adenomas and colorectal cancers in the two periods, we found that in patients older than 70 years there was a decline in the ratio as opposed to patients younger than 70 years, where there was an increase. Iida et al. [9] showed that in age groups younger than 70 years, the female-to-male ratio is relatively low, but it increased in age groups older than 70 years. In our study, colonic adenomas and cancers were equally found in men during both periods; however, there was an increase in the distribution of women in 2010 when compared to 1990. This increase in the number of women suffering from colorectal adenoma and cancer can be explained by their change in lifestyle habits and the increasing number of women who are examined and subsequently diagnosed, given the fact that there was an initial resistance many women felt towards

colonoscopy, which was seen as potentially painful and embarrassing [35].

In 2010, we found that there was an increase in the number of adenomas sized 0–5 mm compared to 1990. Another study, which analyzed the size of adenomas, had different results. De Oliveira et al. [8] showed that the number of adenomas sized ≥ 1 cm increased (from 10.8% to 19.8%) during the time under investigation. In our study, the number of adenoma size 6–10 mm, 11–20 and > 20 mm decreased. Adenoma detection rate (ADR) is an important parameter for colonoscopy. Studies have shown that with an increase in ADR, there is a drop in the risk of diagnosis of advanced stage colorectal cancer [36]. In our study, ADR remained at the same level in both periods (14.02% in 1990 and 14.69% in 2010).

By analyzing the indications for colonoscopy, we noticed that in both periods the most common indications were rectal bleeding and colonic discomfort. The incidence of rectal bleeding is on the decline, while the incidence of fecal occult blood testing is on the rise, which means that more and more affected patients are detected in early stages. Rectal bleeding is the most common late manifestation of colorectal cancer and as such, it further complicates the treatment of these patients [37].

Conclusion

On the basis of our results along with similar studies, we can conclude that the presence of proximal colon adenoma and cancer is increasing. This finding should be taken into account during the planning of CRC screening methods. Total colonoscopy should be employed over other methods. Future studies must focus on resolving the causal link between physiological microflora and the increased incidence of proximal colon cancer.

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The correlation between the level of 25-hydroxyvitamin D [25(OH)D] and residency of multiple sclerosis patients in Montenegro – higher levels only in men in the north of the country

Povezanost nivoa 25-hidroksivitamina D [25(OH)D] i mesta stanovanja bolesnika sa multiplom sklerozom u Crnoj Gori – viši nivoi samo kod muškaraca na severu zemlje

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Abstract

Background/Aim. Multiple Sclerosis (MS) is a chronic neurological disease associated with low serum levels of 25-hydroxyvitamin D [25(OH)D]. The aim of this study was to determine the association between serum levels of 25(OH)D and the latitude as well as clinical MS severity and progression expressed by expanded disability status scale (EDSS) and multiple sclerosis severity score (MSSS). **Methods.** A total of 196 patients, from North and South of Montenegro, aged 18 to 65 years, with confirmed diagnosis of MS were recruited for the study. Serum samples were collected for 25(OH)D measurement. Control group consisted of 196 health controls, randomly selected from medical staff employed in health centers from three cities in North and Clinical Centre of Montenegro from the South. **Results.** The serum levels of 25(OH)D were significantly lower in MS patients compared to controls ($p < 0.001$). The serum levels of 25(OH)D were significantly different in regard to gender, with women showing lower levels. Although in the entire group of patients there was no statistical correlation between the levels of 25(OH)D and their residence, the significantly higher levels of 25(OH)D were detected in men from the North compared to women. The course of the disease had an impact on the 25(OH)D serum levels. 25(OH)D levels also significantly correlated with clinical parameters of both, disability (Spearman's r = -0.23, p = 0.001) and progression (Spearman's r = -0.25, p = 0.0004) of MS. **Conclusion.** Serum levels of 25(OH)D were associated with disability and progression in MS patients. Lower levels of 25(OH)D were detected in female patients from the North. The low level of 25(OH)D cannot be solely explained with unfavorable latitude and insufficient sun exposure, therefore further genetic analysis is needed.

Key words:
multiple sclerosis; vitamin d; geography, medical; severity of illness index; disease progression; sex factors; montenegro.

Apstrakt

Uvod/Cilj. Multipla skleroza (MS) je hronična neurološka bolest, povezana s niskim serumskim nivoom 25-hidroksivitamina D [25 (OH)D]. Cilj rada bio je da se ispitaju povezanost nivoa 25(OH)D u serumu sa geografskom širinom mesta boravka obolelih i onesposobljenošću i progresijom MS, izraženim preko proširenog skora stepena onesposobljenost (EDSS) i stepena spasticiteta obolelih od multiple skleroze (MSSS). **Metode.** U studiju je bilo uključeno ukupno 196 bolesnika sa severa i juga Crne Gore, starosti između 18 i 65 godina, sa definitivnom dijagnozom MS. Od svakog pojedinačnog bolesnika je na dan prijema uziman serum za analizu nivoa 25(OH)D. Kontrolna grupa se sastojala od 196 zdravih ispitanika, koji su metodom slučajnog uzorka birani među medicinskim osobljem tri bolnice sa severa i Kliničkog centra Crne Gore, sa juga zemlje. **Rezultati.** Nivoi serumskog 25(OH)D bili su značajno niži kod bolesnika sa MS u odnosu na kontrolnu grupu ($p < 0.001$). Nivo 25(OH)D značajno se razlikovao u odnosu na pol, pri čemu su kod žena registrovani niži nivoi. Mada kod svih ispitanika nije zabeležena statistički značajna korelacija između nivoa 25(OH)D i prebivališta, nađen je značajno viši nivo 25(OH)D kod muškaraca sa severa u odnosu na žene. Tok bolesti je uticao na nivo 25(OH)D u serumu. Nivo 25(OH)D bio je u značajnoj korelaciji sa kliničkom nesposobnošću (Spearmanov r = -0.23, p = 0.001) i progresijom bolesti (Spearmanov r =

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-0.25, p = 0.0004). **Zaključak.** Serumske koncentracije 25(OH)D povezane su sa nesposobnošću i napredovanjem bolesti kod bolesnika sa MS. Niži nivoi 25(OH)D nađeni su kod žena sa severa. Nađene niske koncentracije 25(OH)D ne mogu se objasniti samo geografskom širinom i nedovoljnim izlaganjem suncu, zbog čega su potrebna dalja genetska istraživanja.

Ključne reči:
multipla skleroza; vitamin d; geografija, medicinska; bolest, indeks težine; bolest, progresija; pol, faktor; crna gora.

Introduction

Multiple sclerosis (MS) is a complex neurological disorder which etiology is still unknown. Researchers in this area believe that the interaction of several different factors (genetic predisposition and environmental factors) may be involved. Although heritage plays an important role in the pathogenesis, migration and other studies have shown that the environment is very important for its development.

Epidemiological studies suggest that living in certain geographical areas and/or migration in these areas before the age of 15 increases the incidence of MS. The incidence of MS is low in the tropics and increases with distance from the equator towards both hemispheres [1, 2]. Thus, under-exposure to UV rays can predispose a person to develop MS later on [3]. This hypothesis has led to an extensive research of potential role of vitamin D in MS. The possible relationship is further confirmed by the observation of a lower risk of developing MS in areas with high consumption of fatty fish rich in vitamin D, despite the unfavorable latitude [4]. Over the last 50 years there has been a dramatic increase in the incidence of not only MS but also other autoimmune and immune-mediated diseases. This increase is presumably caused by the changes in our environment, rather than genetic changes, which would take much longer to manifest themselves [5]. Dobson et al. [6] in their study indicated more clinical relapses and MRI activities in the spring/summer and less in the autumn/winter season in the northern hemisphere [6]. The reverse case was observed in the southern hemisphere [7].

In addition to its fundamental role in the homeostasis of calcium and bone metabolism, there is growing evidence that vitamin D has additional, immunoregulatory function, making it a promising candidate in the pathogenesis and treatment of autoimmune diseases like MS [8].

In patients already diagnosed with MS, a number of studies suggested that the consistently higher serum vitamin D levels were associated with the favorable course of the disease [9–11]. In a small Finnish study, lower concentration of 25-hydroxyvitamin D [25(OH)D] were measured in patients having their first relapse compared to healthy individuals in the control group [9]. The concentration of 25(OH)D were significantly lower during relapse compared to periods of remission, which could indicate the regulatory role of vitamin D in the disease activity [12].

The aim of this study was to assess the possible difference between 25(OH)D serum levels in MS patients from north and south of Montenegro and to investigate the association between 25(OH)D serum levels and disability in MS patients.

Methods

A total of 196 patients, aged 18 to 65 years, with clinically and magnetic resonance imaging (MRI) confirmed MS, using McDonald criteria [13] were recruited from consecutive patients admitted to the Neurology Outpatient Clinic in the period 2013–2015. Patients were coming from the southern, northern and central areas of the country. Twenty-four patients from the central area were grouped together with the patients from the North due to very similar amount of registered sunny days in both parts of the country. Written informed consent was obtained from all study participants, and the study was approved by the local ethics committee.

Blood for the analysis was taken from each patient on the day of admission (during late spring and summer – late April till the end of August 2013, 2014 and 2015). The blood samples were taken from patients exclusively during remission. Samples were shielded from direct light after collection and stored at -20°C. Chemiluminescence immunoassay (COBAS-e601, Rosche) was used to determine the 25(OH)D levels. According to Smolders et al. [12] it was proposed that a 25(OH)D concentration of 70–80 nmol/L is adequate for a normal calcium metabolism [12]. The patients recruited for the study were not on any kind of vitamin D supplementation prior to blood sampling.

The control group consisted of 116 subjects from the North and 80 subjects from the South of Montenegro. They were collected among random sample of medical staff employed in health centers from three cities in North (Berane, Bijelo Polje and Pljevlja) and from Clinical Centre of Montenegro (Podgorica) from the South. They had no prior or current history of any known disease (on the sampling day) and they were age matched to MS patients.

Demographic characteristics of MS patients and clinical variables regarding MS phenotype were retrieved from our patient database and included sex, age, date of birth, residence as well as relapse remitting (RR) MS, secondary progressive (SP) MS and primary progressive (PP) type of MS. Patients with PP MS were excluded from further analysis due to a very small number of patients (only two). Database also included age of disease onset, imaging results (brain and spine MRI), spinal tap results and isoelectric focusing of cerebrospinal fluid and serum. Expanded Disability Status Scale (EDSS) was scored on the day of admission prior to blood sampling [14]. Disease severity was estimated using the Multiple Sclerosis Severity Score (MSSS) [15] which corrected the EDSS for disease duration at the moment when blood samples were taken.

Official data regarding the number of sunny days for the cities from the North, South and Central parts of Monte-

negro were obtained from the Institute of Hydrometeorology and Seismology of Montenegro [16]. Data included the average amount of sunshine during the period from 1976–1985, when our participants were born, and during 2013–2015 when study was being conducted.

Statistical analysis

Statistical software (Stat Soft Inc, version 8) was used for statistical analysis. Mean values are provided with standard deviation (± SD) and mean differences (MD) with standard error (± SD). Normality test was performed using Kolmogorov-Smirnov test with Lillieform's correction for all continuous variables. As the distribution of investigated variables was skewed, the Mann-Whitney *U* test was used for the comparison of differences between two independent variables. The Spearman's rank correlation test was used to investigate the correlation of given variables. A 2-sided *p* value < 0.05 was considered statistically significant.

Results

Description of the study population is presented in Table 1. The 137 patients with RR and 59 patients with SP form of MS were included in the study. One hundred and sixteen patients (80 females and 36 males) were from the North and 80 (62 females and 18 males) from the South of Montenegro.

According to the official data from the Institute of Hydrometeorology and Seismology of Montenegro, there were two time periods (1976–1985 and 2013–2015) when the average number of the sunny days in the north was significantly lower than in the south (53.2 ± 22.9 *vs* 106.5 ± 9.8, Mann-Whitney *U* test $p < 0.01$ and 56.4 ± 24.9 *vs* 109.2 ± 24.4, Mann-Whitney *U* test $p < 0.01$, respectively). The measurements of sunny days were conducted in 5 cities in the south and 9 cities in the north. There was no significant difference in the number of sunny days between the two periods of time (1976–1985 vs 2013–2015) neither in the south (106.5 ± 9.8 vs 109.2 ± 24.4, *p* non significant) nor in the north (53.2 ± 22.9 *vs* 56.4 ± 24.9, *p* non significant).

The serum levels of 25 (OH) D were significantly lower in MS patients compared to controls ($p < 0.001$) as shown in Table 2. The controls (141 female and 55 male, average age: 42.3 ± 11.6) were matched to the patients according to the age. Vitamin D significantly correlated with age in controls ($p = 0.004$), but not in MS patients ($p = 0.30$). The serum 25(OH)D was significantly different in regard to gender with women showing lower levels in both, MS patients and controls (Table 2).

Table 1

Clinicodemographic characteristics of the multiple sclerosis (MS) patients

Parameter	Patients		
	MS total, (n = 196)	RR MS, (n = 137)	SP MS, (n = 59)
Age (years), mean ± SD	41.2 ± 10.9	38.0 ± 9.7	48.5 ± 9.9
Gender (female/male), n	142/54	98/38	44/16
Disease onset age (years) , mean ± SD	31.3 ± 9.8	30.6 ± 9.5	32.7 ± 10.5
Disease duration (years) , mean ± SD	12.2 ± 16.2	10.0 ± 17.0	17.3 ± 13.2
EDSS, mean ± SD	3.7 ± 1.9	2.8 ± 1.2	5.5 ± 1.7
MSSS, mean ± SD	5.2 ± 2.3	4.7 ± 2.2	6.1 ± 2.1

Values of continual parameters are presented as mean ± standard deviation (SD); n – number of subjects; EDSS – expanded disability status scale; MSSS – MS severity score; RR MS – relapse remitting MS; SP MS – secondary progressive MS.

Table 2

Serum levels of 25-hydroxyvitamin D [25(OH)D] in the study participants

Subjects	n	Vitamin D (nmol/L)	*p* (M-W U Test)
Controls, total	196	61.24 ± 24.94	$< 10^{-6}$***
Patients, total	196	41.80 ± 27.51	
Controls gender			
female	141	57.23 ± 19.62	0.0002**
male	55	71.72 ± 33.24	
Patients gender			
female	142	38.61 ± 26.24	0.01 *
male	54	49.83 ± 29.74	
Controls origin			
North Montenegro	116	63.93 ± 27.15	0.07
South Montenegro	80	57.29 ± 20.82	
Patients origin			
North Montenegro	116	44.07± 30.16	0.40
South Montenegro	80	38.76 ± 23.12	
Patients, type of MS			
RR	137	45.11 ± 28.95	0.007**
SP	59	34.12 ± 22.23	

Vitamin D levels are presented as mean ± standard deviation (SD); MS – multiple sclerosis; n – number of subjects; RR MS – relapsing-remitting MS; SP MS – secondary progressive MS; M-W *U* test – Mann-Whitney *U* test; * – statistical significance when $p < 0.05$;

**** – statistical significance when $p < 0.01$; *** – statistical significance when $p < 0.001$.**

The significantly lower vitamin D serum levels were registered in patients with SP MS, compared to RR MS (Table 2).

Although the entire group of patients had no statistically significant correlation among the 25(OH)D levels and their residence (divided by latitude 42′38″ north and south), the significantly higher levels of 25(OH)D were detected in men from the north compared to women (Figure 1a). In the south, the 25(OH)D levels were similar in both men and women (Figure 1b). The same relation was found between levels of 25(OH)D and residence, by latitude, in controls. Only in the north, men (n = 36) had significantly higher 25(OH)D compared to women (n = 80) (77.27 ± 33.93 mmol/L, *vs* 57.93 ± 21.10 mmol/L, respectively, M-W *U* test $p = 0.0006$).

Vitamin D levels also significantly correlated with clinical parameters of both, disability (EDSS, Spearman's r = -0.23, $p = 0.001$) and progression (MSSS, Spearman's r = -0.25, $p = 0.0004$) of MS in entire patient group. The significant correlation with MSSS was found in the north (MSSS, Spearman's r = -0.22, $p = 0.02$) and the south groups (MSSS, Spearman's r = -0.25, $p = 0.03$) and in women (MSSS, Spearman's r = -0.32, $p = 0.0002$), but not in men (MSSS, Spearman's r = -0.14, $p = 0.3$).

Discussion

In this study significantly lower serum levels of 25(OH)D were detected in MS patients compared to controls. Similar results were obtained in a study by Soilu-Hänninen et al. [17] who compared the levels of vitamin D in patients with MS with healthy controls. They found the level of vitamin D to be significantly lower during the summer among MS patients compared to controls, while the difference between the groups was not found during the winter period. Other studies that investigated the correlation between the MS phenotype and levels of vitamin 25(OH)D reported that 25(OH)D serum levels were significantly lower in the RR patients compared to the healthy controls [18, 19].

We found that women both in patient and in control group had significantly lower 25 (OH) D serum levels than men. Kragt et al. [9] concluded that higher levels of vitamin D in women reduced the risk of MS, while the lower level was negatively correlated with EDSS findings in the study group.

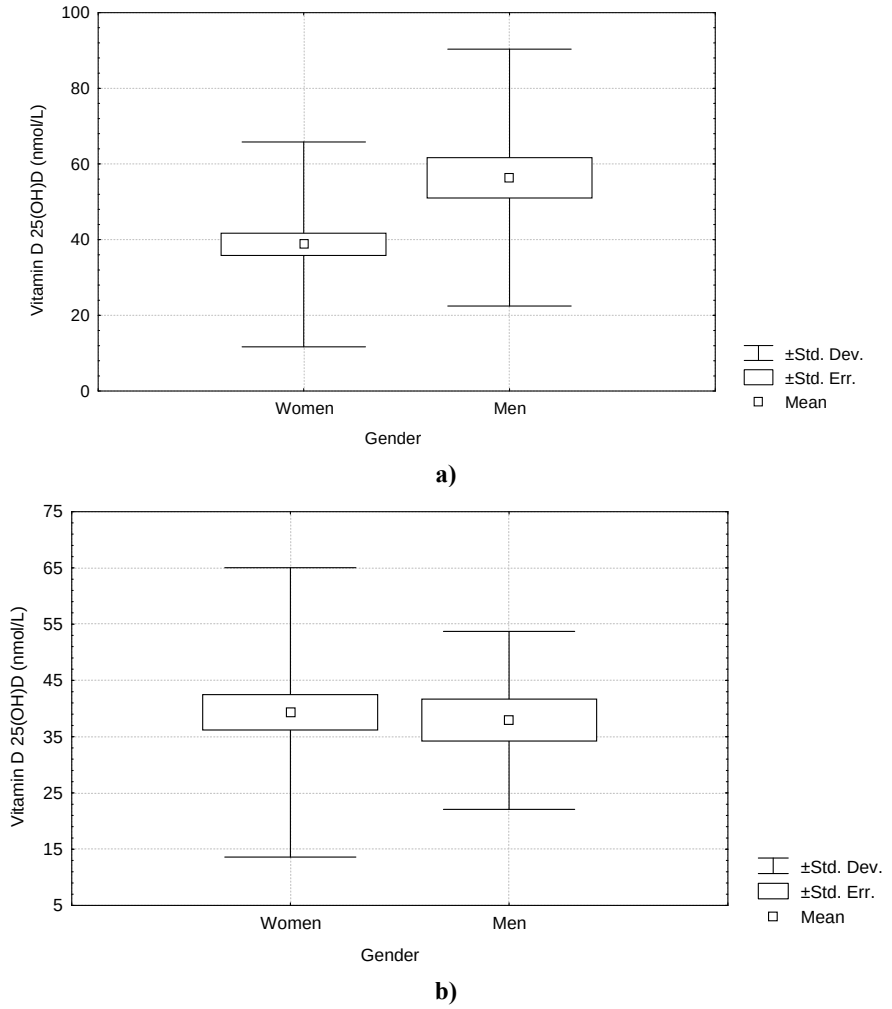

Fig. 1 – The serum concentration of 25-hydroxyvitamin D [25-(OH)D] in: a) women (n = 80) and men (n = 36) from the north (M-W *U* test, p = 0.004); b) women (n = 62) and men (n = 18) from the south (M-W *U* test *p* = 0.62). M-W *U* test – Mann-Whitney *U* test.

The authors implied clues to the pathogenesis of the gender difference in risk and to the nature of the environmental factors involved in MS. Authors of this manuscript cannot offer proper explanation for the lower levels of vitamin D among women in the control group. Possible reasons, besides latitude (above 40th parallel), include several factors such as low sun exposure, genetic factors, a large proportion of smokers in the population of Montenegro and nutrition. We also found significantly lower 25(OH)D serum levels among the patients with SP MS compared to the RR patients. Comparable results were found in a Dutch study, in which both metabolite levels were significantly lower in the progressive forms compared to the relapsing remitting MS phenotype [12]. Serum levels of 25(OH)D in our study group were associated with both disability and progression of MS. Smolders et al. [19] noted a similar effect of low levels of vitamin D in course of the disease, i.e. a lower level of of 25(OH)D during relapses compared to the periods of remission. These results are suggestive for a disease modulating effect of the serum concentrations of 25(OH)D on MS.

The effect of latitude on the risk of MS has long been known and it is universally acknowledged; prevalence of the disease being minimal at the equator and increasing with either north or south latitude [20]. Accordingly, a problem of vitamin D supply affects a larga number of people, namely those who live beyond the 40th parallels North or South [21, 22]. Relatively limited amounts of sun are mainly related to Canada, the northern part of the United States, almost all of Europe (40th parallel runs through the center of Spain), Russia and several areas in the southern hemisphere, such as New Zealand, Tasmania and Patagonia which include only about 15% of the world's population while the remaining 85% live in sunny regions [22].

Montenegro extends between 41º51' and 43º33' north latitude, which according to the above mentioned data suggests that lower levels of vitamin D should be expected in our country as well, in both general population and among MS patients. In our study group, serum levels of vitamin D were significantly lower in MS patients compared to controls, which is in accordance with other similar studies [23]. Further, health controls had a low mean level of vitamin 25 (OH) D. Recent epidemiological studies conducted in 40 countries, located mainly above 40th parallel, showed low levels of 25(OH)D among adult Caucasians [24]. Zadshir et al. [25] found mean serum level of 25(OH)D to be 74 nmol/L in a large cohort distributed throughout the US. However, a more recent analogous American cohort revealed even lower mean serum vitamin D level. Low mean serum 25(OH)D levels were also reported among healthy adult population in Australia [26], New Zealand [27] and Canada [28].

In our study the serum levels of vitamin D in patients from both groups (north and south) were low. The significantly higher levels of vitamin D were registered in male patients from the north compared to the female ones. In the south, the vitamin D levels were similar in both genders**.** Higher serum levels of vitamin D in men from the north could be explained by cultural milieu in Montenegro (the north of Montenegro is rural and men care about household and therefore are more exposed to the sun. Women are mainly involved in household chores. Likewise, the great proportion of inhabitants from the northern parts of a country are Muslims and the women wear traditional skin covering clothes. Other authors presented different results in regard to gender. Women tended to have borderline significantly higher mean serum level of 25(OH)D than men [29].

Our study did not detect the difference in vitamin D levels among MS patients compared to latitude which is quite the opposite what other studies have reported. Even though there was found significantly lower average number of sunny days in the north than in the south, the result we obtained can be partly explained by a small difference in latitudes between this two regions. On a world-wide scale, in a meta-analysis based on 394 studies, a significant correlation was observed between 25(OH)D serum levels and latitude in Caucasian subjects [28]. In Nordic countries the serum levels of vitamin D are often lower compared to countries with more sunny days [29], whereas in tropical regions the serum levels are generally higher [30].

However, exceptions are not infrequent. The reason may be due to differences in lifestyle, cultural habits or diet. Low serum levels of vitamin D can be found in people from sunny countries, if they avoid the sun, or, on the other hand, relatively high serum levels in people of Northern regions, who take more advantage of the sun in summer and consume diet rich in vitamin D in winter [31].

Conclusion

The serum levels of vitamin D were lower than expected in the entire study group. The serum levels of 25(OH)D were significantly lower in the MS patients and were associated with disability and progression. There was no significant difference in the levels of vitamin D among patients from the north and south of Montenegro, although the amount of sunshine in the south is significantly higher. The male patients from the northern part of the country had significantly higher level of vitamin D than women. The low levels of vitamin D cannot be explained solely with unfavorable latitude and insufficient sun exposure, thus further genetic analysis is needed.

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The effects of extreme low frequency pulsed electromagnetic field on bone mineral density and incidence of fractures in patients with end – stage renal disease on dialysis – three year follow up study

Efekti pulsnog elektromagnetnog polja ekstremno niske frekvencije na gustinu kosti i incidenciju preloma kod bolesnika sa terminalnom bubrežnom slabošću na dijalizi: trogodišnja studija praćenja

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Abstract

Background/Aim. A variety of physical therapy options has been developed for the treatment of musculoskeletal disorders including those characterized with low bone mineral density (BMD). Extreme low frequency pulsed electromagnetic field (ELF-PEMF) can accelerate bone formation. Patients with end stage of renal disease (ESRD) are predisposed to high incidence of fractures due to bone disorder with multifactorial pathogenesis. Vitamin D, calcium supplements, antiresorptive and anabolic drugs in those patients have changed pharmacodynamics and pharmacokinetics and have minimal or limited effects. The aim of this study was to assess the effectiveness of long-term ELF-PEMF therapy applied in concordance with physical exercise on bone mass, incidence of new bone fractures and parathyroid hormone concentrations in ESRD patients on dialysis. **Methods.** In this 3-year prospective clinical trial, 151 patients with ESRD on dialysis program were subjected to treatment with ELF-PEMF (18 Hz, 2 mT) applied during 40 min after 10 consecutive dialysis procedures, 4 times through one year (120 treatments in total during three years) together with kinesitherapy (study group) or only with kinesitherapy (control group) on the voluntary basis. **Results.** Total of 124 patients have completed the study. In the study group (n = 54), regardless of sex, significant improvements of BMD, T-score and Z-score on both lumbar spine and femoral neck were achieved after 3-year treatment with ELF-PEMF. In the control group (n = 70), significant decreases of BMD, T-score and Z-score as well as the higher incidence of new bone fractures were recorded. **Conclusion.** ELF-PEMF could be a convenient and safe non-pharmacological therapeutic strategy for fracture prevention in nephrology practices.

Key words:
kidney failure, chronic; renal dialysis; electromagnetic fields; bone density; fractures, bones; incidence; treatment outcome.

Apstrakt

Uvod/Cilj. Različite metode fizikalne terapije koriste se u lečenju mišićno-skeletnih oboljenja uključujući i ona koja se karakterišu sniženom mineralnom koštanom gustinom (BMD). Pulsno elektromagnetno polje ekstremno niske frekvencije (ELF-PEMF) stimuliše formiranje koštanog tkiva. Zbog poremećaja koštanog tkiva multifaktorijalne patogeneze bolesnici sa terminalnom bubrežnom slabošću (TBS) imaju visoku učestalost preloma. Vitamin D, suplementi kalcijuma, antiresorptivni i anabolički lekovi kod ovih bolesnika, zbog izmenjene farmakodinamike i farmakokinetike imaju minimalne ili ograničene efekte. Cilj ovog rada bio je da se ispitaju efekti dugotrajne primene ELF-PEMF u kombinaciji sa kineziterapijom na BMD, učestalost novih preloma kostiju i koncentraciju parathormona kod bolesnika sa TBS na programu hemodijalize. **Metode.** U 3-godišnjoj prospektivnoj kliničkoj studiji bolesnici, njih 151, sa TBS na programu hemodijalize na dobrovoljnoj bazi, svrstani su u dve grupe: studijska grupa (ELF-PEMF, 18 Hz, 2 mT, pri-

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menjivana tokom 40 min posle 10 uzastopnih procedura hemodijalize, četiri puta tokom jedne godine, ukupno 120 tretmana tokom tri godine uz kineziterapiju) i kontrolna grupa (samo kineziterapija). **Rezultati.** Ukupno 124 bolesnika je završilo ispitivanje. U studijskoj grupi (n = 54), nezavisno od pola, posle tri godine primene ELF-PEMF postignuto je značajno poboljšanje BMD, T-skora i Z-skora na lumbalnoj kičmi i vratu butne kosti. U kontrolnoj grupi (n = 70), primećeno je značajno smanjenje BMD, T-skora i Z-skora uz veću incidencu novih preloma kostiju. **Zaključak.** Tehnika ELF-PEMF mogla bi predstavljati korisnu i bezbednu nefarmakološku metodu u programu prevencije preloma kod bolesnika sa TBS.

Ključne reči:
bubreg, hronična insuficijencija; hemodijaliza; elektromagnetna polja; kost, gustina; prelomi; incidenca; lečenje, ishod.

Introduction

In the treatment of musculoskeletal disorders, a variety of physical therapy options has been developed. Among them, pulsed electromagnetic fields (PEMF) have reached significance and attracted attention in both clinical and basic research [1].

Following convincing evidence that electromagnetic currents can accelerate bone formation, PEMF have been used as therapeutic agent for over the 40 years. It seems that most of different effects strongly depend on parameters of applied electromagnetic fields [2, 3]. Extreme low frequency PEMF (ELF-PEMF), available and applicable in biomedicine, are electromagnetic fields with frequency below 60 Hz, induction value 1 pT- 15 mT, volume 130 V/m and triangle or 4 angle oscillations magnetic field. They are sufficient to maintain bone mass even in the absence of physical activity and reducing the frequency to 15 Hz made the field extremely osteogenic [4]. Since 1979, on the basis of strong empirical evidence, PEMF have been approved by the Food and Drug Administration (FDA) for treating non-healing fractures and related problems in bone healing [5]. ELF-PEMF has also analgesic (antinociceptive) effects and this method of physical therapy is suggested as adjunctive therapy in other chronic pain medical conditions such as painful diabetic peripheral neuropathy and a variety of different disorders including spasticity in multiple sclerosis and benign prostate hyperplasia [6, 7].

There is no discomfort or known risk associated with ELF-PEMF and therefore it is a non-invasive, long-term safe and easy to apply, low-cost method [4]. The occurrence of adverse events is indicated by a relative risk of 1.4.

Chronic kidney disease (CKD) affects 5–10% of the world population and is associated with many adverse outcomes including bone disorders and fractures [8]. Decreased bone mineral density (BMD) and disruption of micro architecture occur early in the course of CKD and worsen with the progressive decline in renal function, so that at the time of initiation of dialysis at least 50% of patients had a fracture [9]. The etiology of fractures in patients with CKD on dialysis is multifactorial [10]. Dialysis modality, sex, age, presence of cardiovascular disease, diabetes, diuretics, steroids, vitamin D and low BMD had statistically significant associations with hip fracture [11]. Furthermore patients with end stage renal disease (ESRD) are predisposed to many risk factors of low bone strength, including low dietary calcium intake, reduced exercise, heparin therapy, low body weight, amenorrhea, and premature menopause. The term renal osteodystrophy failed to describe the entire spectrum of bone and mineral abnormalities that include mineral disturbance and abnormal metabolism of bone, its regulating hormones, as well as, various calcifications of soft tissues and cardiovascular system. According to Kidney Disease: Improving Global Outcomes (KDIGO) recommendations, this term has been replaced with the term chronic kidney disease-mineral and bone disorder (CKD-MBD) [12].

The first step towards decreasing the morbidity and mortality associated with fractures in patients with ESRD on dialysis is to direct appropriate preventative and treatment strategies. Changed pharmacodynamics and pharmacokinetics of vitamin D, calcium supplements, antiresorptive drugs including bisphosphonates, and anabolic drugs, as well as, a multifactorial pathogenesis of bone and vascular disease in ESRD patients on dialysis, are responsible for undesirable, adverse, minimal or limited effects [13]. Therefore, the physical therapy, especially ELF-PEMF, could be a convenient non-pharmacological step in the strategies for fracture prevention in nephrology practices.

The aim of this study was to assess the effectiveness of long-term osteogenic ELF-PEMF therapy applied in concordance with physical exercise on BMD, frequency of new bone fractures and parathyroid hormone (PTH) concentrations in ESRD patients on dialysis.

Methods

Patients

This study was preformed as a 3-year prospective clinical trial. All study protocols were in accordance with the Declaration of Helsinki and International Committee on Harmonization-Good Clinical Practice (ICH-GCP) and were approved by the Independent Ethics Institutional Review Committee of the University hospital "Zvezdara" as part of the School of Medicine, University of Belgrade, Serbia on April 19, 2011. All patients have signed written informed consent for the entry into the clinical trial on the voluntary basis.

Total of 151 patients of both sexes were initially included in the study. All patients had a chronic renal failure of a different origin (primary chronic glomerulonephritis, tubulointerstitial nephritis, nephroangiosclerosis, diabetic nephropathy) and were on dialysis program with hemodialysis product 36, for at least one year. Further inclu-

sion criteria required patients to be at least 25 years old. All patients have continued with their basic therapeutic regimen (vitamin D, calcium and phosphate binder supplementation) during the observation period. Exclusion criteria were: any relative or absolute contraindication for either ELF-PEMF or kinesitherapy treatment, any disorder affecting the bone metabolism (except renal failure and hyperparathyreoidism) and any medication affecting the bone metabolism (except vitamin D, calcium and heparin during hemodialysis). Early menopause was defined as having occurred before the age of 40.

Collection of demographic and case history data was performed by reviewing case notes and treatment records.

According to the applied physical therapy procedure patients were divided into two groups. Patients included in the study group (n = 64) were subjected to treatment with ELF-PEMF together with kinesitherapy, while patients assigned to the control group (n = 87) were subjected only to kinesitherapy.

Physical therapy procedures

ELF-PEMF (18 Hz, 2 mT) was applied during 40 min after 10 consecutive dialysis procedures, 4 times through one year (120 treatments in total during 3 years). The source of magnetic field was a Magomil 2 pad (35 × 27 × 13 cm) with computed device for ELF-PEMF (Electronic Design Medical, Belgrade, Serbia).

Kinesitherapy treatment (active and passive-assisted exercises per segments in two series with 10 repeats) was dosed individually according to general shape during 30 min after every hemodialysis procedure by the same physiotherapist who had been trained in the treatment scheme according to the usual program.

BMD measurements

All subjects underwent dual-energy x-ray absorptiometry (DXA) densitometry (Hologic explorer, USA). Lumbar spine and femoral neck BMD (g/cm^2) were measured twice: at the beginning of the study (baseline) and after three years. Results are reported as actual values and T and Z scores, that reflect the number of standard deviations (SDs) by which a patient's value differs from the mean of a group of young normal (T score) or age- and sex-matched controls (Z score).

Biochemical measurements and body mass index (BMI) calculation

Blood sampling was performed routinely using standard certified procedures for measuring of investigated parameters. Serum urea, creatinine, albumin, calcium, and phosphate were measured using standard autoanalyser techniques. Calcium levels were corrected for albumin concentration. Intact PTH levels were measured by a chemiluminescent enzyme immunometric assay performed with an automated analyzer (Immulite®, Diagnostic Products Corporation). The weight used for the calculation of body mass index (BMI) was the average of 3 postdialysis weights recorded in the week prior to entry.

Statistical analysis

For statistical analysis the patient data were entered on a computer Excel® (Microsoft Office) sheet and subsequently analyzed with the Origin Pro 8.5 statistical software (Stata Corporation, College Station, TX, USA). Group data are expressed as mean ± standard deviation (SD). One-sample Kolmogorov-Smirnov test was used for testing of normal distribution of data. Summary statistics, including mean, SD, range and percentiles were calculated for demographic data, fracture incidence, BMDs, T-scores, Z-scores, urea, creatinine, PTH, thyroid-stimulating hormone (TSH), calcium, phosphate serum concentrations and alkaline phosphatase activity. One way ANOVA and *t*-test for depended samples were used to investigate differences between groups for parametric variables and χ^2 test for nonparametric ones. Observations were considered significant if two-tailed *p* values were below 0.05.

Results

Of 151 patients initially enrolled in the study (64 in the study group and 87 in the control group), total 124 patients (54 in the study group and 70 in the control group) have completed all treatments and testing after 3 years. Ten patients in the study group and 17 in the control group dropped out of the study: 2 (one from each group) due to change in concomitant therapy and 25 (9 from the study and 16 from the control group) due to death related to cardiovascular events. During the follow-up period, not a single patient underwent renal transplantation, was transferred to another dialysis center or changed the dialysis mode. Finally, there were 29 females and 25 males in the study group and 36 females and 34 males in the control group.

Demographic and clinical data of the patients that have completed the study are presented in Table 1 for female and male patients. It is important to note that the patients in finally analyzed groups were comparable in relation to age, duration of dialysis, BMI, smoking history, presence of bone fractures, parameters measured by DXA and PTH levels at the beginning of investigation.

Effects of 3-year follow-up on DXA results, frequency of new bone fractures and concentration of PTH in female patients on dialysis in the study and control group are presented in Table 2.

In the study group, females achieved significant improvements of BMD, T-score and Z-score (on both lumbar spine and femoral neck) after 3-years treatment with ELF-PEMF. However, after the same period, significant decrease of BMD and T-score on both lumbar spine and femoral neck and Z-score only on femoral neck was recorded in females from the control group. Also, the higher frequency of new bone fractures was noticed but this change did not reach statistical significance. Concentrations of PTH were not changed in both groups.

Table 1

Demographic and clinical data of female/male dialysis patients in the study and the control group at the beginning of investigation

Parameter	Study group (n = 29/25)	Control group (n = 36/34)	*p*
Age (years), mean ± SD	56.9 ± 6.4/63.2 ± 7.4	61.2 ± 7.6/61.2 ± 13.6	F = 1.89; *p* = 0.13/ F = 0.55; *p* = 0.85
Duration of dialisis (years), mean ± SD	9.3 ± 5.6/8.8 ± 3.7	9.2 ± 6.6/8.7 ± 3.4	F = 1.64; *p* = 0.17/F = 1.46; *p* = 0.20
BMI (kg/m^2), mean ± SD	23.7 ± 3.2/25.9 ± 2.8	24.9 ± 5.4/23.7 ± 3.5	F = 2.15; *p* = 0.09/ F = 10.9; *p* = 0.08
[1]Duration of menopause (years), mean ± SD	9.0 ± 4.5	10.8 ± 6.2	F = 1.72, *p* = 0.15
[1]Early menopause (% of patients)	20.7	16.7	χ = 0.07, *p* = 0.98
Smoking history (% of patients)			
ever smoked	44.8/72.0	47.2/61.7	χ = 0.011, *p* = 0.99/χ=0.131; *p*=0.87
present smoking	20.7/40.0	19.4/41.1	χ=0.006, *p*=0.99/χ=0.002; *p*=0.99
Bone fractures (% of patients)	31.0/24.0	22.2/20.5	χ = 0.264, *p* = 0.88/χ = 0.043; *p* = 0.99
BMD L1-L4, (g/cm^2), mean ± SD	0.812 ± 0.114/0.774 ± 0.065	0.993 ± 0.182/1.060 ± 0.143	F = 0.52, *p* = 0.88/F = 4.74; *p* = 0.18
T-score L1-L4, mean ± SD	-2.8 ± 1.2/-2.9 ± 0.8	-1.7 ± 1.4/-1.3 ± 1.1	F = 1.83, *p* = 0.14/F = 1.45; *p* = 0.39
Z-score L1-L4, mean ± SD	-1.3 ± 1.1/-1.3 ± 1.0	-1.4 ± 1.4/-0.9 ± 1.1	F = 1.39, *p* = 0.31/F = 3.04; *p* = 0.057
BMD femur (g/cm^2) , mean ± SD D	0.866 ± 0.132/0.831 ± 0.173	0.745 ± 0.174/0.831 ± 0.146	F = 1.17, *p* = 0.51/F = -64.48; *p* = 1
T-score femur, mean ± SD	-1.9 ± 0.9/-2.9 ± 0.8	-2.4 ± 1.2/-2.1 ± 1.0	F = 1.93, *p* = 0.12/F = 0.46; *p* = 0.89
Z-score femur, mean ± SD	-0.7 ± 0.9/-1.0 ± 0.5	-1.1 ± 1.2/-1.2 ± 0.8	F = 1.34, *p* = 0.36/F = 0.46; *p* = 0.89
PTH (pg/mL) , mean ± SD	760.7 ± 125.0/795.5 ± 119.4	788.4 ± 147.2/774.0 ± 114.7	F = 1.08, *p* = 0.61/F = 1.18; *p* = 0.55

[1]Getting data on women only.

BMI – body mass index; BMD – bone mineral density; PTH – parathyroid hormone; SD – standard deviation.

Baseline and closing results of DXA measurements, frequency of new bone fractures and concentrations of PTH in male patients on hemodialysis after 3 years are presented in Table 3. The results are similar to those found in the females, except for the absence of significant decrease of T-score and Z-score on femoral neck in the control group.

During the investigation period, no side-effects of ELF-PEMF were noticed.

Discussion

In this study, the results of a 3-year follow-up investigation of the effects of ELF-PEMF on osteodensitometric parameters and incidence of new bone fractures in patients with ESRD treated with dialysis are presented. At the beginning, the study and control groups were similar according to demographic and all investigated parameters. In the study group, compliance to ELF-PEMF was very high, no one dropped out because of poor adherence.

Our results clearly demonstrated that ELF-PEMF significantly increased BMD, T-scores as well as Z-scores at all measured sites. Although there is some controversy about the significance of measuring BMD in ESRD patients [9], our findings strongly indicate beneficial effects of this physical procedure in ESRD patients. Evaluation of the effects of ELF-PEMF in our patients did not have the aim to investigate the effects on osteoporosis because, as mentioned above, the role and usefulness of DXA in assessing bone status is not well defined. But it was demonstrated that patients with ESRD and low BMD have a significantly shorter survival and that reduced BMD is also predictive of increased all-cause mortality and cardiovascular mortality [14–17]. According to the eldest cross-sectional study of von der Recke et al. [17], low hip BMD seems to predict all-cause mortality in ESRD patients after adjustment for age, years of menopause, presence of hypertension, smoking, and abnormalities in the lipid profile. Indices of osteoporosis predict also cardiovascular mortality. In the study of Kohno et al. [18] the relationship of BMD reduction with increased mortality in hemodialysis patients was examined as a single-center prospective observational study conducted on 269 male hemodialysis patients followed for 61 months. The results suggested that BMD reduction might be a clinically relevant marker that predicts an increased risk of mortality in male hemodialysis patients. According to Matsubara et al. [19], even after adjustment for several confounders and risk factors, all-cause and cardiovascular mortality remained significantly associated with low BMD as an independent predictor in ESRD patients. The association between arterial calcification and bone loss is believed to be one of the links that explains the relationship between decreased BMD and poor cardiovascular outcomes [10, 18–20]. BMD in these patients has been shown to be inversely associated with vascular calcifications. The lack of an association between lumbar spine bone mass measurements and mortality was not unexpected and explained by the fact that spinal osteophytes and abdominal aortic calcification may elevate lumbar BMD and therefore obscure any associations with other factors [17]. The number of patients in our study is too small to bring daring conclusions, but the results demonstrated that low BMD may be a predictor of mortality in maintenance hemodialysis patients. The overall mortality rate was 1.7 times greater in the control group. On the other hand, overall mortality in our control group is similar as expected in clinical trials (about 7.9 deaths/100 person-years) [17].

Table 2

Effects of 3 year treatment with ELF-PEMF on bone mineral density, frequency of new fractures and concentration of PTH in female patients on dialysis in the study and the control groups

Parameter	Study group (n = 29)			Control group (n = 36)		
	before treatment	after treatment	*t*; DF; *p*	before treatment	after treatment	*t*; DF; *p*
BMD L1-L4 (g/cm^2), $\bar{x} \pm SD$	0.812 ± 0.114	0.906 ± 0.188	4.28; 28; < 0.05	0.993 ± 0.182	0.917 ± 0.179	4.02; 35; < 0.05
T-score L1-L4, $\bar{x} \pm SD$	-2.8 ± 1.	-2.3 ± 1.0	3.12; 28; < 0.05	-1.7 ± 1.4	-2.1 ± 1.4	14.06; 35; < 0.05
Z-score L1-L4, $\bar{x} \pm SD$	-1.3 ± 1.1	-0.9 ± 0.8	6.79; 28; < 0.05	-0.4 ± 1.4	-0.5 ± 1.4	0.89; 35; 0.38
BMD femur (g/cm^2), $\bar{x} \pm SD$	0.866 ± 0.132	1.094 ± 0.291	3.26; 28; < 0.05	0.745 ± 0.174	0.625 ± 0.097	5.55; 35; < 0.05
T-score femur, $\bar{x} \pm SD$	-1.9 ± 0.9	-1.4 ± 0.6	-4.10; 28; < 0.05	-2.4 ± 1.2	-2.877 ± 0.804	3.27; 35; < 0.05
Z-score femur, $\bar{x} \pm SD$	-0.7 ± 0.9	-0.3 ± 0.5	10.19; 28; < 0.05	-1.1 ± 1.2	-1.5 ± 0.9	2.73; 35; < 0.05
Bone fractures (% of patients)	31.0	34.4	χ = 0.026; 1; 0.88	22.2	41.6	χ = 1.065; 0.37
PTH (pg/mL), $\bar{x} \pm SD$	760.7 ± 125.0	724.5 ± 85.0	1.03; 28; 0.31	788.4 ± 147.2	791.7 ± 115.4	*t* = -0.88; 35; 0.38

ELF-PEM – extreme low frequency pulsed electromagnetic field; FBMD – bone mineral density; PTH – parathyroid hormone; $\bar{x}$ – mean value; SD – standard deviation.

Table 3

Effects of 3 year treatment with ELF-PEMF on bone mineral density, frequency of new fractures and concentration of PTH in male patients on diaiysis in the study and the control group

Parameter	Study group (n = 25)			Control group (n = 34)		
	before treatment	after treatment	*t*; DF; *p*	before treatment	after treatment	*t*; DF; *p*
BMD L1-L4 (g/cm^2), $\bar{x} \pm SD$	0.774 ± 0.065	0.906 ± 0.188	4.02; 24; < 0.05	1.060 ± 0.143	0.917 ± 0.179	4.28; 33; < 0.05
T-score L1-L4, $\bar{x} \pm SD$	-2.9 ± 0.8	-2.3 ± 1.0	14.06; 24; < 0.05	-1.3 ± 1.1	-2.1 ± 1.4	3.12; 33; < 0.05
Z-score L1-L4, $\bar{x} \pm SD$	-1.3 ± 1.0	-1.2 ± 0.5	11.25; 24; < 0.05	-0.9 ± 1.1	-1.4 ± 0.9	2.66; 22; < 0.05
BMD femur (g/cm^2), $\bar{x} \pm SD$	0.831 ± 0.173	0.850 ± 0.058	6.92; 24; < 0.05	0.831 ± 0.146	0.997 ± 0.115	3.59; 33; < 0.05
T-score femur, $\bar{x} \pm SD$	-2.3 ± 0.4	-1.4 ± 0.6	6.95; 24; < 0.05	-2.1 ± 1.0	-2.6 ± 1.0	1.95; 33; 0.06
Z-score femur, $\bar{x} \pm SD$	-1.0 ± 0.5	-0.6 ± 0.4	5.67; 24; < 0.05	-1.2 ± 0.8	-1.4 ± 0.8	1.01; 33; 0.32
Bone fractures (% of patients)	6 (24.0%)	8 (32.0%)	χ = 0.142; 1; 0.94	7 (20.5%)	12 (35.2%)	χ = 0.658; 1; 0.91
PTH (pg/mL), $\bar{x} \pm SD$	795.5 ± 119.4	712.2 ± 52.6	1.21; 24; 0.25	774.0 ± 114.7	792.0 ± 123.3	1.76; 33; .38

ELF-PEM – extreme low frequency pulsed electromagnetic field; BMD – bone mineral density; PTH – parathyroid hormone; $\bar{x}$ – mean value; SD – standard deviation.

The presence of fractures in the ESRD patients on dialysis can significantly influence their outcome [21]. The important finding of the present study is lower incidence of new fractures in the ESRD patients subjected to the treatment with ELF-PEMF, especially in females. The CKD–MBD clinical practice guideline by KDIGO suggests that BMD does not predict fracture risk as it does in general population, although this evidence level is 2B, meaning a weak recommendation with moderate grade of evidence [12]. However, Iimori et al. [22], followed-up 485 hemodialyzed patients during 6 years and demonstrated a significant predictive power of BMD. These authors found that BMD, especially at the total hip and other hip regions, was useful to predict any type of incident of fracture in females with low PTH or to discriminate prevalent spine fracture for every patient. Furthermore, among 13 cross-sectional studies which were the basis for KDIGO CKD–MBD guideline for the association between BMD and fractures in CKD [12], 7 studies did not find a relationship between BMD and fracture rate, whereas 6 studies found a relationship at least in one skeletal site. If only the studies that used DXA for BMD in ERSD receiving hemodialysis are selected, then 9 studies (4 negative and 5 positive results) remained [22].

It is well known and proved in previous studies, that age, gastric acid suppression therapy, female gender, age at menarche, history of previous fractures and especially serum PTH levels, were identified as important negative determinants of BMD in chronic hemodialysis patients [14]. Secondary hyperparathyroidism, common among patients with ESRD directly affects bone turnover and mineralization and is associated with pain and fractures [23]. Our results did not show any effects of ELF-PEMF on PTH levels.

There is a large body of evidence that ELF-PEMF has high potential in osteogenesis, but the mechanisms has not been clarified yet. It seems that in effect on bone repair a number of different mechanisms are included [4]. PEMF has been shown to stimulate calcification in the extracellular space between the bone cells, to increase blood supply that arises due to PEMF effects on ionic calcium channels, to have an inhibitory effect on the resorptive phase in bone remodeling, leading to the early formation of osteoids and calluses and to increase the rate of bone formation by osteoblasts. On subcellular level, there are at least two aspects - biomechanical and biochemical.

ELF-PEMF can mimic and potentiate effects of physical activity on osteogenesis [4]. The frequencies and field intensities when ELF-PEMF technique is used are most effective in the exogenous stimulation of bone formation when they are similar to those produced by normal physical activity. The application of physical stress on bones promoted the formation of very small electric currents, piezoelectric potentials that are related to bone formation [24]. Piezoelectric potentials are due primarily to movement of fluid-containing electrolytes. When these electrolytes move in the bone channel, which has organic constituents with fixed charges, they generate streaming potentials transforming mechanical stress into an electrical phenomenon capable of stimulating synthesis of matrix components. Using an *in vivo* model, it was also demonstrated that the bone resorption can be prevented or even reversed by the exogenous induction of electric fields [4]. Importantly, the manner of the formation, turnover or resorption are exceedingly sensitive to subtle changes in electric field parameters induced at frequencies between 50 Hz and 150 Hz for 1 h/day. They were sufficient to maintain bone mass even in the absence of function and reducing the frequency to 15 Hz made the field extremely osteogenic [4]. We used similar very low frequency, 18 Hz, which is safe for use in applied therapeutic regiments.

Time varying EMF also generates changes in metabolic activity in the living bone. Interaction between cell membrane and PEMF modulates critical events in signal transduction mechanisms such as Ca^{2+} influx and mobilization, surface receptors redistribution and protein kinase C activity [25]. Cellular production of cAMP in response to PTH is significantly reduced. PEMF can produce a modification of membrane cytoskeleton organization, together with an alteration of protein kinase activity, modify membrane structure and interfere with initiation of signal cascade pathway.

PEMF stimulation is reported to enhance the osteoblast differentiation and to increase bone formation through protein kinase A, protein kinase C and protein kinase G pathways, transcriptional upregulation of bone morphogenic proteins (BMP) 4, 5 and 7, increased levels of BMP-2 and BMP-4 messenger rilonucleic acid (mRNA). The similar effects are observed in mesenchymal stem cells. Several cellular mechanisms, including increases in growth factors, have been implicated as the possible causes of osteogenesis from PEMF stimulation. On the other side, PEMF can also target osteoclasts through increasing the number of adenosine A2a receptors which lead to a decrease in lysosomal enzyme activities [26].

Significant reduction of proinflammatory cytokines like tumor-necrosis factor alpha (TNFα) and interleukin (IL)-6 and inflammatory mediators like prostaglandin PGE2 are noticed.

PEMF increase serum bone formation markers, including osteocalcin and N-terminal propeptide of type 1 procollagen with minor inhibitory effects on bone resorption markers, including C-terminal crosslinked telopeptides of type I collagen and tartrate-resistant acid phosphatase 5b [27]. Bone histomorphometric analysis demonstrated that PEMF increased mineral apposition rate, bone formation rate, and osteoblast numbers in cancellous bone, but PEMF caused no obvious changes on osteoclast numbers. Real-time PCR showed that PEMF promoted gene expressions of Wnt1, LRP5, β-catenin, OPG, and OC, but did not alter receptor activator of nuclear factor kappa-B ligand (RANKL), receptor activator of nuclear factor K (RANK), or Sost mRNA levels [28]. PEMF attenuated deterioration of bone microarchitecture and strength in rats by promoting the activation of Wnt/LRP5/β-catenin signaling rather than by inhibiting RANKL-RANK signaling [29]. The results of some studies show that PEMF frequency is an important factor with regard to the induction of human mesenchymal stem cell differentiation. Furthermore, a PEMF frequency of 50 Hz was the most effective at inducing human mesenchymal stem cell osteoblast differentiation *in vitro* [30]. In mice models the expression levels of angiopoietin-2 and fibroblast growth factor-2 in the bone marrow

were significantly higher by the PEMF [31]. Such angiogenesis acceleration represents one possible mechanism for the acceleration of bone fracture healing by PEMF. The results found in rat models demonstrate that PEMF stimulation can efficiently suppress bone mass loss through promoting transforming growth factor (TGF)-beta1 secretion and inhibiting IL-6 expression [32]. Some studies hypothesized and confirmed that PEMF increase nitric oxide (NO), which induces vasodilation, enhances microvascular perfusion and tissue oxygenation [33]. PEMF can facilitate the osteogenic differentiation of bone marrow mesenchymal stem cells *in vitro* [29]. The PEMF stimulation, could induce expression of osteoblast specific genes and proteins including alkaline phosphatase and osteocalcin, as well as gene expression of BMP-2, Runx2, β-catenin, Nrf2, Keap1 and integrin β1.

Conclusion

Our study provides evidence for a beneficial effect of ELF-PEMF on BMD and risk of fracture in ESRD patients on dialysis. Physical therapy in general and magnetobiology in particular provide non-invasive, safe and easy to apply methods to directly treat the site of injury or the source of pain, inflammation and dysfunction. As observed earlier, ELF-PEMF has a marked osteogenic potential proved by clinical, animal and tissue culture studies over a period of 20 years. Our findings suggest that ELF-PEMF has clinical relevance as a successful adjuvant option in the management of low BMD in ESRD for the first time without reports of side-effects. In future study, design ELF-PEMF effects need to prove this assumption in order to consider accurate results. A clearer definition of the mechanisms might also help in choosing patients and modalities that are more likely to benefit from such a treatment. The limitation of the study is a lack of possibility to study subgroups by energy levels or other parameters of treatment in order to produce recommendations.

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Diagnosis and surgical treatment of the posterior knee instability

Dijagnostika i operativno lečenje zadnje nestabilnosti kolena

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Abstract

Background/Aim. Posterior cruciate ligament is the primary stabilizer of the posterior tibia translation and secondary stabilizer of external tibial rotation as well as *varus*, *valgus* knee angulation. It is the strongest ligament in the knee that hurts the rarest. The aim of this study was to show the indications for surgery, present the surgical technique and give results of surgical treatment of posterior knee instability. **Methods.** The study icluded 12 patients who were tretaed surgically for posterior knee instabilility at the Institute for Orthopaedic Surgery "Banjica", Belgrade, in the period from 1st January 2010 to 1st January 2014. All of them had arthroscopically assisted anatomic reconstruction of posterior crucuate ligament done with 4-strand hamstring tendon graft. Postoperative follow-up lasted approximately 42 months and Lysholm values and International Knee Documentation Committee (IKDC) score were compared as well as the clinical status. **Results.** All treated patients had Grade III of posterior instability. Combined injuries of the posterolateral corner and anterior cruciat ligament (75%) were very frequent. Preoperative mean value of Lysholm score was 45.92 and postoperative 85.92 what was statistically significant improvement, the same as subjective IKDC score whose mean value was 38.58 preoperatively and 89.75 after the surgery and rehabilitation. Clinical examination showed better posterior knee stability although in 50% of patients certain level of instability remains. **Conclusion**. Arthroscopic reconstruction with 4-strand hamstring tendon gives satisfactory result with posterior cruciate ligament reconstruction. The result of subjective feeling of patient is much better then objective clinical examination. Although surgical procedure is technically demanding, with physically active patients having grade III of posterior instability it provides better result than non-surgical treatment.

Key words:
knee injuries; diagnosis; posterior cruciate ligament; orthopedic procedures; arthroscopy; treatment outcome.

Apstrakt

Uvod/Cilj. Zadnji ukršteni ligament je primarni stabilizator zadnje translacije tibije i sekundarni stabilizator spoljašnje rotacije tibije kao i *varus*, *valgus* angulacije u kolenu. To je najjača ligamentarna struktura u kolenu koja se najređe povređuje. Cilj ovog rada bio je da se prikažu indikacije za operaciju, operativna tehnika i rezultat operativnog lečenja zadnje nestabilnosti kolena. **Metode.** Studijom je bilo obuhvaćeno 12 pacijenata operativno lečenih zbog zadnje nestabilnosti kolena na Institutu za ortopedsko-hiruške bolesti „Banjica", Beograd, u periodu od 1.1.2010. do 1.1.2014. godine. Kod svih pacijenata rađena je artroskopski asistirana anatomska rekonstrukcija zadnjeg ukrštenog ligamenta četvorostrukim graftom tetiva *hamstrings*-a. Prosečno postoperativno praćenje bilo je 42 meseca (24–60) a upoređivane su vrednosti Lysholm i *International Knee Documentation Committee* (IKDC) skora, kao i klinički status. **Rezultati**. Svi operisani pacijenti imali su III stepen zadnje nestabilnosti. Udružene povrede posterolateralnog ugla i prednje ukrštene veze bile su česte – 75%. Srednja vrednost Lysholm skora preoperativno bila je 45,92, a postoperativno 85,92, što je statistički značajno poboljšanje, slično kao i vrednost subjektivnog IKDC skora čija je preoperativna srednja vrednost bila 38,58, a nakon operacije i rehabilitacije 89,75. Klinički pregled je pokazao bolju zadnju stabilnost kolena, mada je kod 50% pacijenata ostao određeni stepen nestabilnosti. **Zaključak**. Artroskopska rekonstrukcija četvorostrukom tetivom *hamstrings*-a daje zadovoljavajući rezultat kod rekonstrukcije zadnje ukrštene veze. Subjektivni osećaj pacijenata bolji je nego objektivan klinički nalaz. Mada je sama operacija tehnički zahtevna, kod fizički aktivnih pacijenata sa III stepenom zadnje nestabilnosti ona daje bolji rezultat od neoperativnog lečenja.

Ključne reči:
koleno, povrede; dijagnoza; ligament, zadnji, ukršteni; ortopedske procedure; artroskopija; lečenje, ishod.

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Introduction

Posterior cruciate ligament (PCL) is very strong structure, according to literature data, maximum tensile strength is 739–1,627 N [1–3]. Starting from posterior tibial attachment set 10 mm below the knee level it goes anteromedially to medial condyle of femur spreading into two functional bundles – anterolateral and posteromedial [4]. PCL is the primary stabilizer with posterior tibia translation (posterior instability) and secondary stabilizer of external tibial rotation as well as *varus*, *valgus* knee angulation [5, 6].

Injuries of PCL are quite less frequent in comparison to injuries of anterior cruciate ligament (ACL) and according to data from the literature they make 3.4–23% of all knee injuries and they occur isolated in less than 3.5% [7]. The most frequent injury mechanism in traffic is an impact on the anterior surface of proximal tibia – dashboard, while in sports it is knee hyperflexion and rather less common knee hyperextension as well as extreme *varus*, *valgus* stress. Combined injuries of posterior capsule and posterolateral knee corner are frequent and also, in case of serious trauma, the damages of anterior cruciate ligament, collateral ligament, meniscus and cartilage occur.

The ligament itself has a good potential of healing thanks to good vascularization and very specific position – intraarticular and extrasynovial [8, 9]. That is why partial and isolated tear is mostly treated nonsurgically – with cast immoblization and physical procedures [10, 11]. Still, the quality of such healing and tissue structure may not be adequate to keep normal knee kinematics. Disturbed biomechanics and nonphysiological micromovements with such joint lead to degenerative changes more often [9]. That is especially emphasized with complete tear followed by damages of posterior capsule and posterolateral corner. Dejour et al. [9] and Lobenhoffer et al. [10] differentiate 3 phases of adaptation which the knee goes through after the injury of PCL: the first phase of functional adaptation lasting 3–18 months, the second phase of functional tolerance lasting 10–20 years and the third phase of degenerative decompensation.

The objective of surgical treatment is to regain the knee stability and normal kinematics in order to prevent its rapid deterioration. The good result requires an adequate preoperative diagnostics and patient's evaluation [12]. The clinical examination is preceded with the medical history of typical injury mechanism. There are numerous tests for posterior instability (Table 1) and the most important of which is posterior drawer test, posterior sag and quadricepcs test [13]. Posterolateral corner is evaluated with dial test and reverse pivot shift test [13]. It is mandatory to perform tests for other knee structures because isolated injury is quite rare. With an acute trauma within 3 weeks the neurovascular status should always be evaluated.

The most frequently used test for evaluation of instability grade is the test of posterior drawer which evaluates the ratio between medial tibial plateau and medial femure condyle [14]. With normal knee, medial tibial plateau is 1 cm in front of medial femure condyle [15] (Table 2).

Additional diagnostics includes standard and stress imaging as well as nuclear magnetic resonance (NMR) imaging which has the highest sensitivity (97%) [16, 17].

Acute injury of PCL [18, 19] frequently remains overlooked. Patients complain of pain, swelling and limited movements so it is difficult to perform the above- mentioned tests. We begin with nonsurgical treatment using the cast immobilization and then follow the physical procedures. After that, most often the patients do not have big problems but depending on instability degree, it comes to degenerative changes development sooner or later. Arthrosis occurs at first in patellofemoral joint and medial compartment [20]. Thanks to better perceiving of consequences of such treatment, there are increasingly more advocates of surgical treatment [20, 21].

There are numerous dilemmas regarding surgical treatment in terms of graft choice, tunnel position, mode of tunnel placement, double or single reconstruction [22, 23]. In our

Table 1

Physical examination tests for posterior and posterolateral instability [13]

Test	Clinical target, description
Posterior drawer	Knee is flexed to 90°; posteriorly directed force is applied to proximal tibia
Posterior sag	Ipsilateral hip and knee are flexed to 90°; observe the knee from a lateral position for abnormal contour or sag at proximal anterior tibia
Quadriceps	Knee is flexed to 90°; patient either contracts quadriceps muscle or active test slides foot down table. Observe for tibia translating anteriorly from a posteriorly subluxed position
Dial test	External rotation of legs is compared with the knee at 30° and 90° of flexion
Reverse pivot shift	With leg externally rotated, *valgus* stress is applied to knee while it is extended from 70° to 80° of flexion. Test is positive when tibia reduces at approximately 20° of flexion

Table 2

Grading posterior knee instability [15]

Grade	Description of posterior knee instability
I	Tibia is still located anterior to the medial femoral condyle and can only be translated 0 to 5 mm posterior to the femoral condyle
II	Tibia is situated flush with the medial femoral condyle and can be translated 5 to 10 mm posterior to the femoral condyle
III	Tibia is displaced posterior to the medial femoral condyle and can be translated greater than 10 mm posterior to the femoral condyle

work we used arthroscopically assisted single bundle technique by using four-strand hamstring tendon graft.

Methods

The study includes 12 patients who had surgery at Institute for Orthopaedic Surgery "Banjica", Belgrade in the period from 1st January 2010 to 1st January 2014, and had PCL reconstruction performed. Patients with grade III of clinical instability who had difficulties in terms of pains and feeling of instability had surgery. The reconstuction of posterolateral corner was performed in 5 patients and the reconstruction of anterior cruciate ligament (ACL) was done in 3 patients during the same procedure. With 1 patient the ACL reconstruction was done afterwards. The technique used was arthroscopically assisted anatomic reconstruction with four-strand hamstrings tendon graft. This observational analytical study, follow-up and analyzed the following parameters: clinical exmination, Lysholm and subjective International Knee Documentation Committee (IKDC) scores before the surgery and 2 years after the surgical treatment.

Surgical technique

Surgeries were done in ischiofemoral block or spinal anaesthesia, with the use of Esmarch bandage. Clinical examination in anaesthesia was done preoperativelly and then the diagnostical arthroscopy through standard anterolateral and anteromedial portals was performed. The tear of PCL and diagnosed combined injury of ACL, meniscus and chondral lesion were verified. If needed, partial meniscectomy and damage debridman on cartilage were done. Performing diagonal cut as high as *pes anserinus*, distal attachment of *musculus* (m) *gracilis* and m. *semitendinosus* were approached. Tendons were preparated and removed and then 4-strand graft was made out of them. Under arthroscope control, the debridman notch and medial femure condyle were performed, then under arthroscope control posteromedial portal was opened. Debridman of posterior tibial edge and of tibial attachment of PCL was performed on about 1 cm of plateau edge (Figure 1). With the help of guide and under control of arthroscope a guide needle was set for transtibial tunnel. The tibial tunnel whose size was determined by graft size was placed over the guide needle. A guide needle for femoral attachment on medial femure condyle was set through AL portal.

Then, the femoral tunnel was also placed (Figure 2). The passing suture was pulled through tibial tunnel back and forth into femoral tunnel. The mentioned graft was pulled out through it. It was being fixed first femorally and then tibially by interference biodegrading screw with the knee at 90 degree flexion.

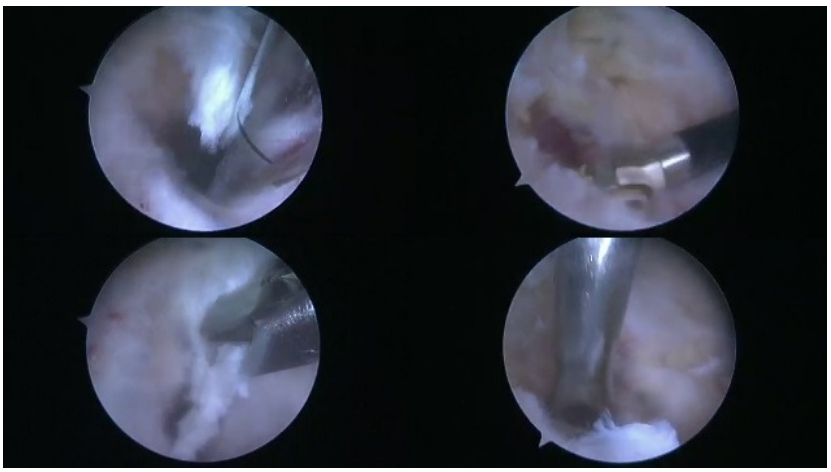

Fig. 1 – Debridman of posterior tibial edge and of tibial altachment of posterior cruciate ligament done on about 1 cm of platea edge – arthroscopic view.

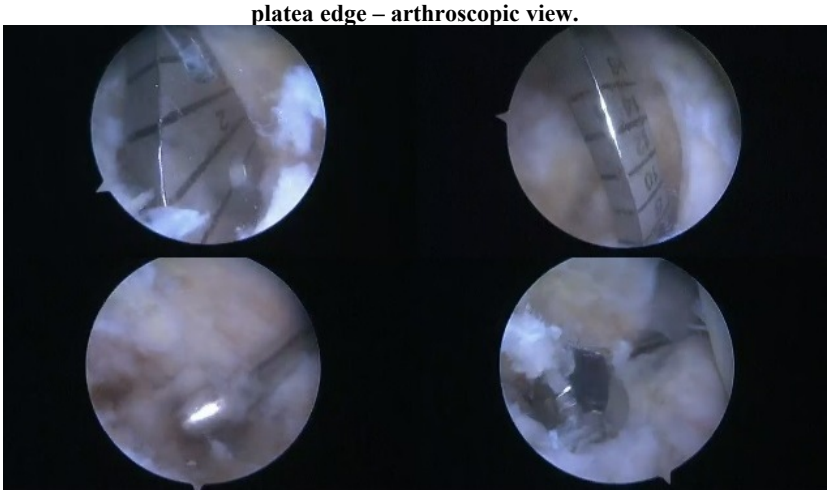

Fig. 2 – The procedure for femoral tunel placement – arthroscopic view.

In patients with posterolateral instability, the reconstruction of posterolateral corner was done with tendon of m. *semitendinosus* by technique per Coobs et al. [24].

In cases when there was a tear of ACL, the reconstruction of this ligament was done by Bone-Patellae tendo-Bone (B-Pt-B) graft from the other leg.

Rehabilitaion protocol

Postoperative surgically treated leg was immobilized with splint in extension up to 6 weeks. The patient was verticalized on the first postoperative day and started walking using crutches with partial weight-bearing. Patients started with passive movements from week 4, slowly increasing their weight-bearing. Active exercises of open kinetics chain avoiding flexion exercises started from month 3. Rehabilitation was long and gradual, so the complete recovery was expected after 9–12 months [25, 26].

Results

In this group of 12 patients who had surgery there were 9 men and 3 women, 34 years old on average (20–43). An average follow-up time was 42 months (from 24–60 months). The most frequent cause of injury was traffic trauma occured at 7 patients, then sports trauma at 4 and falls with bended knee at 1 patient. Average time from injury to surgery was 12 months (from 6 to 36 months). All patients were primarily treated nonoperatively. Eight patients had cast immobilization in the period from 2 to 6 weeks and 4 patients were treated with rest and elastic bandage. Futher treatment continued with physical procedures. All patients had primarily radiology images x-ray (XR) and physical examination done. Knee effluence was present with all patients suffered from pain and limited movements. Not all tests could have been done due to swelling and pain and test of posterior drawer was primarily positive in 6 cases (50%). The XR findings were mostly normal – there were no signs of fresh bone trauma. Additional diagnosis, NMR was primarily done at 7 patients and 5 had it done afterwards, upon completion of physical therapy.

Stress XR imaging was made to 4 patients after the rehabilitation in a way that the patient was kneeling and weight-bearing first his/her injured and then his healthy knee. In all cases posterior tibial translation was emphasized with injured knee (Figure 3).

After conducted physical therapy patients still had problems in terms of pain, limited movements and they felt instability. All patients had obvious hypothrophia of the above-knee muscles. Clinical tests were performed more easily and they precisely showed the posterior knee instability of grade III (Figure 4). Dilemma existed only with patients having torn both anterior and PCLS due to combined anterior and posterior instability.

Arthroscopic examination with all patients verified complete tear of PCL while distribution of accompanying damages was shown in Figure 5. Cartilage damages were dominantly in medial and patellofemorally compartment. Out of 6 patients who had ACL tear, 3 had reconstruction done of both anterior and posterior within the same procedure and 1 patients had the ACL reconstructed afterwards. Two patient with ACL lesion had no subjective feeling of disfunction and they did not want additional surgical treatment. Meniscus damage was treated with partial meniscectomy while cartilage damage was treated with debridman and microfractures technique. Posterolateral corner reconstruction was performed at 5 patients. In average, surgical procedure lasted for 1 h and 45 min.

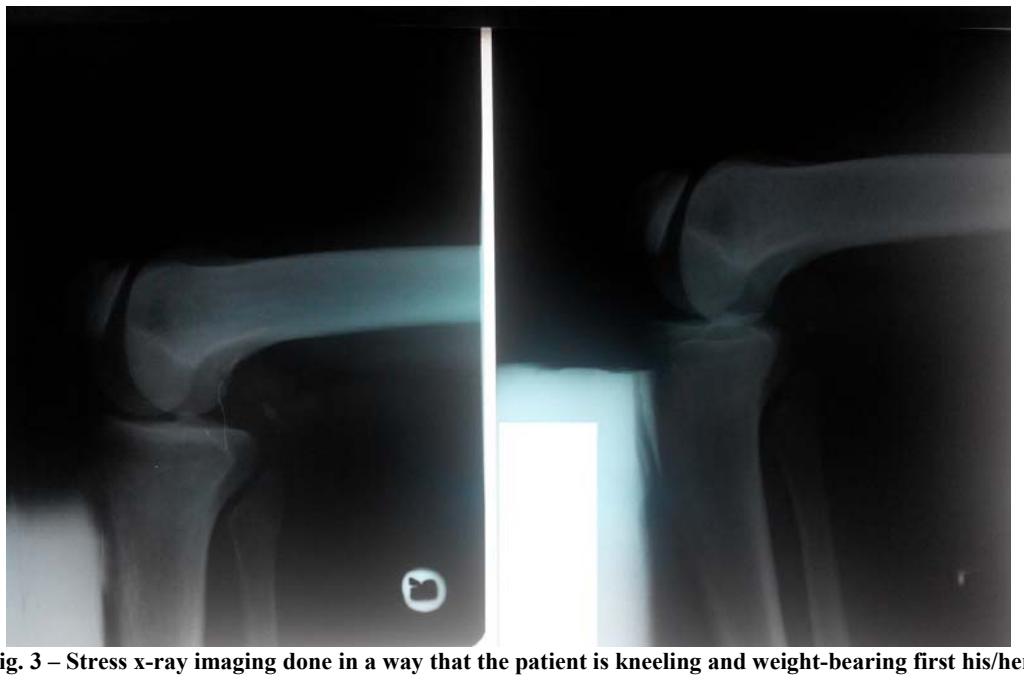

Fig. 3 – Stress x-ray imaging done in a way that the patient is kneeling and weight-bearing first his/her injuried and then his/her healthy knee revealed posterior tibial translation is emphasized with injured knee.

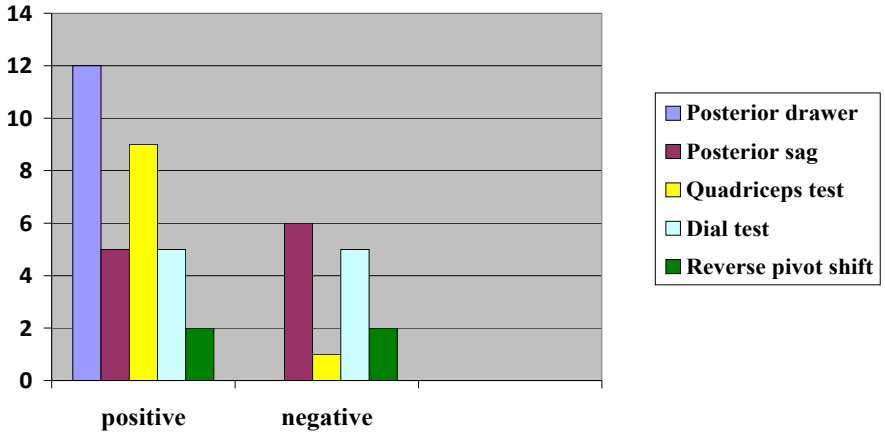

Fig. 4 – Physical examination tests after physical therapy.

Fig. 5 – Arthroscopic knee examination.
PCL – posterior cruciate ligament; LCA – ligamentum cruciale anterior.

Lysholm knee scores

Average value of Lysholm score was preoperatively 45.92 ± 5.6 (39–55) and 2 years after the intervention it was 85.92 ± 8.898 (65–95). There is an important statistical difference in value of this score after the operation ($p < 0.02$, Wilcoxon signed rank test).

Subjective IKDC scores

Preoperative average value of IKDC score was 38.58 ± 7.948 (25–48), after the surgery and adequate rehabilitation, 2 years later, it came to significant improvement and therefore the average value was 89.75 ± 4.864 (80–96) of subjective IKDC score, which is, according to Wilcoxon signed rank test ($p < 0.02$), statistically important difference.

Clinical examination

Clinical examinations after rehabilitation showed the improvement of posterior stability measured through posterior drawer test, although in 6 patients certain grade of posterior instability remained (Figure 6). Other tests were not always done, however they were improving (Figure 7).

Complications

One patient had deep infection and an additional intervention was required, infection calmed down but the patient stopped coming to check-ups. Sensibility problem was recorded in 5 cases in the knee region on the spot below taking the tendon graft. We had 3 cases of deep venous thrombosis. Pain and limited movements occurred in 3 patients which required prolonged physical rehabilitation.

Discussion

The PCL injury is the rarest knee ligament injury. We have very little experience regarding surgical treatment of this injury. In the literature there are also numerous dilemmas regarding surgical treatment [10, 11, 27]. Generally, it is accepted that a tear with instability of grades I and II should be

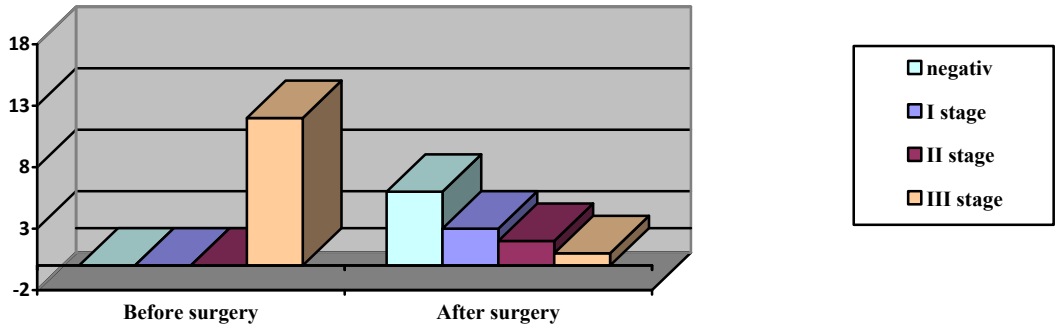

Fig. 6 – Posterior drawer test.

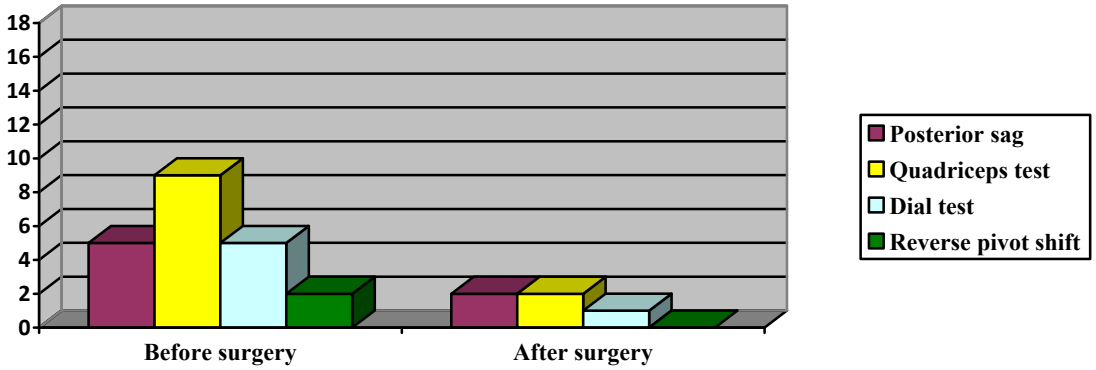

Fig. 7 – Other tests for posterior instability.

treated non-operatively [28, 29] while III of instability and multiligament injuries should be treated surgically [30–32]. The surgical procedure by itsef is technically very demanding. It takes a lot of time when not performed very often and that is related to risk of neurovascular structures injury, increased risk of infection and thromboembolic complications. The surgery objective is to gain stable joint of normal kinematics to prevent rapid deterioration – gonarthrosis. Most often injury is not isolated but it is combined with other ligaments, meniscus and cartilage injuries which affect the final results of the treatment. Dilemmas regarding the operative treatment are choice of surgical technique, graft choice, graft position and rehabilitation protocol.

Surgical technique could be open or arthroscopic, transtibial or inlay technique. It could also be one-bundle or double-bundle reconstruction. Arthroscopic transtibial technique, if done properly, gives satisfactory and comparable result in most patients [14, 33, 34]. There are also dilemmas regarding graft choice. B-PT-B graft of patella ligament was often used before; it has good potential of healing, but technically it is more demanding for placing arthoscopic transtibial and it brings complications in the donor place (pain and patella fractures). Tendon graft of Achilles tendon is acceptable as alograft and has adequate power; the morbidity of donor place is avoided but it is not yet available in our country. Quadriceps tendon graft is becoming more popular. It has adequate power, it is easily taken and easily placed to adequate position. At the moment, 4-strand hamstring tendon graft is the most used graft with this surgery – it has adequate power, it is easily placed and there are no bigger complications of donor's place [35–37]. More important than the graft choice is the graft position, i.e. position of tibial and femoral attachment. Anatomic reconstruction which places the graft into the center of original attachment femorally and tibially will provide the best functionality, isometrics and potentially better graft ingrowth [38–40]. Rehabilitation after such intervention is also specific and very important for the final outcome. It is long-lasting, gradual and individual for each patient. It begins with adequate immobilization aiming to prevent early graft damage. Then, the patient starts gradually with movement exercises and strengthening the muscles avoiding the load in tibiofemoral and patellofemoral joint [26, 41].

The final functional result of surgical treatment of PCL is not easily predicted due to numerous factors affecting it [42]. First of all, it depends on injury grade and combined injuries of other knee structures. According to data from the literature, 50–90% of PCL injuries are combined with injuries of some other knee structures [43]. In our series out of 12 patients, 4 had the ACL tear, 3 had injury of posterolateral corner, 2 patients had accompanying injury of both structures, 8 had meniscus damage and 6 patients had osteochondral lesions. The frequency of combined ligament injuries was 75%. The injury of posterolateral corner is, according to the literature, the most frequent accompanying ligament injury with LCP

damage. According to Fanelli et al. [38], 60% of 222 patients in their series had posterolateral corner injury. Such injury requires additional treatment in terms of reconstruction and in our series it was done in 5 (41.67%) patients. We think that if there is a damage of posterolateral corner, its reconstruction should be done following the same procedure with the LCP reconstruction. Without recognizing these combined ligament lesions there would certainly come to poor postoperative result. Therefore, we emphasize the importance of additional diagnostics (NMR, stress XR), clinical examination (after the injury, after the physical procedures and in anaesthesia) and diagnostic arthroscopy, if required. Only after that, the surgical treatment plan is prepared.

Sex distribution in our series shows significantly more men than women and the ratio is 3:1. This was probably affected by the mechanism of injury since in 58.33% of cases it was traffic trauma, while in the second place there were sports injuries 33.33%. All of them had grade III of injuries and after conducted nonsurgical treatment they still had problems. Average time until the surgery was 12 months. The average age of patients was 34.

The main difficulties that patients complained were pain and feeling of instability. Knee arhtroscopic examination discovered cartilage damage with 6 patients which makes 50%. We cannot say with certainty if they occurred at the moment of injury or they are resulting from the instability. Predominantly, damages were in the medial and patellofemoral part of the knee joint. It could be explained with disturbed biomechanics of movements and bigger pressure in the medial and patellofemoral part [44]. Findings of other authors showed similar results: Strobel et al. [45] – medial damages in 36.6% and patellofemoral in 34.1%; Geissler and Whipple [46] – 49% damage of the medial compartment in patients with the PCL tear who did not have surgery.

Clinical examination after 2 years showed that there were no posterior instability in 6 patients, while in other 5 certain instability remained (3 of grade I and 2 of grade II) and 1 patient showed no improvement. Other tests were not always done in a routine manner but the postoperative findings were better in most cases. It should be mentioned that Dial test and Reverse pivot shift are important for making decision for surgical treatment of posterolateral corner. The impression is that obtained posterior stability after this intervention is better, but still some degree of instability remains in 50% of patients. Other authors are of similar opinion in their series [17, 47, 48]. Anyway, patients treated nonsurgically after the PCL injury do not show improvement in posterior stability after the treatment completion.

Opposite to clinical examination that showed certain level of instability, the patients were mostly satisfied after the intervention and therapy. Average value of Lysholm score preoperatively was 45.92 ± 5.6 (39–55) and 2 years afer the intervention 85.92 ± 8.898 (65–95), which is a significant difference in values in terms of statistics. Also, the average value of subjective IKDC score preoperatively was 38.58 ± 7.948 (25–48), while after the surgery and adequate rehabilitation, significant improvement occurred and the average value was 89.75 ± 4.864 (80–96). We could find similar results in these scores with other authors, too [49, 50].

We did not have any bigger surgical complications during the surgeries. One patient had early postoperative infection, which was treated with arthroscopic washout and debridman while graft was not touched. Later on, the patient did not conduct rehabilitation in accordance with the protocol so we did not have complete follow-up of this case.

The question is whether this technique could regain knee stability required for prevention of its further deterioration. The difference in objective clinical examination and subjective feeling of patient could mislead us. It has been known that patients most often do not mention posterior instability as a big problem. Clinical tests showing stability improvement are static tests. It should be also mentioned that we were not able to objectively measure this instability using some of devices such as K1000, K2000, what is probably one of the shortages of this study. Dynamical instability which occurs while moving in everyday life is the cause of unbalanced load and knee deterioration. We need the devices which could measure dynamic instability. Only based on such measurement and longer follow-up period for patients, we could say whether the knee after such surgery has normal kinematics as the healthy one, and it will not come to rapid degenerative deterioration.

Conclusion

Arthroscopic reconstruction with 4-strand hamstring tendon gives satisfactory result with posterior cruciate ligament reconstruction. The result of subjective feeling of patient is much better then objective clinical examination. Although surgical procedure is technically demanding, with physically active patients having grade III of posterior instability it provides better result than non-surgical treatment.

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Intraoperative tissue expansion as an alternative approach for hand syndactyly management to avoid skin grafts in children

Intraoperativna tkivna ekspanzija kao alternativni pristup u rešavanju sindaktilija šake kod dece bez primene kožnih transplantata

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Abstract

Background/Aim. A great number of syndactyly release techniques have been described over last two centuries. The aim of our study is outcome assessment of congenital syndactyly surgery using temporary tissue expansion of the dorsal hand and local flaps, without skin grafts. **Methods.** This study included children with congenital hand syndactyly treated in period from 2009–2015 by operative technique with temporary tissue expansion of the dorsal hand skin and local flaps, without skin grafting. In all cases surgery was performed under general anesthesia. According to Weber's descriptive method, the functional outcome at the end of the follow-up period was categorized as good, fair or bad. All patients were evaluated for associated anomalies. **Results.** A total of 26 children (20 males, 6 females), aged from 6 months to 6 years (average age of 23 months), were operated by previously described technique. There were 20 patients with complete syndactyly and 6 with incomplete, mostly involving the third web. Associated anomalies were diagnosed in 9 patients. The follow-up period ranged from 1 to 5 years with average duration of 2.6 years. The functional results were good in 20 patients, fair in 5 and bad in 1 patient. **Conclusion.** Surgical procedure with temporary tissue expansion of the dorsal hand skin and local flaps, without skin grafting is effective method of congenital syndactyly treatment in children with good functional and aesthetic results. The advantages of this technique are the reduction of surgery duration and avoiding certain complications, such as web hair growth, hyperpigmentation and hypertrophic scars.

Key words:
congenital abnormalities; polydactyly; reconstructive surgical procedures; infant; child, preschool; treatment outcome.

Apstrakt

Uvod/Cilj. U rešavanju sindaktilije šake kod dece u proteklih 200 godina primenjivan je veliki broj hirurških tehnika. Cilj rada je bila procena ishoda lečenja kongenitalne sindaktilije šake primenom tehnike privremene tkivne ekspanzije i lokalnih režnjeva bez upotrebe kožnih transplantata. **Metode.** Studijom su obuhvaćena deca sa urođenom sindaktilijom šake koja su u periodu 2009–2015. operativno lečena primenom tehnike privremene ekspanzije kože sa dorzalne strane šake i lokalnih režnjeva bez upotrebe kožnih transplantata. Sve operacije su urađene u opštoj anesteziji. Funkcionalni ishod lečenja određivan je prema Weberovoj deskriptivnoj metodi kao dobar, zadovoljavajući i loš. Svi bolesnici su ispitivani radi dijagnostikovanja udruženih anomalija. **Rezultati.** Ukupno 26 dece (20 dečaka i 6 devojčica), uzrasta od šest meseci do šest godina (srednji uzrast 23 meseca), operisano je opisanom tehnikom. Dvadeset bolesnika imalo je potpunu, a šest nepotpunu sindaktiliju šake. Najčešće su bili zahvaćeni treći i četvrti prst. Udružne anomalije su otkrivene kod devet bolesnika. Period praćenja trajao je od jedne do pet godina, u proseku 2,6 godina. Funkcionalni ishod lečenja bio je dobar kod 20 bolesnika, zadovoljavajući kod pet i loš kod jednog deteta. **Zaključak.** Hirurška tehnika privremene ekspanzije kože dorzalne strane šake sa lokalnim režnjevima bez upotrebe kožnih transplantata predstavlja efikasnu metodu za rešavanje urođene sindiktilije šake, sa dobrim funkcionalnim i estetskim rezultatima. Prednost ove tehnike su vremenski kraća operacija i izbegavanje komplikacija kao što su pojava maljavosti, hiperpigmentacije kože i hipertrofičnih ožiljaka.

Ključne reči:
anomalije; polidaktilija; hirurgija, rekonstruktivna, procedure; odojče; deca, predškolska; lečenje, ishod.

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Introduction

Congenital hand differences may significantly affect human's professional abilities and social lives. Syndactyly is one of the most common congenital anomaly of the hand in children. It occurs with an incidence of one in every 2,000 births [1]. Fingers are webbed, they create functional limitations and an abnormal appearance. In most cases, it presents an isolated malformation, while less frequently it is combined with other congenital abnormalities, such as typical cleft hand or asa part of a syndrome (Apert's and Poland's syndrome). Syndactyly is classified as complete if it extends up to the tip of the involved fingers, or incomplete if the involved fingers are partially connected. It is defined as simple if only the skin and the underlying soft tissue of the fingers are fused, or as complex, in the presence of concomitant bone fusion [1, 2]. The treatment goal for syndactyly is to create web space as natural as possible in order to improve the function and appearance of each finger. A great number of syndactyly release techniques have been described over the last two centuries to provide adequate interdigital space and cutaneous coverage for every aspect of the affected digit. The classical teaching has been that skin graft is necessary for covering the dorsolateral surfaces of separated fingers, since the primary closure is not possible. Zigzag incisions along the full length of the fused digits are used to create interdigitating flaps for wound closure since the separation of the digits by longitudinal incisions will invariably cause scar contractures. Kozin [3] reported that the skin grafts have a tendency to contract and lead to finger flexion contractures and "creep"of the web space. We have developed a surgical technique with temporary intraoperative skin expansion that does not require skin grafts. With this technique, we have reduced the surgery time and the possibility of hypertrophic scar formation and avoided certain complications such as web hair growth and hyperpigmentation involving skin grafts.

The aim of our study was to present our own results of temporary intraoperative tissue expansion of the dorsal hand side and local flaps without skin grafts in the treatment of congenital hand syndactyly in children.

Methods

Our prospective study included children with congenital hand syndactyly treated in our Institute by operative technique with temporary tissue expansion of the dorsal hand skin and local flaps, without skin grafting in the period from January 2009 to January 2015. The following conditions were excluded to make the study group more uniform: patients older than 10 years of age, children with complicated hand syndactyly (skeletal abnormalities), Apert's syndrome, Poland's syndrome and amniotic band syndrome. In all cases surgery was performed under general anesthesia and the loupe magnification. The collected variables covered data such as: patient age at the time of operation, sex, type and location of syndactyly, the presence of associated congenital anomaly, complications and postoperative outcome. According to Weber's descriptive method, the functional outcome at the end of the follow-up period was categorized as good, fair or bad. The results are considered to be good if all of the following criteria are fulfilled: natural appearance of the commissure, a flat, smooth scar, a good color match between local skin and skin flaps, full flexion and extension of the operated digit when compared to the contralateral side [or no impairment of range of motion (ROM)] and to preoperative findings in complex syndactylies. The results are considered to be fair by the author if there was a slight aesthetic deficit such as hypertrophic scars that did not compromise the full ROM of the separated fingers. The results were poor if the severe hypertrophic scars or keloids were found, or the patient needed to be reoperated [4]. This investigation was approved by the Institutional and the University Ethical Board. Informed consent was obtained by parent of each patient before operative treatment.

Surgical technique

The operation was done under tourniquet control without exsanguinations for better visualization of the neurovascular bundle (Figure 1).

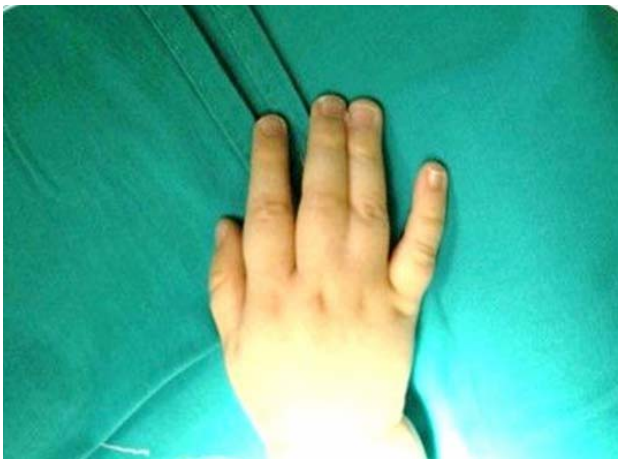

Fig. 1 – Preoperative photograph of the patient with complete syndactyly of the third web space.

Incision markings on the dorsal side of conjoined fingers were made in traditional zigzag fashion to create triangular flaps, with the mirror image incision marked on the palmar side to create interdigitating flaps. Markings for the interdigital commissure on the dorsal side were composed in "sand clock" form modified by D'Arcangelo et al. [5] (omega flap). The apex of the flap was designed to reach the level of the middle portion of the proximal phalanges. Incisions were marked on the volar side to create an anchor shape with two lateral flaps at the base of the two adjacent fingers (Figure 2). Before starting the procedure Foley silicone catheter was put under the skin through a small incision on the dorsal side of interdigital region of web fingers. The incision to insert catheter balloon expander was made at the line surface between apex of the dorsal skin omega flap and the beginning of the triangular flap for lateral side of the digit. Balloon on the distal end of catheter was insufflated with 5 mL saline and

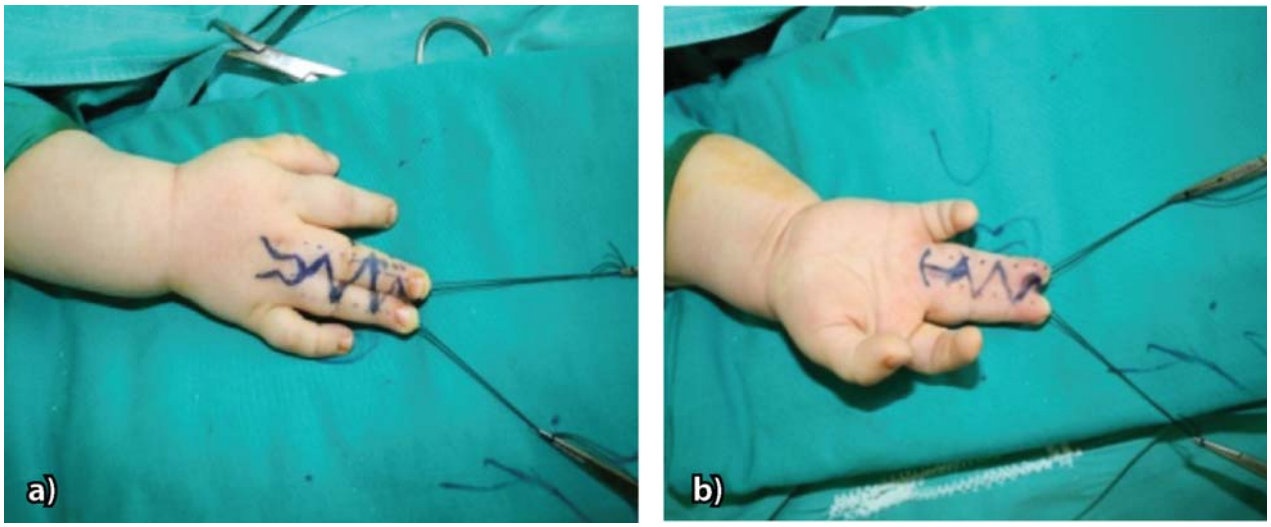

Fig. 2 – Preoperative markings for incisions of the dorsal (a) and volar (b) surface of the conjoined fingers.

expanded the skin (Figure 3). The fingers were separated along the zigzag incisions and 20 min later the temporary skin expansion silicon catheter was moved out. Dorsal full-thickness flap created from the expanded skin was advanced through web spaces and distal tip was sutured to the palmar skin to make commissure (Figure 4). Small areas of the dorsal proximal parts of the fingers were covered with local flaps created from the expanded skin. The technique did not need skin grafts to constitute the web space. The extra fat was trimmed under magnification avoiding injury to the underlying neurovascular bundles. Triangular flaps were mobilized and sutured using absorbable suturing material in

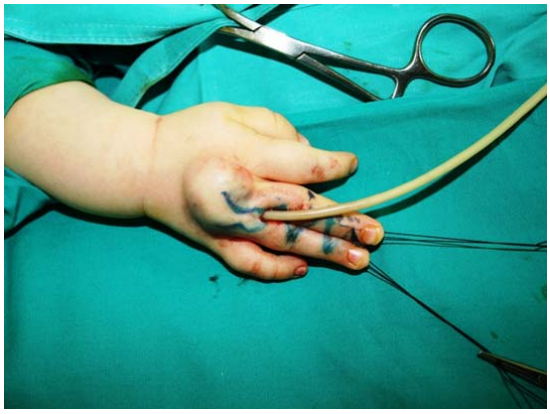

Fig. 3 – Intraoperative temporary tissue expansion of the dorsal hand skin using silicone catheter.

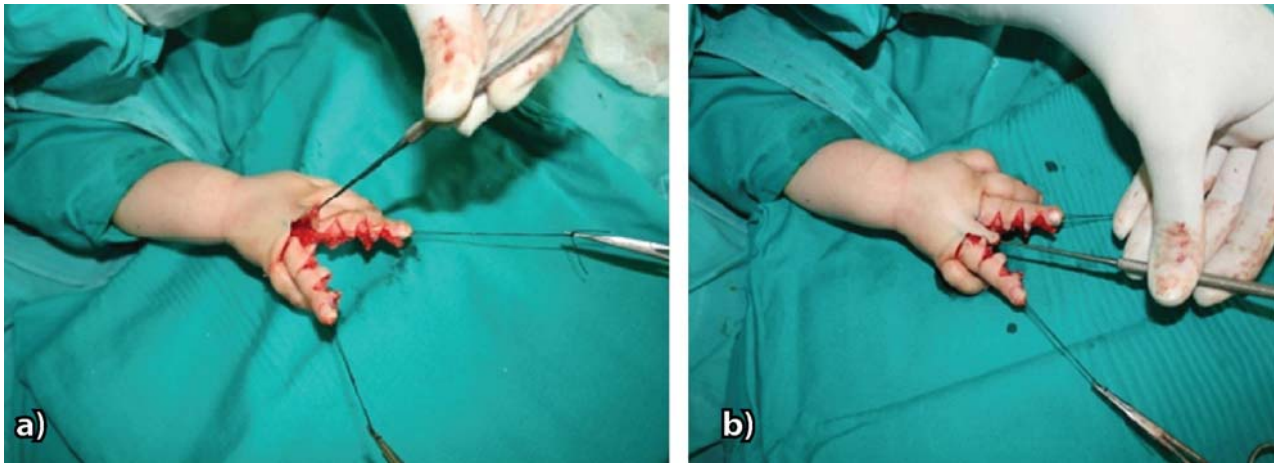

Fig. 4 – The modified omega flap being raised from the dorsum expanded skin of the hand: a) and b). The flap is modilized and advanced distally and volarly to fill the newly created interdigital commissure.

place to completely primarily close the defects along the sides of the two separated fingers. For complete syndactyly in which the nails are united, laterally based skin flaps from the distal pulp were elevated to create the nail fold as advocated by Buck Gramko [6]. After suturing with absorbable stitches, the tourniquet was released for control of hemostasis and assessing flap circulation (Figure 5). The operated area was dressed using topical antibiotic cream, cotton foam and dry gauze in the web space. A usual hand adhesive dressing was done with tape bandage immobilization.

Results

All reviewed patients in our study were operated by the presenting author. There were 20 (76.9%) males and 6 (23.1%) females out of 26 children operated by described technique over the period studied.

The age at which the first surgery was done ranged from 6 months to 6 years with the median age of 23 months. Totally patients 18 (62.3%) were operated before 24 months of age and 8 children (37.7%) were treated between 2 and 6 years of age.

In relation to the type of the fingers webbing, 20 (76.9%) patients had complete, while 6 (23.1%) children had incomplete syndactyly. Twenty four of syndactylous webs were simple and 2 were complex in which fingers, except the soft tissue connection, had bones united in the distal part of the distal phalanges.

Considering location of syndactyly, the third web was most commonly involved (13 children). The second web was affected in 8 cases, while the fourth web was involved in 3 patients; 2 children had conjoined middle, ring and small fingers at the same time (Figure 6). The complete functional recovery of one such patient using described operative technique can be viewed in the Figure 7. There were 6 patients with bilateral syndactyly, 7 with right hand involved and in 13 children the left hand was affected.

Associated congenital anomalies were diagnosed in 9 patients including: hand hypoplasia, hand polydactyly, foot syndactyly and obstructive megaureter.

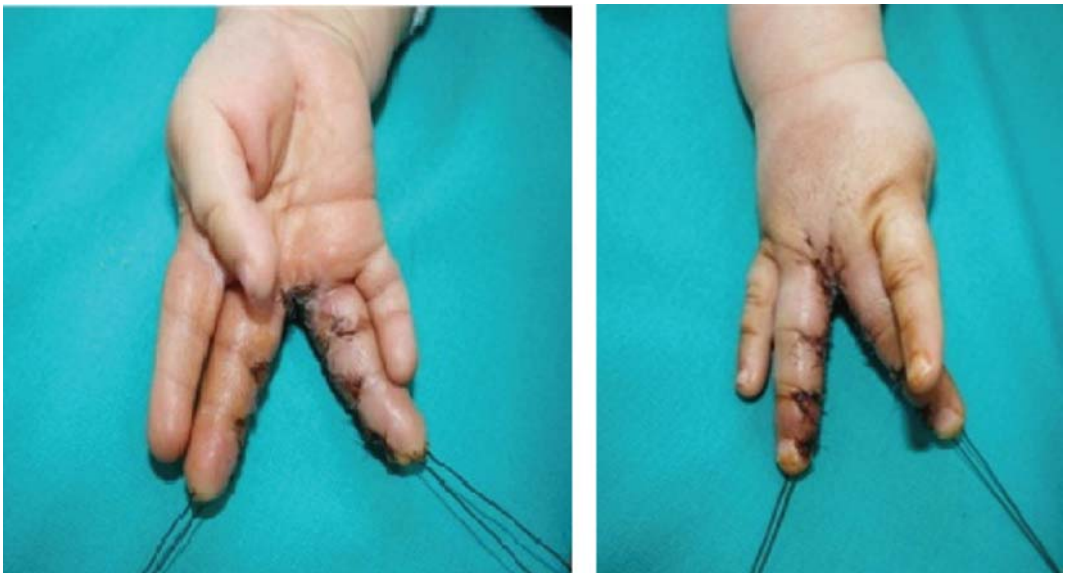

Fig. 5 – Postoperative photographs of the separated fingers.

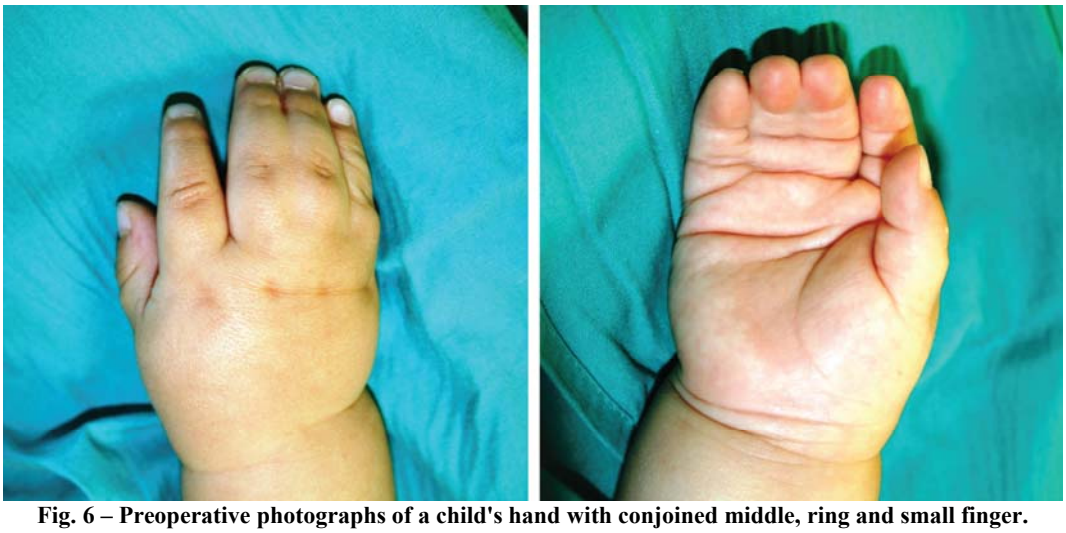

Fig. 6 – Preoperative photographs of a child's hand with conjoined middle, ring and small finger.

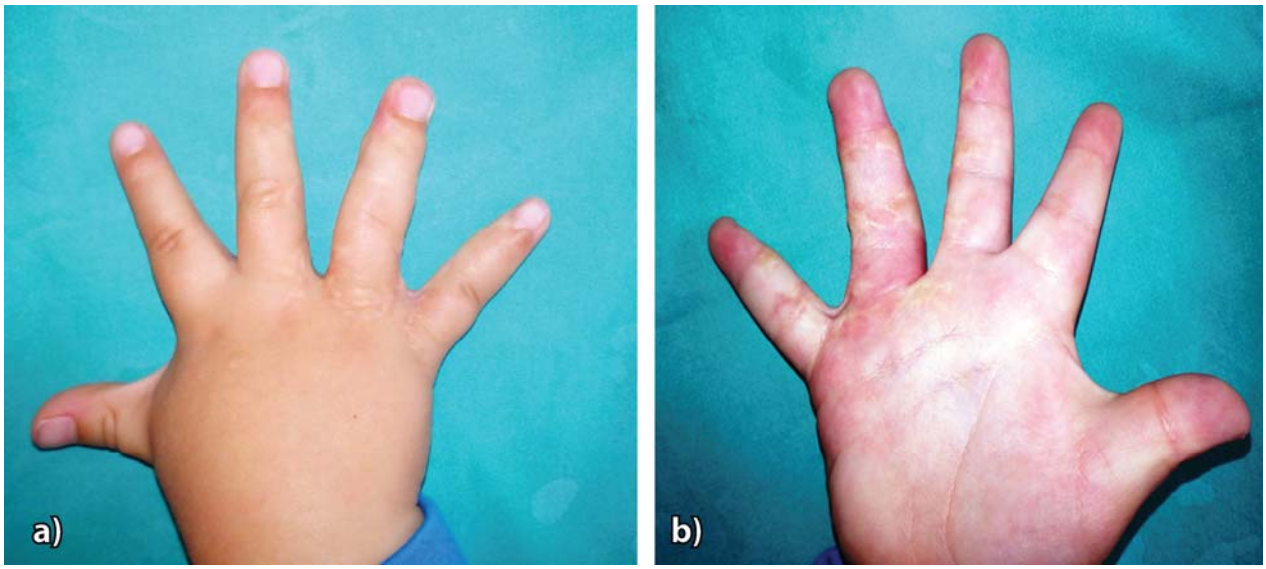

Fig. 7 –Postoperative views of the separated fingers taken at four years of age after three years follow-up of a patient with complete syndactyly of the third and fourth web space at 12 month of age: a) dorsal, b) volar surface of the hand.

All children in our study were treated by described operative technique with dorsal hand skin expansion and local flaps. In all cases we put absorbable sutures (monocril 5.0) to avoid suture removal. The skin grafts were not used for the surgical treatment in any of the patients. We did not have any intraoperative complications.

Considering all the patients together, 24 did not have postoperative complications such as: hematoma, infection, disturbance of the circulation or flap loss. One patient had distal phalanx of index finger deformity, while one had "web creep".

The follow-up period ranged from 1 to 5 years, with the average period of 2.6 years.

Functional results according to the Weber descriptive method were: good in 20 patients, fair in 5 and bad in 1 case. We achieved a natural appearance and normal shape of the commissure with smooth scar in more than 76% of the cases. In 96.1% of the patients full ROM was found. Out of the 5 patients with fair results, 4 had slightly hypertrophic scars and 1 had little web creep. One bad case preoperatively had complex and complete syndactyly of the second web with double distal phalanges of the index finger. After separation of the distal phalange digits deformity was developed and the function of the distal interphalangeal joint was compromised. Considering the age when operation was done in the group of patients younger than 24 months of the age, the results were as follows: 15 (83.3%) patients good, two (11.1%) patients fair and one (5.6%) child bad. In the group of the children between 2 and 6 years of the age, the results were as follows: good in 5 (62.5%) patients and fair in 3 (37.5%) cases with no bad results (Figure 8).

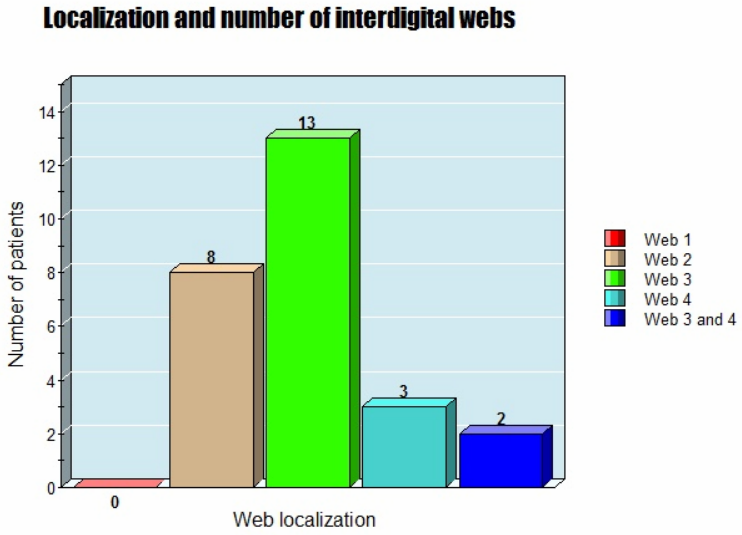

Fig. 8 – Localization and number of interdigital webs.

Discussion

Analyzing surgical results from the operated children with congenital hand syndactyly is always challenging. Among the classification systems for functional evaluations of the hands that exist, none of them is easily applicable to pediatric population.

Among 26 children who underwent syndactyly repair in our study, male patients predominated (76.9%) as it was also found in the literature consulted [7].

The timing of surgery is controversial in syndactyly release. Hand function was usually established between 6 and 24 months of age. Most surgeons advocate that the operation should be performed before the age of two. They consider that surgical procedure at a later age would be less satisfactory and would have increased complication rate [8]. In our study, good results were observed in 83.3% patients younger than 24 months and 62% children aged from 2 to 6 years. According to our opinion the results are more encouraging if surgery is done at the earlier age because younger children have more elastic skin. The patients mean age at the time of the surgery in our study was 23 months and we agree with the mentioned opinion.

It was reported in relevant literature that most of the patients had incomplete soft tissue syndactyly and that the third web was most commonly involved, as was found in our investigation.

Many techniques of syndactyly release have been described over the last two centuries [9]. Syndactyly surgery include the following three steps: dividing the fingers, commissure reconstruction and resurfacing borders of the separated digits.

Traditional operative procedures for hand syndactyly have used flaps from the dorsum of the web fingers and dorsal and palmar interdigitating flaps. The two separated digits have a greater surface area than a single conjoined digit and most of these techniques employ skin grafts. Historically, split thickness and full thickness skin grafts have both been used to cover remaining surgical defects [10]. Deunk et al. [11] reported complications associated with skin grafts for syndactyly release. Hands that received skin grafts had a higher incidence of hyperpigmentation, hair growth, scar contracture, web creep and limited spreading of the digits. Review of Moss and Foucher [12] showed 5% to 59% rates of web creep and Percival and Sykes [13] found 13% of secondary flexion contracture and 15% of web creep in children after skin grafting. Ekerot [14] reported that the use of skin grafts in syndactyly treatment required more time for surgery and more time for complete healing.

For these reasons, surgeons have recently developed several techniques to avoid the use of skin grafts in syndactyly repair. The skin of the normal web is inclined distally in a dorsopalmar direction at almost 40 degrees. The base of the web commissure is normally located at the mid portion of the proximal phalanx. Reconstruction of the new web spaces is the most challenging and the key point in the syndactyly treatment. Niranjan and De Carpentier [15] first described a technique for correction of syndactyly without skin graft. They used dorsal trilobed flap wider than the currently used flaps and completely covered the interdigital space with no web creep recurrence. Ekerot [14] showed the advantages of non-grafting technique and absorbable skin sutures used in syndactyly release. Several authors recommended V Y dorsal metacarpal advancement flap to create new web space which allows easier primary closure of the proximal phalanges of the separated fingers, without the use of skin grafts [10, 16]. Extensive defatting of the fingers and the interdigital space has been performed in study of Gruese and Coessens [17]. They believed that the removal of fat tissue around the neurovascular pedicle in the interdigital space and along the full length of the fingers allowed for primary closure of the digital flaps without inducing tension. Cetik et al. [18] developed operative procedure with dorsal and volar quadrilateral flaps for the web space that did not require skin grafts. To obtain adequate coverage of the separated digits they used intermittent skin incision on the radial and ulnar side of the fingers in the levels of proximal interphalangeal and distal interphalangeal joint.

Since its introduction by Neumann [19] and refinement by Radovan [20] tissue expansion has revolutionized the treatment of skin deficiencies in certain circumstances. Dorsal hand skin near the web space has a good elastic structure and can be easily elongated to the interdigital space. It offers an excellent color, thickness and texture matching the adjacent fingers. Several authors have tested skin expansion of the dorsal hand to increase local tissue available for flap reparation following syndactyly release with various results [21, 22]. Most of them performed two surgical procedures using small commercial tissue expander to avoid skin graft in syndactyly treatment. Coombs and Mutimer [21] advocated two operations with skin expansion for reconstruction of the first web in Apert's syndrome hand syndactyly. In the first procedure the authors put tissue expander under the skin and after few weeks following expansion they did second operation consisted of removing the expander and separatingthe fingers. In some cases, they needed a small skin graft. Two stage skin expansion procedure in Apert`s syndrome hand syndactyly was reported with unacceptable rate of complications and higher rate of revision [22].

In our study we developed technique of intraoperative temporary skin expansion and local flaps with no grafting surgery to divide conjoined digits in children. Instead of small tissue expander we used Foley silicone catheter with a balloon to expand the dorsal hand skin. With temporary intraoperative expansion lasting 20 min, we got enough skin surface to create adequate flap for new web space and local flaps to cover small proximal phalanges defects of the separated fingers. In that way, we avoided one more operation under general anesthesia and all possible risks. Using Foley silicone catheter with a balloon is a safe method for children and cheaper than traditional skin expander. This is a good solution for conditions when a commercial tissue expander is not available. Dorsal cutaneous flap creates skin of good quality, color and growth into the web compared with skin grafts. We believe as other authors that zigzag incisions along full length of the fingers show lower rate of digital scar

contracture than straight line closure. We agreed with surgeons who recommended defatting of the interdigital space and along the fingers to allow primary closure of the lateral triangular flaps without tension. This maneuver is not easy to perform in young children. The major potential intraoperative complication is injury to the digital artery or nerve while separating and defatting the fingers. This can easily be avoided by carefully identifying and preserving the neurovascular bundle under loupe magnification during dissection. There were also no cases of neurovascular injury of the digits in this series. We recommended using fast absorbable sutures as advocated by Weber and Schiestl [4] and Ekerot [14]. No local side effects were noted and we avoided removal of the suture material which could cause discomfort to the infant. The described technique was used for complete and incomplete hand syndactyly with good results in most of the operated children in our study. It offers adequate soft tissue coverage without skin grafts in all of the cases. The flaps we used have all advantages of a local flap, namely color match, thickness and texture, which make them perfect for web reconstruction. The full range of motion of the digits was not compromised in great majority of the reviewed patients. We have only one bad case with deformity of index distal phalange because the child had double distal phalange of index finger preoperatively. The comparison with other series is difficult because there is no standard assessment score. In our experience, this surgical procedure for separation of web fingers can be applied easily and safely to pediatric population. This study presents a single center experience with some limitations which have to be corrected in future investigation.

Conclusion

The described technique is an alternative approach for congenital hand syndactyly treatment in children. The advantages of this technique are the reduction of surgery duration and the possibility of hypertrophic scar formation, avoiding certain complications, such as web hair growth and hyperpigmentation involving skin grafts. In addition, there is no donor site morbidity.

Surgical procedure with temporary tissue expansion of the dorsal hand skin and local flaps is an effective method, simple and inexpensive, giving good aesthetic and functional results in most of the patients.

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SHORT COMMUNICATIONS

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Thoracoscore: Predicting risk of in-hospital mortality for patients undergoing pulmonary resection

Thoracoscore: Procena rizika intrahospitalnog mortaliteta bolesnika nakon resekcije pluća

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Abstract

Background/Aim. Thoracic surgery is in need of a widely recognized and dependable risk model which could prospectively make objective conclusions and retrospectively allow comparison of outcomes. Thoracoscore is the first model with multiple variables developed for predicting in-hospital mortality following pulmonary resections. It is integrated in the British Thoracic Society and National Institute of Health and Clinical Excellence guidelines. However, additional evaluation of Thoracoscore is considerably advised in order to demonstrate its validity and potentially make it a dependable tool for thoracic surgeons across the world. Our study assesses the accuracy of Thoracoscore scoring system in estimating in-hospital mortality in patients undergoing pulmonary resections. **Methods.** Between September 2013 and October 2014 data were retrospectively collected on 196 patients operated on at the Thoracic Surgery Clinic, Institute of Pulmonary Diseases of Vojvodina. The procedures performed were: pneumonectomies, lobectomies and modified lobectomies (including bilobectomy and sleeve-lobectomy), Wedge resections and atypical resections. The Thoracoscore was calculated based on these nine variables: age, sex, American Society of Anaesthesiologists' (ASA) class, performance status classification, dyspnea score, priority of surgery, procedure class, diagnosis group and co-morbidities score. **Results.** Study included one hundred and ninety-six patients, average age of 62 ± 9 years, and 61% were males. Predicted mean in-hospital mortality was 3.6 ± 3.2% 95% confidence interval (CI) 3.16–4.06, and mean actual in-hospital mortality was 6/196 (3.1%) (95% CI 1.78–4.42). Patients who were > 65 years old contributed to 3/6 (50%) of in-hospital mortality, and 4/6 (67%)were males. Four of 6 (67%) patients underwent pneumonectomy due to malignant pathology. Thoracoscore was divided into 4 risk groups: low (0–3), moderate (3.1–5), high (5.1–8) and very high (> 8). The correlation between observed and expected mortality was 0.99, by category of risk. Old age, male gender and malignancy showed to be strong indicators of in-hospital mortality. **Conclusion.** At our department Thoracoscore presented with good performance and as a practical tool for predicting in-hospital mortality among patients undergoing lung resections. However, any risk scoring system needs further validation before implementation and outcomes must be compared to those of other programs.

Key words:
thoracic surgical procedures; lung diseases; hospital mortality; risk factors; prognosis; treatment outcome.

Apstrakt

Uvod/Cilj. U oblasti grudne hirurgije prisutna je potreba za široko priznatim i pouzdanim modelom rizika na osnovu kojeg bi se mogli prospektivno donositi objektivni zaključci i koji bi omogućio retrospektivno poređenje ishoda. *Thoracoscore* je prvi model koji se sastoji od nekoliko parametara za procenu intrahospitalnog mortaliteta nakon resekcije pluća. Ovaj model je usvojen od strane udruženja kao što su *British Thoracic Society* i *National Institute of Health and Clinical Excellence*. Ipak, savetuje se dodatna evaluacija *Thoracoscore* bodovnog sistema kako bi se ustanovila njegova validnost i pouzdanost u oblasti grudne hirurge širom sveta. U našoj studiji smo pokušali ustanoviti tačnost *Thoracoscore* bodovnog sistema u proceni intrahospitalnog mortaliteta bolesnika nakon resekcije pluća. **Metode.** U periodu od septembra 2013. do oktobra 2014. godine podaci su retrospektivno prikupljeni za 196 bolesnika operisanih na Klinici za grudnu hirurgiju Instituta za plućne bolesti Vojvodine. Izvršene hirurške procedure bile su pneumonektomije, lobektomije i modifikovane lobektomije (bilobektomije i *sleeve*-lobektomije). *Thoracoscore* je izračunavan na osnovu devet parametara: starost, pol, *American Society of Anesthesiologists* (ASA) skor, dispneja skor, procena opšteg stanja bolesnika, komorbiditeti, dijagnostička grupa, hitnost operacije i hirurška procedura.

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Rezultati. U studiju je bilo uključeno 196 bolesnika, prosečne starosti 62 ± 9 godina, od kojih je 61% bilo muškog pola. Prosečna stopa intrahospitalnog mortaliteta na osnovu *Thoracoscore* modela bila je 3.6 ± 3.2%, interval pouzdanosti (IP) 3.16–4.06, dok je prosečna vrednost stvarnog intrahospitalnog mortalita iznosila 6/196 (3.1%) (95% IP 1.78–4.42%). Najveća stopa mortalita, 3/6 (50%), bila je kod bolesnika starijih od 65 godina. Od ukupnog broja intrahospitalno preminulih bolesnika, 4/6 (67%) bili su muškog pola. Pneumonektomija je urađena kod 4/6 (76%) bolesnika zbog malignog patološkog nalaza. *Thoracoscore* je bio podeljen u 4 grupe rizika: nizak rizik (0–3), umeren rizik (3.1–5), visok rizik (5.1–8) i veoma visok rizik (> 8). Korelacija između stvarnog i očekivanog mortaliteta iznosila je 0.99, na osnovu kategorije rizika. Starija dob, muški pol i malignitet su se pokazali kao najznačajniji indikatori intrahospitalnog mortaliteta. **Zaključak.** Na našoj klinici *Thoracoscore* se pokazao kao praktičan model za procenu intrahospitalnog mortaliteta bolesnika nakon resekcije pluća. Ipak, ovaj bodovni sistem mora biti dodatno ispitan pre zvanične upotrebe, dok se ishodi moraju uporediti sa ishodima drugih klinika.

Ključne reči:
hirurgija, torakalna, procedure; pluća, bolesti; mortalitet, bolnički; faktori rizika; prognoza; lečenje, ishod.

Introduction

Over the past twenty years, scoring systems have become a useful methods for patient assessment, especially because the patients who require pulmonary resection have become more complex, with more comorbidities. The risk of mortality is one of the crucial elements when trying to decide if surgery is the best option for the patient. Usefulness of an objective risk stratification model were acknowledged by cardiac surgeons more than two decades ago. Today, they substantially rely on several models of risk assessment for patients facing cardiac surgery. However, as of now, broadly accepted risk model for thoracic surgery has yet to be established. Thus far, only two risk scoring systems have been evaluated, but neither become a standard. Thoracoscore is the first model with multiple variables developed for predicting in-hospital mortality following pulmonary resections [1]. This model was acquired from data of 15,183 patients who underwent thoracic surgery in 59 French hospitals [1, 2]. It was integrated in the British Thoracic Society and National Institute of Health and Clinical Excellence guidelines [1–3]. Thoracoscore was verified internally and externally by some groups which is not sufficient and the results were diverse. The observed versus predicted mortality rates showed notable differences among European countries. This fact indicates a necessity for creating an objective risk stratification model [1, 4, 7]. Thoracoscore opened up new horizons in thoracic surgery and its beginnings would hopefully lead to development of an objective and reliable risk stratification model that would help in providing patients with better quality of treatment.

This study assesses the accuracy of Thoracoscore scoring system in a major Serbian university-based thoracic surgery centre with a population of patients undergoing variety of pulmonary resections.

Methods

Patient population

Between September 2013 and October 2014, data were retrospectively collected on 196 patients operated on at the Thoracic Surgery Clinic, Institute of Pulmonary Diseases of Vojvodina. The procedures performed were: 50 pneumonectomies, 109 lobectomies and modified lobectomies (including bilobectomy and sleeve-lobectomy), 9 Wedge resections and 28 atypical resections. The Thoracoscore was calculated using these nine variables: age, sex, American Society of Anaesthesiologists (ASA) class, performance status classification, dyspnea score, priority of surgery, procedure class, diagnosis group and comorbidities score. Data were collected from the patients' charts and were entered into the hospital information system by thoracic surgeons. Thoracoscore was calculated for all patients undergoing elective, urgent or emergency pulmonary resections at the Institute for Pulmonary Diseases of Vojvodina.

Data analysis and statistical methods

Variables were noted as percentages and continuous variables as mean value ± 1 standard deviation. Descriptive statistics were used for all applicable variables. Mortality rate for all patients undergoing lung resection was calculated using Thoracoscore, and presented as the ratio of observed deaths to expected deaths. The formula used for calculating mortality in the original work of Falcoz et al. [1] was as follows: Odds = exp[−7.3737 + (0.7679 if code of age is 1 or 1.0073 if code of age is 2) + (0.4505 × sex score) + (0.6057 × ASA score) + (0.6890 × performance status classification) + (0.9075 × dyspnea score) + (0.8443 × code for priority of surgery) + (1.2176 × procedure class) + (1.2423 × diagnosis group) + (0.7447 if code of comorbidity is 1 or 0.9065 if code of comorbidity is 2)] [1]. Procedures were stratified into 4 groups: pneumonectomy, lobectomy and modified lobectomy (including bilobectomy and sleeve-lobectomy), Wedge resection and atypical resection. The groups presented as follows: Group 1 – low risk group (≤ 3%); Group 2 – moderate risk (3.1–5%); Group 3: high risk group (5.1–8%); Group 4: very high risk group (> 8%). Because the original model underestimated mortality in the moderate risk group and overestimated mortality in the high risk group, our risk groups have been modified to have different values from those in the original study by Falcoz et al. [1] In-hospital mortality for each group was observed, predicted and assessed. Calculation of the area under the reciever operating characteristic (ROC) curve was used to interpret Thoracoscore's

validity. The area under the ROC was calculated as *C* statistic. The discriminative power of the model was excellent if the area under the ROC was > 0.80, very good if > 0.75 and good if > 0.70 [6]. All data were evaluated using Statistics Package for the Social Sciences (SPSS) version 2.0 (SPSS, Inc, Chicago, IL, USA).

Results

The study included 196 patients, average age of 62 ± 9 years where 61% were males. (Table 1). Mean predicted probability of in-hospital mortality was 3.6 ± 3.2%, 95% confidence interval (CI) 3.16–4.06%, while mean actual in-hospital mortality was 3.1% (6/196) (95% CI 1.78–4.42%). Patients who were > 65 years old contributed to 3/6 (50%) of in-hospital mortality, and 4/6 (67%) of patients who died in hospital were males. Four of 6 (67%) patients underwent pneumonectomy due to malignant pathology. Each of the 4 incremental risk groups was analyzed for predictive and observed mortality (Table 2). The correlation between observed and expected mortality was 0.99, by a category of risk. Thoracoscore showed outstanding discriminatory ability with *C* statistic (0.78, 95% CI).

Discussion

Out of 9 variables in the Thoracoscore model, age,

Table 1

Patient preoperative characteristics

Characteristics	Cohort	Alive	Died perioperatively
Patients, n (%)	196	190 (96.9)	6 (3.1)
Age (years), mean ± SD			
median	62 ± 9		
range	22–80		
< 55, n (%)	33 (16.9)	32 (97.0)	1 (3.0)
55–65, n (%)	102 (2.0)	100 (98.0)	2 (2.0)
> 65, n (%)	61 (31.1)	58 (95.0)	3 (5.0)
Gender, n (%)			
male	119 (60.7)	115 (96.6)	4 (3.4)
female	77 (39.3)	75 (97.4)	2 (2.6)
Diagnosis group, n (%)			
benign	19 (9.7)	19 (100)	0 (0)
malignant, n (%)	177 (90.3)	171 (96.6)	6 (3.4)
Procedure clases			
pneumonectomy	50 (25.5)	46 (92)	4 (8)
lobectomy and modified lobectomy	109 (55.6)	107 (98.2)	2 (1.8)
wedge resection	9 (4.6)	9 (100)	0 (0)
atypical resection	28 (14.3)	28 (100)	0 (0)
ASA class, n (%)			
≤ 2	16 (8.2)	16 (100)	0 (0)
≥ 3	180 (91.8)	174 (96.7)	6 (3.3)
Performance status classification, n (%)			
≤ 2	188 (96)	184 (97.9)	4 (2.1)
≥ 3	8 (4)	6 (75)	2 (25)
Dyspnea score, n (%)			
≤ 2	147 (75)	144 (98)	3 (2)
≥ 3	49 (25)	46 (93.9)	3 (6.1)
Priority of procedure, n (%)			
elective	196 (100)	190 (96.9)	6 (3.1)
urgent	0 (0)		
Comorbidities, n (%)			
0	32 (16.3)	32 (100)	0 (0)
≤ 2	126 (64.3)	123 (97.6)	3 (2.4)
≥ 3	38 (19.4)	37 (97.4)	1 (2.6)

SD – standard deviation; n (%) – number percentage of patients.

Table 2

Predicted *vs* observed perioperative mortality in incremental risk groups and their confidence intervals (CI)

Risk group	Patients	Mean predicted mortality (%)	CI (%)	Mean observed mortality (%)	CI (%)
Group 1 (≤ 3)	122	1.3	0.93–1.67	0.8	0.62–0.98
Group 2 (3.1–5)	36	3.4	2.92–3.88	2.8	2.47–3.13
Group 3 (5.1–8)	8	3.5	2.83–4.17	2.5	1.81–3.19
Group 4 (> 8)	31	10.1	9.53–10.67	9.7	9.35–10.05
All	196	3.6	3.16–4.06	3.1	2.65–3.55

malignancy, pneumonectomy, ASA class, performance status and dyspnea score had greatest effect on in-hospital mortality risk. Our results correspond with the results presented by Falcoz et al. [1], in their initial study. Alike independent variables for in-hospital mortality after lung resection which were recognized by Berrisford et al. [7] and Harpole et al. [8], Ferguson and Durkin [9] noted performance status as a predictor for postoperative complications. Additionally, Prause et al. [10] and Chamogeorgakis et al. [2,3] noted the ASA score as a strong indicator of perioperative mortality overall. One of the largest pneumonectomy series from the Mayo Clinic showed that pneumonectomy conveys an important risk for in-hospital mortality, contributing to 11% of deaths [11]. On the contrary, Bradley et al. [12] and Sharkey et al. [13] disclosed setbacks of Thoracoscore, highlighting its inability to predict postoperative mortality, and suggested the need for an improved scoring system in the area of thoracic surgery.

It should be mentioned that Thoracoscore model analyzes only in-hospital mortality, eliminating other risks, such as the risk of death regarded to surgery. Also, Thoracoscore consists of only 9 variables, not taking into account other factors that could possibly be as important.

Our study has a few limitations as well. First, long-term survival is not monitored, since this is the first time a scoring system for thoracic surgery was used and validated in Serbia. Second, our study is derived from a single-center database, and patient profiles greatly vary from the population in other countries. Taking into account everything listed, additional evaluation of Thoracoscore is considerably advised.

Conclusion

At our department Thoracoscore presented good performance and came across as a practical tool for predicting in-hospital mortality among patients undergoing lung resections. Older age, male gender and malignant pathology showed to be the strongest indicators of in-hospital mortality in our study. This scoring system is easy to use and, if further validated, could find its practical value in thoracic surgery units.

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SHORT COMMUNICATION

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Is surgical treatment necessary in all hydronephrotic kidney allografts?

Da li je hirurški pristup neohodan u svim slučajevima lečenja hidronefroze transplantiranog bubrega?

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Abstract

Background/Aim. The management of kidney graft hydronephrosis (KGH) is usually surgical, although some cases require expectant management and follow-up. The aim of the study was to discuss the criteria for expectant management or immediate surgical intervention in the series of patients with KGH. **Methods**. The paper is based on a retrospective study of 42 patients with KGH. The patients underwent kidney transplantation from January 2007 to December 2012. There were 19 cadaveric donor recipients and 23 living donor recipients. The average follow-up was 15,2 (range 12–21) months. The average recipient`s age was 41,6 years. In every case study, the diagnosis of graft hydronephrosis was established using abdominal ultrasonography. The degree of hydronephrosis was estimated on the basis of measuring the maximal diameter of the pelvicalyceal dilatation (PD). **Results**. There were no patients with graft failure after the period during which they were under medical observation. Hydronephrosis resolved completely in six (14%) patients. The median maximal PD was 28 ± 9 (range 14 –38) mm and the median last PD was 23 ± 11 (range 0–35) mm and they did not differ significantly ($p = 0.23$). The last serum creatinine was significantly lower than the maximal creatinine value ($p < 0.05$). In twelve (29%) patients renal function normalized. Renal function remained stable during the period of medical observation. At the end of the follow-up, all patients had sterile urine culture. **Conclusion**. The traditional doctrine, according to which KGH represents an absolute indication for surgery, can be debated; the majority of the patients observed require just active surveillance. Prompt surgical correction is recommended only in cases with increasing pelvicalyceal dilatation and the development of symptoms, progressively decreasing renal function or recurrent urinary tract infection.

Key words:
kidney transplantation; postoperative complications; hydronephrosis; kidney function tests; prognosis; conservative treatment.

Apstrakt

Uvod/Cilj. Pristup lečenju hidronefroze transplantiranog bubrega (HTB) je obično hirurški, iako neki slučajevi zahtevaju ekspektativni pristup i praćenje. Cilj rada bio je utvrditi kriterijume za ekspektativni pristup ili neposredan hirurški pristup na seriji bolesnika sa hidronefrozom transplantiranog bubrega. **Metode**. Rad se bazira na retrospektivnom istraživanju koje je obuhvatilo 42 bolesnika sa HTB. Ispitivanjem su obuhvaćeni bolesnici kod kojih je učinjena transplantacija bubrega u periodu od januara 2007. godine do decembra 2012. godine. U posmatranom periodu učinjeno je 19 kadaveričnih transplantacija i 23 transplantacije sa živog donora. Prosečno vreme praćenja bilo je 15,2 (raspon 12–21) meseca. Prosečna starost osobe koja je primila bubreg bila je 41,6 godina. Dijagnoza hidronefroze u svakom slučaju je postavljana ultrazvučnim pregledom. Stepen hidronefroze procenjivan je na osnovu merenja maksimalnih prečnika proširenih bubrežnih čašica i karlica. **Rezultati**. Tokom perioda praćenja nije bilo slučajeva nefunkcionalnosti grafta. Problem hidronefroze u potpunosti je bio rešen kod šest (14%) bolesnika. Prosečno maksimalno proširenje bubrežnih čašica i karlica bilo je 28 ± 9 (raspon 14–38) mm, a prosečna vrednosti proširenja pijelona i čašica na kraju praćenja bila je 23 ± 11 (raspon 0-35) mm. Nije postojala statistički značajna razlika ($p = 0.23$). Poslednja kontrolna vrednost serumskog kreatinina bila je značajno niža od maksimalne vrednosti kreatinina ($p < 0.05$). Bubrežna funkcija je normalizovana kod 12 pacijenata (29) i ostala je stabilna tokom perioda posmatranja. Na kraju praćenja svi bolesnici su imali sterilan nalaz urinokulture. **Zaključak**. Tradicionalan pristup, po kome HTB predstavlja apsolutnu indikaciju za operativno lečenje, može se dalje istraživati; većina bolesnika koja je ovde praćena zahtevala je samo pažljivo praćenje. Neodložna hirurška intervencija preporučuje se samo u slučajevima sa izrazitim proširenjem bubrežnih čašica i karlice kao i razvojem simptoma progresivno smanjene bubrežne funkcije ili rekurentne infekcije urinarnog trakta.

Ključne reči:
transplantacija bubrega; postoperativne komplikacije; hidronefroza; bubreg, funkcijski testovi; prognoza; lečenje, konzervativno.

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Introduction

Kidney graft hydronephrosis (KGH) is an increasing problem in kidney transplant recipients. Patients with this condition show a higher prevalence for developing irreversible graft failure. The incidence of kidney transplant obstruction ranges from 2–12% [1]. The presence of KGH can be due to an obstruction, or it may appear because of other reasons [2]. Hydronephrosis alone, or associated with additional pathological conditions, can lead to irreversible damage of renal graft and graft loss [3]. Therefore, all factors affecting renal function have to be explored in details.

The mainstay in the management of KGH is immediate curative treatment. The most recent studies favor early surgical repair because of the adequate functional results with preservation of renal graft function [4, 5]. It is considered that urgent surgical intervention should be the first choice in managing KGH because of satisfying functional outcome coupled with low morbidity. Delayed repair may lead to prolongation of morbidity and negatively affect kidney graft function [6]. Just a small number of authors advocate delayed repair because hydronephrosis may be due to factors other than obstruction [2, 7]. In the past, a significant portion of patients with renal transplant underwent open surgical procedures for the treatment of obstruction [8]. However, with advances in technology, these complications are now treated more often by percutaneous and/or endoscopic techniques [3, 9]. No study has yet evaluated the outcome of patients with asymptomatic and non complicated KGH who underwent expectant management. However, only clinically insignificant KGH is suitable for active surveillance without the need for immediate surgical intervention. The surgical significance of KGH may be suggested with the underlying cause of hydronephrosis, a degree of pelvicalyceal dilatation and deterioration of renal function. All factors affecting renal function in addition to hydronephrosis must be explored in detail. Close monitoring of several parameters of renal function should be the basis of active surveillance of patients with KGH. Therefore, the need for routine surgery in patients with KGH may be debated. The traditional doctrine that KGH represents an absolute indication for surgery has recently been questioned. The aim of this study was to present our experience with active surveillance of clinically insignificant KGH and recommend criteria for surgical interventions in these patients.

Methods

During a 6-year period, a retrospective review of our institution kidney transplantation database was performed. All transplantations were performed at our institution, the Clinic of Urology, Clinical Center of Serbia, from January 2007 to December 2012. After institutional review board approval, 42 patients who underwent kidney transplantation were included in this retrospective study. There were 23 kidney transplants from living donors and 19 from cadaveric donors. The average age of recipients was 41,6 (range 23–54) years. Lich-Gregoire ureteral implantation was performed in all kidney recipients and the ureter was stented with indwelling double-J catheter. The ureteral double-J catheter was removed 21 days after transplantation. After removal of the double-J catheter, ultrasonography detected hydronephrosis in all kidney grafts.

Patients had a complete follow-up at least 1-year, 15.2 months on average (range 12–21 months) and were evaluated with frequent clinical examinations. All patients were closely followed-up with serial ultrasonography (US), urine culture (UC) and serum creatinine (SCr) determination. The maximal diameter of the pelvicalyceal dilatation was used as a US parameter. SCr and UC determination as well as US were repeated every week in first 3 months, every two weeks in 3 to 6 months and after that period they were performed once a month. In the follow-up, we determined the variables for SCr level and pelvicalyceal dilatation (PD) and compared them to previous measurements. Once these values become stable, the follow-up continues for at least 2 months, and if the values remain stable over that period, the follow-up ends. SCr values are considered normal by a SCr < 115 μmol/L. Urinary tract infection (UTI) is defined as any culture that yielded ≥ 10^5 colonies. Recipients with UTI were treated with targeted antibiotic therapy.

Additional measurements were performed during the follow-up protocol and their repetition was decided on case-by-case basis. Graft failure was defined as the date of return to chronic dialysis, graft nephrectomy or death with a functioning graft. All values are represented as the median ± standard deviation (range). Relationship among parameters was analyzed using the unpaired *t*-test. *P* values < 0.05 were considered statistically significant.

Results

During the follow-up, the median maximal SCr level was 245.8 ± 78.6 (range 118.2–425.8) μmol/L and the median SCr level at the end of the follow-up was 133.8 ± 58.9 (range 90.1–172.6) μmol/L. The difference was statistically significant ($p < 0.05$). Normalized renal function as defined by the SCr < 115 μmol/L confirmed by last SCr value was found in 12 (29 %) patients. Last SCr level remained stable as constant value during the period at least 3 months, in median 6.3 ± 2.8 (range 3–10) months. US demonstrated KGH in all patients at initial presentation. The median maximal PD was 28 ± 9 (range 14–38) mm and the median last PD was 23 ± 11 (range 0–35) mm and they did not differ significantly ($p = 0.23$).

Hydronephrosis resolved completely in six (14%) patients. During the follow-up period in 34 (81%) patients associated pathological conditions were treated. These were: graft rejection, acute tubular necrosis (ATN), cytomegalovirus (CMV) infection and immunosuppression drug nephrotoxicity and UTI. Clinical rejection was reported in 16 (38%) patients. In the half of these patients, rejection was proven by biopsy. Thirteen (31%) patients with delayed graft function due to ATN required postoperative dialysis. With respect to immunosuppression nephrotoxicity the SCr levels remained stable after drug therapy which was modified in 8 (19%) patients. Specific therapy for cytomegalovirus

(CMV) infection was noted in 14 (33%) patients. UTI with positive urine culture developed in 28 (67%) patients. In 17 (40 %) patients recurrent UTI was documented.

In Figures 1 and 2c and b ultrasonography images of kidney graft hydronephrosis showing stable renal function during the period of observation are given.

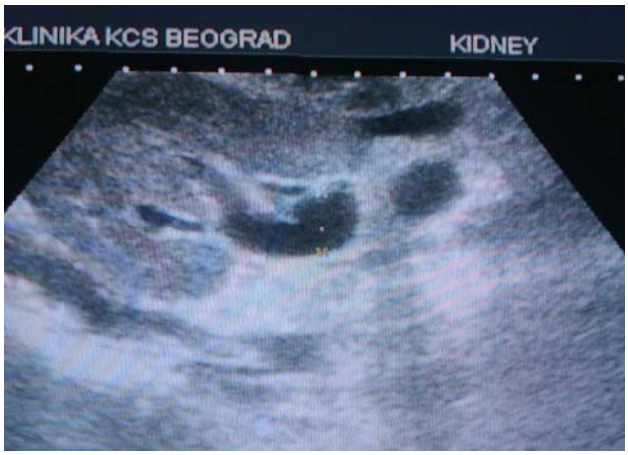

Fig. 1 – Ultrasonography image of kidney graft hydronephrosis in 28 years old female living-donor recipients 21 months after transplantation with pelvicalyceal dilatation 20 mm and serum creatinine 144 µmol/L remained stable during 7 months.

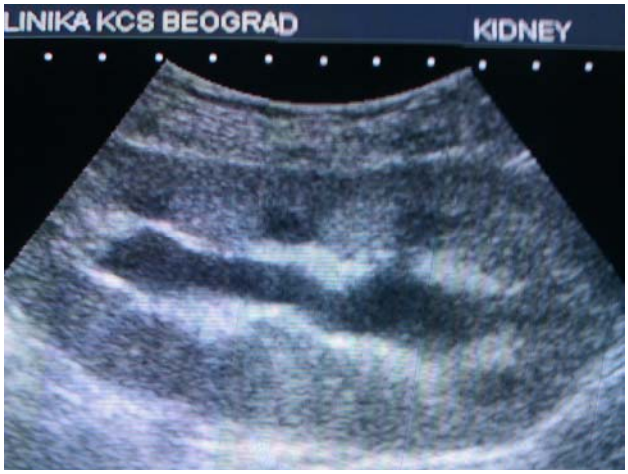

Fig. 2a – Ultrasonography image of kidney graft hydronephrosis associating with biopsy proved rejection in 41 years old male cadaveric-donor recipient 3 months after transplantation with pelvicalyceal dilatation 26 mm and serum creatinine 385 µmol/L.

Discussion

Urological complications after kidney transplantation have been reported in 2–14% of patients. KGH is the most common complication [10]. Both obstructive and non-obstructive KGH was reported in patients who participated in this study.

The incidence of kidney transplant obstruction ranges from 0.5–10% with approximately 90% at the ureterovesical junction [11]. The most common cause of obstructive hydronephrosis in early post-transplant period includes edema of ureteroneocystostomy. Late obstruction occurs usually as a result of ureteral fibrosis due to ischemia, rejection or infection. Less common cause includes compression by pelvic fluid collection such as hematoma, urinoma, seroma or lymphocele [12]. Renal stones are rare in the transplant kidney with a reported frequency less than 1% [13].

The frequent cause of non-obstructive KGH is decreased ureteral tone from denervation which is often coupled with ischemia, rejection or infection. Because its denervation, the short ureter could be the possibility of functional hydronephrosis. Vesicoureteral reflux (VUR), with or without incomplete bladder emptying, could be a factor that influences the development of hydronephrosis in up to 86% of cases [3].

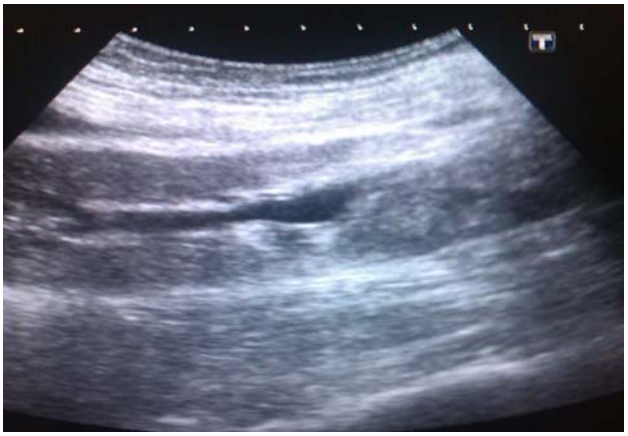

Fig. 2b – US image of the same patient 14 months after transplantation with pelvicalyceal dilatation 12 mm and serum creatinine 110 µmol/L remained stable during 5 months.

KGH is most often identified with US, but its significance should be interpreted in conjunction with renal function and clinical data (Figure 1). There are three indicators that should be considered when determining the surgical significance of hydronephrosis: the underlying cause, degree of pelvicalyceal dilatation and deteriorisation of renal function. Serial ultrasounds graft monitoring and control the kidney function parameters are necessary. Recipients should be carefully monitored for deterioration of renal function. Progressive SCr elevation was a strong predictor of graft dysfunction. There is no standard cut-off value of PD in predicting the need for surgical intervention. It must be in conjugation with other parameters, mainly the SCr level. However, the higher PD is, the possibility of graft failure rises and surgery will be necessary.

The cause of KGH in our analyses is likely to be multifactorial. In our series, 34 (81%) patients were treated for associated pathological conditions. Appropriate treatment of associated pathological conditions leads to the improved graft function and may potentially influence hydronephrosis (Figures 2a and 2b). Therefore, in patients with KGH we must explore all possible factors affecting renal function in details. Our analyses confirmed the causal relationship between infection and obstruction. The polyomavirus type BK has been listed as a possible reason for causing transplant ureteric stenosis [14]. In our study CMV infection compromised renal function in 14 (33%) patients. CMV infection, even

in the absence of systemic symptoms, could be present with ureteric damage and hydronephrosis, too [15].

Another cause of decreased renal function is immunosuppression-based nephrotoxicity [16]. In 2–5% of immunosuppressive agent-treated patients after kidney transplantation, hydronephrosis is a possible side-effect. This occurred due to ischemic injury and edema formation in transplanted ureter. Therefore, minimizing the negative effects of immunosuppressive therapy is an important objective in a long-term management of kidney transplant recipients. In our study, the change of immunosuppressants used to treat immunosuppression-based nephrotoxicity, was done in 8 (19%) patients.

Kidney graft rejection could be associated with hydronephrosis due to local inflammation and ischemic injury leading to edema and fibrosis [17]. Also, the cause could be a decreased ureteral tone resulting from denervation. In our study clinical rejection was presented in 16 (38%) patients. ATN with delayed graft function is a common clinical problem occurring after cadaveric renal transplantation and occurs in more than half of the cadaver grafts [18]. In our study 13 (31%) patients required dialysis within the follow-up period due to ATN-caused delayed graft function. UTI is a very common condition seen in patients with KGH. Infection could cause spasm, edema formation and ischemic damage of ureter. Hydronephrosis was associated with pyelonephritis and pyelonephritis was associated with worsening renal function [19]. In our analyses 28 (67%) patients had UTI. In 17 (40%) patients UTI was recurrent. All our patients were treated successfully and had sterile urine culture at the end of the follow-up.

The PD values are not changed significantly during the follow-up, but the SCr levels were changed significantly with a tendency to improve renal function. Some data indicate that for the stability of renal function the correlate of long-term graft outcome is more important than the absolute level of SCr [20]. In our study, renal function was stable in median during 6,3 (range 3–10) months. Spontaneous resolution of hydronephrosis is possible. Female patients may develop hydronephrosis after radical hysterectomy. During this procedure dissection of the ureter from its adventitia may induce ureteric obstruction resulting from local edema and lack of vascularization. Hydronephrosis disappeared spontaneously at 6 months after the operation in more than 60% of cases [21].

Some transplant patients resolve the hydronephrosis of graft with time. In our study hydronephrosis spontaneously disappeared in 6 (14%) patients. The possible causes may be the disturbances in pelvic and ureteric peristalsis due to transient edema and ischemia. Consequently, the peristaltic waves from the pelvis cannot propagate across the ureter and result in hydronephrosis. Transient vesicoureteral reflux (VUR) and incomplete bladder emptying could be also causal.

Our study had several limitations. It included the short follow-up and retrospective design. Therefore, a randomized prospective study with longer follow-up would allow further analyses. Also, the limited number of patients in our series was an obstacle to reporting any significant prognostic factors regarding preservation graft function in our patients. The single-institutional nature of the study might have, to some degree, limited the possibility to draw general conclusions out of it. Despite these limitations, we believe our findings may offer clinicians a way to identify patients with KGH for safe and active surveillance.

Conclusion

The traditional doctrine, according to which KGH represents an absolute indication for surgery, can be debated. In our study it was shown that some patients with KGH can be safely managed expectantly with the close follow-up. Prompt surgical correction is recommended in case of increasing pelvicalyceal dilatation with symptoms develop, progressive decreasing renal function or refractory UTI. It is important to focus on the etiology of hydronephrosis and recognize and treat associated pathological conditions which could damage graft function alone. Because of an unpredictable clinical course, an individual evaluation and approach is crucial to avoid the kidney graft failure.

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Pathophysiology of the abdominal compartment syndrome in acute pancreatitis: Dilemmas and critical points

Patofiziologija abdominalnog kompartment sindroma u akutnom pankreatitisu: dileme i kritične tačke

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Key words:
pancreatitis, acute, necrotizing; compartment syndromes; pathology; physiology; intra-abdominal hypertension; systemic inflammatory response syndrome; multiple organ failure; therapeutics.

Ključne reči:
pankreatitis, akutni, nekrotizirajući; kompartment sindromi; patologija; fiziologija; hipertenzija, intraabdominalna; sindrom sistemske zapaljenske reakcije; insuficijencije više organa; lečenje.

Introduction

Abdominal compartment syndrome (ACS) has been frequently described in patients with abdominal trauma, inflammatory conditions in abdominal cavity or as a consequence of a major and urgent abdominal surgery [1]. The influence of intraabdominal pressure (IAP) on lung functioning and abdominal content was the subject of scientific research in the 19th century. At that time the hypothesis of a reciprocal relationship between intrathoracic pressure and IAP was entrenched, and it was concluded that the lowering of the diaphragm was accompanied with elevation of IAP [2]. The effects of elevated IAP was noticed in the first half and the middle of the 20th century by several investigators. Bradley and Bradley [3] concluded that raised IAP reduces renal plasma flow and glomerular filtration rate while Emerson [4] found that excessive IAP reduces heart preload significantly with cardiac failure. Baggot [5] described the clinical effects after abdominal wall suture under tension and, for example, he demonstrated a death of a child after surgery for congenital abdominal wall deffect. In contrast to etiological factors and pathophysiology of muscular compartment syndrome that were described in the middle of the 19th century, the physiological mechanisms of the ACS were only proposed at the end of 19th and beginning of the 20th century [6].

Nowadays, the ACS is well described entity which importance in various clinical conditions was recognized in the last two decades. It is defined as a state of serious organ dysfunction resulting from sustained increase in IAP [7]. There is growing evidence in the literature data that the development of ACS in patients with severe form of acute pancreatitis (AP) has strong influence on the course of disease [8–11]. The incidence of intraabdominal hypertension (IAH) in patients suffering from severe form of AP is approximately 70%, while ACS can be found in up to 27% of patients with this form of AP [9, 10, 12, 13]. When we add to this a mortality rate of 49% of patients with severe form of AP and ACS [11], it is clear that IAH and ACS have become an issue of concern in patients with AP. In addition, it has been recently mentioned that the number of patients with AP and this complication increased, but still there have no standard recommendations for interventional treatment of patients who develop ACS during severe form of AP [14]. The step-up approach for conservative treatment of ACS was proposed several years ago [15]. However, the appropriate interventional procedure, including surgical technique, and optimal time for reacting in the treatment of the AP patients suffering from this serious condition is still discussed.

In a number of scientific papers the pathophysiology of the ACS in AP has been described roughly, without specifying potential crucial mechanisms that lead to the damage or to deterioration of already damaged organs in patients with severe form of AP. The understanding of the development of ACS in the course of AP may help in its prevention and timely administration of the best possible treatment [16].

The purpose of this review is to give the insight on the pathophysiology of ACS complicating AP, with some possible critical points in the ACS evolution which may represent either markers for monitoring or therapeutic targets. Also,

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the pathophysiology insight into ACS should fortify the interest of physicians to make additional research in order to support further strategies for the treatment of patients with this lethal complication of AP.

Definition of ACS

According to the World Society of Abdominal Compartment Syndrome (WSACS) [7], IAH is defined as persistent increase of IAP > 12 mmHg, whereas ACS is the combination of IAP > 20 mmHg and the new-onset organ dysfunction.

Definition of severe form of AP

According the revision of the Atlanta classification in 2012 [17], severe form of AP is characterized by the persistent organ failure (OF) (> 48 h). Persistent OF may be single or multiple OF. Three organ systems should be assessed to define OF: respiratory, cardiovascular and renal. OF is defined as a score of 2 or more for one of these 3 organ systems using the modified Marshall scoring system.

A brief look at the pathophysiology of AP

The AP is not only local disease. It is a systemic disease which is characterized by an inflammatory process that is initiated by intraacinar activation of pancreatic enzymes with subsequent systemic effects. Activated proteolytic enzymes lead to the autodigestive injury of the pancreas which is modulated by cytokines and other inflammatory mediators. Intrapancreatic and extrapancreatic inflammation is almost always accompanied by the systemic inflammatory response syndrome (SIRS) [18].

Although there are several risk factors responsible for the development of AP (gallstones, alcohol, hypertriglyce-ridemia, etc.), the subsequent sequence of events takes place according to a very similar scenario, regardless of the initiating factors. The mechanism of initiating AP is still unclear, but it is generally accepted that it develops only in cases when the intracellular protective mechanisms utilized to prevent trypsinogen activation or reduce trypsin activity are overwhelmed. These mechanisms include synthesis of trypsin as inactive proenzyme trypsinogen, autolysis of trypsin, enzyme compartmentalization, synthesis of specific trypsin inhibitors such as serine protease inhibitor Kazal type 1 (SPINK1) as well as relatively low intracellular ionized calcium concentrations [19].

After the activation of trypsinogen into active trypsin, inflammation is followed by the production of cytokines, nitric oxide, reactive oxygen species and arachidonic acid metabolites from pancreatic acinar cells, endothelial cells, neutrophils, macrophages and lymphocytes. Immune cells attracted by initially released cytokines release more cytokines, free radicals and nitric oxide [20]. The mediators involved in the inflammatory response during AP are proinflammatory and anti-inflammatory and their balance determines the course of the disease [21]. Perhaps this could be an issue where the answer can be found on why some patients develop edematous pancreatitis and others much more severe form of the disease with serious and lethal complications. Another interesting think in the early phase of AP is balance between apoptosis and necrosis. This balance may influence the severity of AP and decide the fate of acinar cells. Both caspase activation and cytosolic calcium signaling have influence on apoptotic and necrotic cell death pathways [22, 23].

Apart from the aforementioned, the alteration of the pancreatic microcirculation plays one of the central roles in the pathogenesis of AP. Derangement of pancreatic microcirculation in the early phase of disease could transform acute self-limited and edematous pancreatitis to severe, necrotizing pancreatitis [24–27]. In response to pancreatic acinar cell injury, multiple proinflammatory cytokines and vasoactive mediators are recruited to the pancreatic microcirculation and delivered to the acinar cells. One of the consequences of this is increasing of the vascular permeability of the capillaries. This causes significant extravasation of fluid leading to the acute edematous changes around the acinus. Also, decreased endothelial tone allows the extravasation of both inflammatory cells and inflammatory mediators [28–30]. Another vascular changes were described in AP which may aggravate the disease course. These changes include the formation of microthrombi, capillary vasoconstriction and vasospasm of intrapancreatic and extrapancreatic arteries [31–33].

Secreted inflammatory mediators and several activated inflammatory cascades have influence on different organs, not only on the pancreas (Figure 1). In the severe form of AP, the local injury rapidly leads to a generalized hyperinflammation, SIRS, what is associated with potential failure of distant organs (Figure 2).

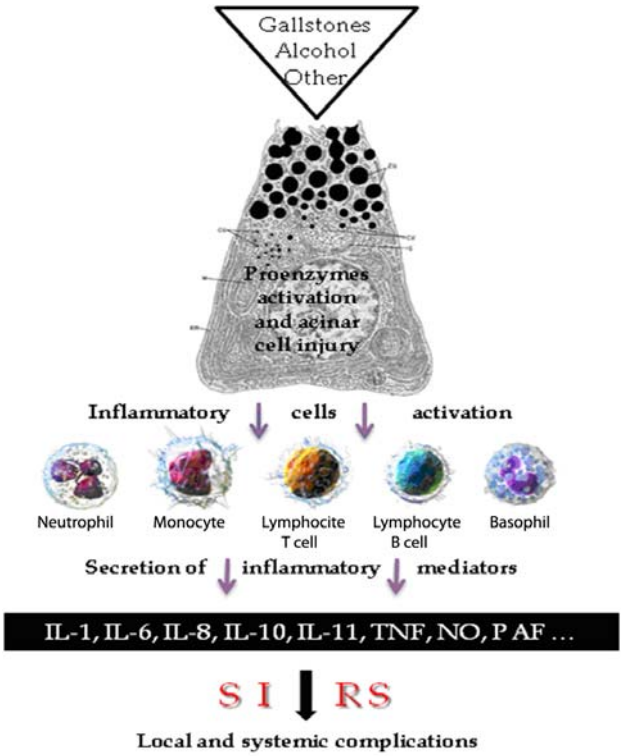

Fig. 1 – The schematic overview of the pathophysiology of acute pancreatitis.
IL – interleukin; TNF – tumor necrosis factor; NO – nitric oxide; PAF – platelet-activating factor;
SIRS – systemic inflammatory response syndrome.

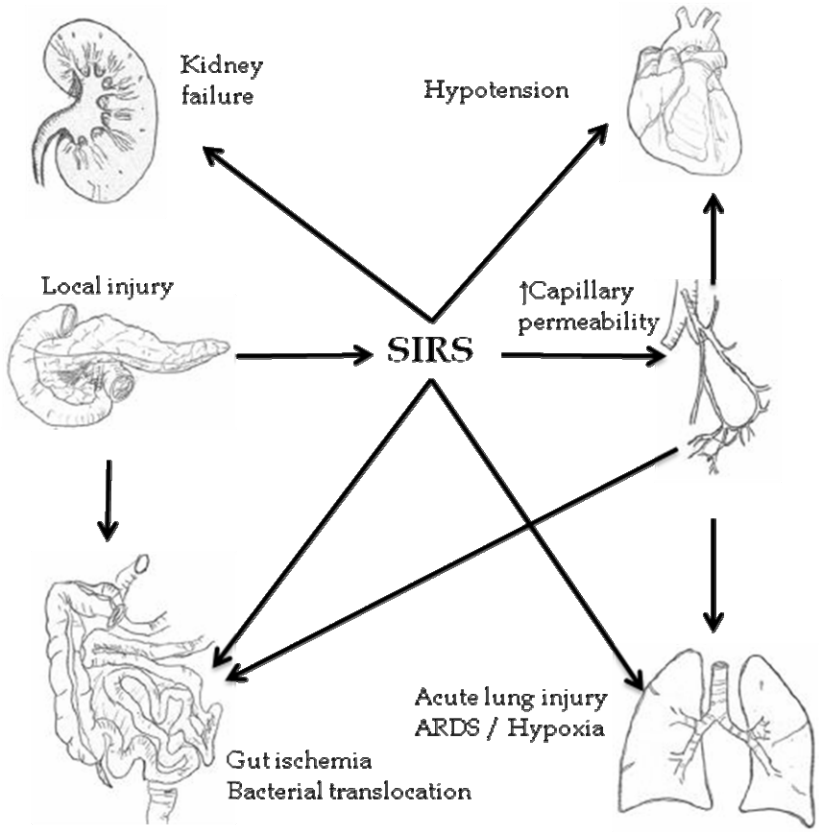

Fig. 2 – The generalized hyperinflammation in acute pancreatitis and its association with organs dysfunction. SIRS – systemic inflammatory response syndrome; ARDS – acute respiratory distress syndrome.

Pathophysiology of ACS during AP

Initial events leading to increasing of IAP

Hypovolemia is common in AP, especially in the severe form of the disease and is a result of a massive fluid loss to the retroperitoneal space and interstitial space overall. A complex series of pathophysiological events that lead to ACS development in patients with AP is shown in the Figure 3. However, an early substantial fluid loss in patients with severe form of the AP occurs in retroperitoneal space and interstitial space of gut. In addition to above mentioned factors resulting in increased capillary permeability, the other factors may contribute to the ischemic insult of the gut during AP. Mucosal ischemia of gut may be related to the endotelin-1 which is a strong vasoconstrictor produced from endothelium and macrophages [34, 35]. Also, intercellular adhesion molecule-1 (ICAM-1) mediates the adhesion of cytokine stimulated leukocytes to the capillary endothelium and their transendothelial migration. A significant increase in the systemic release of ICAM-1 was found in patients with necrotizing AP within 48 hrs of the onset of symptoms [36]. This event is associated with significant increase of leukocytes infiltration with histological changes and decreasing in intestinal and pancreatic perfusion [37, 38]. In the early stages of severe form of AP,

the profound fluid losses in a "third space" associated with inflammation of the pancreas may induce splanchnic vasoconstriction. Hypovolemia also leads to decrease in splanchnic perfusion with consequent cellular hypoxia especially in intestinal mucosa [39, 40]. A retroperitoneal and pancreatic inflammation, increased vascular permeability, interstitial edema, decreased intestinal perfusion and cellular and tissue hypoxia lead to development of a vicious circle with the reactivation of immune cells and secretion of *de novo* synthesized inflammatory mediators [39–41]. On the other hand, inflammatory process and increased vascular permeability allows protein-rich intravascular fluid to pass not only in the interstitial space but in the peritoneal cavity also. It was reported that patients with AP often have liters of intravascular leak to the peritoneum [42, 43].

The abdominal cavity is a single compartment and any change in volume within this cavity can elevate IAP further leading to IAH [44]. Although not fully compliant, the abdominal cavity is more amenable than most confined cavities, but can become increasingly rigid as it distends. It must be noted here that majority of the AP patients have severe abdominal pain which may result in abdominal rigidity causing a decrease in abdominal compliance [45]. All of these events including the paralytic ileus caused by severe inflammation are responsible for the initial bowel edema and subsequent initial elevation of IAP [44, 46, 47].

Reperfusion injury and IAP

Not the all patients with AP develop IAH. Also, the values of IAP are different in various patients on hospital ad-

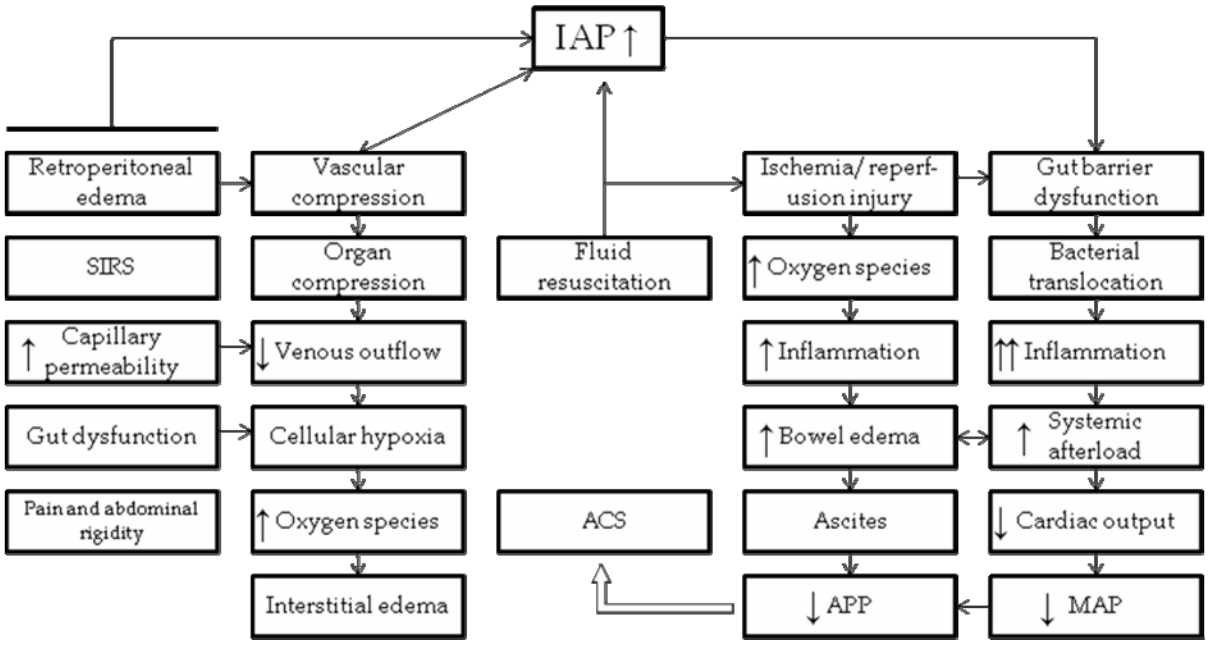

Fig. 3 – The pathophysiological mechanisms involved in the development of abdominal compartment syndrome (ACS) in patients with acute pancreatitis.
SIRS – systemic inflammatory response syndrome; IAP – intraabdominal pressure; APP – abdominal perfusion pressure; MAP – mean arterial pressure.

mission. There are only several papers in literature that reported the value of IAP in patients with AP on hospital admission. In these studies the value of IAP at 24 hrs of hospital admission in patients with AP varies from 12–28 mmHg [11]. This is an important issue because the value of IAP determines the severity and further course of AP [13]. In fact, elevated IAP causes intestinal hypoperfusion even at levels from 8 to 12 mmHg [40, 48], while IAH could contribute to pancreas hypoperfusion [13, 49, 50]. On hospital admission a number of the patients, especially those with severe form of AP, are in hypovolemia which requires aggressive rehydration [42, 51, 52].

Initial treatment of patients with AP is aggressive fluid replacement [51–53]. It seems that early aggressive fluid therapy may be a double-edged sword regarding further patophysiological events in AP. However, there is no evidence whether ACS development is a reflection of severe disease or the result of overzealous fluid resuscitation [52–54].

Without reference to the animal models of AP, the possibility of ischemia-reperfusion injury following volume resuscitation in patients with AP is certainly high. Intestinal reperfusion injury has been shown to have deleterious effects on the gut function and distant organs [55, 56]. Studies on both animals and humans showed that the intestinal ischemia and reperfusion result in a rapid accumulation of the circulating leukocytes and gut-associated macrophages with the subsequent cytokines releasing [57–61]. In addition, an oxygen free-radical injury is important pathophysiological event in AP. This is provided by the evidence showing improved outcomes in animal models using antioxidant therapy [62]. The pancreas is an organ highly susceptible to the ischemic damage and ischemia represents as an important factor in AP [63]. It is known that the ischemic/reperfusion injury may cause AP in the various clinical settings [64]. After the reduction of blood flow and free radicals generation in the early stage of AP, an additional damage of the pancreatic tissue probably occurs after initial fluid replacement. On the other hand, AP can induce mesenteric ischemia by mesenteric vasoconstriction, shock state and/or dehydration [65–68]. Therefore, not only a pancreas is a target for reperfusion injury, but also the all abdominal viscera including gut [69, 70]. This sequence of events leads to the reactivation of the immune response, and almost certainly to the edema of the all abdominal viscera with increasing in the volume of peritoneal free fluid and consequent further elevation of IAP.

Abdominal perfusion pressure and additional ischemia of the abdominal organs

Abdominal perfusion pressure (APP) is determined by the mean arterial pressure (MAP) and IAP that resists blood delivery to the abdominal organs. The APP is defined by the formula: APP = MAP–IAP. APP represents a very important parameter with a better and more accurate prediction of the visceral perfusion than IAP. Also, it was reported that it could be used as a potential endpoint for resuscitation [71]. It is recommended that the APP should be maintained above 60 mmHg and this was shown to correlate with improved outcomes. However, if the APP decreases under 50 mmHg the morbidity and mortality rate is increased [71–73]. In states of paralytic ileus, abdominal pain and abdominal wall rigidity, free fluid in the peritoneal cavity and retroperitoneal inflammation, the abdominal compliance would be decreased. As the abdominal compliance threshold is reached, the IAP rises

and the APP decreases [74, 75]. It has not yet been discovered what critical value of APP leads to a vicious circle of irreversible IAH, to the further elevation of IAP and subsequent organ dysfunction. In fact, it seems that the critical point of this sequence of events is reduced venous outflow in abdominal organs to the extent that affects arterial perfusion [76]. Venous stasis and the development of interstitial edema reduce arterial blood perfusion in the abdominal organs, especially gut, with ischemia and additional inflammation [77, 78]. This may be the beginning of the second insult for the induction of severe organ dysfunction in two-hit model of the multiple organ dysfunction syndrome (MODS) [9, 79]. If untreated, this leads to organ ischemia and ultimately to ACS [9, 13, 74, 75, 79].

IAH and organ dysfunction

When the APP is decreased under the critical level, a cellular hypoxia exacerbates due to low blood perfusion in the abdominal organs. The consequence of this hypoxic state is decline of the adenosine triphosphate (ATP) production. Due to the cellular energy deficit the potassium slowly leaks into extracellular space while sodium and calcium enter the cells along with water. The cells are swelling, the membranes lose their integrity, spilling its intracellular content into extracellular space and causing more inflammation throughout the body, not only in gut [39, 50, 69]. The SIRS triggered initially by AP is usually driven further with efforts to reperfusion aimed to restoring amounts of volume with intravenous fluid replacement. However, this action often promotes further tissue edema with reperfusion injury followed by another cycle of acute inflammatory response [9, 39, 53, 80], as discussed above. As the IAP continues to rise, the probability for the new onset organ dysfunction is higher. It is even higher in severe inflammation such as in patients with the severe form of AP [81].

It is still unknown whether the new onset organ dysfunction in patients with AP and IAH occurs as a result of critical level of IAP or as a consequence of the second-hit resulting from another cycle of inflammatory response [81]. However, it is certain that the gastrointestinal system and liver functions are the most vulnerable to the high IAP. Mainly two functions are altered: the mucosal barrier function (influencing both intermucosal nutrient flow and bacterial translocation) and the gastrointestinal motility. The reduction of splanchnic blood perfusion occurs at the level of IAP of 10 mmHg, with the exception of the adrenal glands [82, 83]. The metabolic changes in the gut, such as acidosis and decreased intestinal oxygenation, are evident at the IAP level of 15 mmHg [84]. It was shown that IAP from 20–25 mmHg in the duration of 60 minutes leads to the bacterial translocation from gut [85]. In our recent study we found a highly significant correlation between IAP and procalcitonin in patients with AP suggesting bacterial translocation [13]. The influence of IAH on the liver function and microcirculatory disturbances in liver parenchyma is apparent at the IAP of 20 mmHg and more [2]. The impact of elevated IAP on the gut is essential due to circumstantial evidences of relationship between bacterial translocation and MODS [50, 69, 86]. The raise of IAP leads to the diaphragm elevation with subsequent reduction of the static and dynamic respiratory compliance [87]. Total lung capacity, residual volume and functional residual capacity are reduced and leading to the ventilation-perfusion imbalance and hypoventilation. These changes are present at the IAP above 15 mmHg [72, 88].

Due to compression of inferior vena cava and portal vein under the elevated IAP, the cardiovascular system is affected throughout reduced venous return to the heart. Nonetheless, the reduction of cardiac output is exacerbated with frequent hypovolemia such as in the patients with AP. These effects occur at levels of IAP as low as 10 mmHg, while hypovolemic patients manifest it at even lower IAP [89].

IAH-induced renal dysfunction manifests as oliguria and anuria at the level of IAP from 15–30 mmHg in the presence of normovolemia and normal initial renal function [90, 91]. It seems that renal dysfunction in AP occurs in much lower IAP due to severe inflammation in such patients [92].

Elevated IAP reduces abdominal wall blood flow by a compression effect leading to the local ischemia and edema. This phenomenon is probably true for all muscles constituting the abdominal wall. Neurogenic mechanism of pain and abdominal rigidity in patients suffering from AP certainly have an impact on the abdominal wall functions. In particular, the blood flow throughout sheath of abdominal rectus muscles decreases to 58% of baseline at an IAP of only 10 mmHg, further worsening at 40 mmHg [93].

Several studies showed increased intracranial pressure as a consequence of elevated IAP. As a consequence of increased intracranial pressure, cerebral perfusion pressure is reduced. This could lead to serious neurological disorders [94].

Based on the all aforementioned, it is clear that AP is characterized by a variety of pathophysiological mechanisms which are interacting between each other, one event can cause another and all of them are involved in the development of IAH. Inflammatory mediators induce end-organ endothelial cell activation with subsequent increased capillary permeability; leaking microvessels cause a loss of intravascular fluid which lead to hypotension along with vasodilatation leading to the development of the shock states; accumulation of inflammatory cells in the tissues, interstitial edema, reperfusion injury along with microvascular coagulation disorders further impair oxygen supply of tissues. The final result of all these events is MODS which develops early during the course of AP [95]. It is still a pathophysiological dilemma which of the above mentioned events is the most responsible for the development of MODS [16, 47]. However, it seems that the increased capillary permeability and the microcirculatory disturbances in the gut are the initial and crucial events leading to a vicious circle of the IAP elevation and further tissues injury in the patients with AP.

Although it is unclear what is a critical value of IAP that leads to the organ dysfunction in the AP patients, it is obvious that if the IAP is higher, the number of organ systems in dysfunction will be higher also [11, 47, 92]. When the IAP reaches a level of 20 mmHg, the sustained derangement of normal physiological function ensues. Whether the ACS

in the AP patients occurs as a result of multiorgan failure or is it occurring with other organ dysfunction, it needs to be proven in the future [13, 14, 81]. Although the unpredictable nature of its course makes it difficult to establish the causal link between AP and ACS, the understanding of the complexity of pathophysiological mechanisms involved in ACS development may help in designing of the experimental and randomized clinical studies and may help in its prevention and timely administration of the best possible treatment.

Conclusion

The complex cascades of pathophysiological events in the patients suffering from AP lead to the initial elevation of IAP. The ACS is a result of a vicious circle of the severe inflammation and impaired perfusion of abdominal organs, especially gut. The understanding of the development of ACS in the course of AP may help in its prevention and timely administration of the best possible treatment.

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Medical expertise in non-contentious proceedings

Medicinsko veštačenje u vanparničnom postupku

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Introduction

Expertise is a kind of evidence in a non-contentious proceeding as well. An expert testimony is introduced in all such cases when the court does not avail with particular professional, specialized knowledge necessary to form the factual basis in the decision-making process [1]. An expert witness is a person summoned to express before the court, using its professional knowledge and experience, his/her observations, and to present his/her findings and opinion on facts which might be relevant for determination of the veracity of allegations subject to proving [2].

The Law on Non-Contentious Proceedings [3] does not contain the rules on the procedural status of experts and the method of adducing this evidence because those are covered by the provisions of the Civil Procedure Law [4] which are applied *mutatis mutandis* in non-contentious proceedings as well. Please note that the 2011 Civil Procedure Law provides for a private expert's findings and opinion, in addition to the expert testimony. The legislator has provided for the possibility that a party may support its motion (claim, counterclaim, response to a claim) with a document containing the findings and opinion of a suitably qualified expert in order to clarify any facts requiring professional knowledge which, in such party's opinion, the court does not avail of [5]. Nevertheless, as regards this private document, the statutory procedural regime concerning the expert testimony as evidence does not apply [6]. According to these rules, the court has to pass a decision on determination of an expert witness from the register of expert witnesses, and identify precisely the objective of such expertise and the time frame for the expert to produce the expertise.

An expert witness is obliged to present his/her findings in writing, with detailed basis of its formulation and to appear before the court when summoned to provide additional explanations to the parties and the court. On request of the court or parties, the expert shall supplement or clarify the presented findings by additional oral explanation. The expert is entitled to a fee for his/her work, comprised of the reimbursement of material labor costs and a consideration for performed work. The court may fine an expert who fails to appear at the hearing, provided that he/she was duly summoned but failed to furnish an excuse for his/her absence. Expert witnesses are formally guaranteed an impartial position in the proceedings and their testimonies are protected by immunity [7]. An expert witness may be held liable for damages inflicted to others arising from a wrongful or untimely testimony, however, only if caused by gross negligence. Besides, the judge has no knowledge of subject matter and, naturally, relies upon experts' opinions; therefore, the issue of experts' procedural discipline needs to be addressed, which would imply their awareness of the court procedure, compliance with deadlines and alike. The provisions of the Law on Non-Contentious Proceedings which regulate particular non-contentious proceedings regard expert testimony as evidence [8] which is supposed to enable the court to form the factual background for its ruling when the court lacks the necessary professional knowledge. In status non-contentious proceedings, medical expertise is proposed as evidence.

Proceedings for removal of legal capacity

One of the non-contentious proceedings in which the medical expertise is particularly important is the proceeding for removal of legal capacity. In such proceedings, the court examines whether an adult, based on the level of his/her ability of articulate reasoning, is capable of protecting his/her own rights and inte-

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rests, and rules on complete or partial removal of legal capacity if it establishes the existence of statutory reasons, as well as on restoring of legal capacity when the reasons for the removal or restriction of legal capacity cease to exist. In addition to the proceedings for removal of legal capacity, the court institutes *ex officio* a proceeding to assert the existence of reasons for further validity of the ruling on removal of legal capacity, since this is a measure which limits the legal capacity as a human right of any natural person guaranteed by the Constitution. The law provides that the court is obliged to review any rendered ruling on removal of legal capacity within specified deadline and in proceedings which are validly terminated.

To decide on removal of legal capacity, the court needs to be aware of mental health status of the person concerned and his/her ability of reasoning. Since the court does not possess the necessary professional medical knowledge, it needs the assistance of a medical expert so as to be able to determine the relevant facts.In these proceedings, the court is obliged to order medical expertise *ex officio* in order to assess the mental health status and the extent of the reasoning ability of the person concerned, which is highly important for determination of the scope of the measure which might be pronounced, extended or modified in the proceedings [9].

Pursuant to the law provisions, the expert testimony on the mental health status should be provided by qualified expert witnesses – at least two doctors of adequate specialties (psychiatrists, neuropsychiatrists, clinical psychiatrists, etc.) appointed by a court decision and registered in the register of expert witnesses for a particular field of expertise. The expert testimony may not be provided by doctors who determined the diagnosis before the institution of the proceedings for removal of legal capacity, and whose expert opinion is attached to the motion by the petitioner. In court proceedings in general, findings and opinions are attributed to a legal function and become legally relevant in court proceedings.

In its decision, the court defines the experts' task, which is to specify in their findings and opinion whether the person subjected to the proceedings for removal of legal capacity is oriented in time and space and in relation to third persons and whether, mindful of the mental health status, he/she is able to protect his/her own rights and to fulfill his/her obligations. In their findings, the experts are supposed to state the actual psychological state of the person concerned, describe the overall health status of that person, and state whether the person is oriented in time and space, establishes verbal communication and, if so, whether such communication is maintained and deepening, whether the train of thoughts includes insane ideas, whether there is a critical attitude to ideas, etc. The appointed experts are obliged to determine the diagnosis and provide an opinion on the capacity of the person concerned, in terms of his/her ability to protect his/her rights and fulfill obligations.

In the provisions of the Law on Non-Contentious Proceedings, the legislator has not provided what happens if the opinions of two medical experts differ. In that case, the general rules on evidence provided under the Civil Procedure Law apply. The court shall first advise the expert witnesses to harmonize their opinions, if possible. Otherwise, the court has to order a new expertise entrusted to either a commission of medical experts specialized in neuropsychiatry (most often three of them) or, in more complex cases, an expert opinion of a health care institution registered in the register of expert witnesses may be asked for (neuropsychiatric hospital and, naturally, in the most difficult cases, the Faculty of Medicine).

All participants in the proceedings may raise an objection to experts' findings. In such a case, the court may present evidence from a new expertise. In its decision determining on the removal of legal capacity, the court shall, mindful of the mental health status, pronounce the measure of full or partial restriction of legal capacity over particular time period, and set the deadline for review the existence of the grounds for further validity of the ruling. If the court finds, based on the findings and opinion of the commission of medical experts, that the person's legal capacity should be partially removed, the decision shall contain the legal actions which may be taken by such a person to the extent of his/her legal capacity. A pronounced measure of removal of legal capacity is not of permanent nature, because its validity period must not exceed three years. Upon expiry of that deadline, the court shall review the presence of conditions for restoration of legal capacity, or for further extension or modification of the pronounced measure. Introduction of periodical review of the court ruling is compliant with the Recommendation of the Committee of Ministers of the Council of Europe no. R (99) 4 Principle 14, stipulating that „the measures of protection should be of limited duration, subject to periodical review". This legal arrangement contributes to a better protection of concerned persons' interests, and to the control of the guardianship authority's performance [10]. For the court to be able to review the existence of reasons for further validity of the measure on removal of legal capacity pronounced through a valid ruling, it is obliged to schedule a hearing where, apart from the person concerned and his/her guardian and guardianship authority, it should summon expert witnesses, preferably those determined in the concluded proceedings, in order to assess the mental health status of the person concerned and decide on the extent of his/her legal capacity.

Proceedings for restoration of legal capacity

In the Proceedings for restoration of legal capacity, the provisions on removal of legal capacity apply *mutatis mutandis*. This practically means that the person shall be re-examined by at least two neuropsychiatrists who shall assess whether the health status has improved. The situation is identical in case of doctors' disagreement about the extent of the health status improvement, therefore, the above described procedure shall be followed.

Proceedings for detention in a neuropsychiatric health care institution

The Law on the Protection of Persons with Mental Disorders [1] provides for special non-contentious proceedings

for detention of persons with mental disorders in a health care institution without his/her consent for the purpose of treatment, when the nature of a mental condition makes it necessary in order to prevent a significant health deterioration, to prevent life and safety threat to others and establish the capacity for consenting to a proposed medical step. For those reasons, a person with mental disorder may be pronounced restricted freedom of movement or communication with external world, when a doctor of medicine and a physician-psychiatrist assess the extent of the mental disorder and inability to apply less restrictive modes of health care provision.

The proceedings for compulsory hospitalization are instituted by court after receiving the notice from a health care institution that a person is admitted for treatment without his/her consent further to assessment of medical reasons for stationary treatment without his/her consent. The court shall schedule and hold a hearing in the psychiatric institution, where it shall hear the person held for treatment and adduce evidence from expert testimony. The court shall order an expert witness to conduct a detailed medical examination and examine the medical dossier of the person concerned. The expert witness is obliged to state in his/her findings the psychological state of the person and whether the person is oriented in time and space, whether he/she establishes verbal communication and whether such communication is maintained and deepened, whether the train of thoughts includes insane ideas, and whether there is a critical attitude to ideas, etc.The expert is obliged to determine a diagnosis. He/she shall state in the findings whether further treatment in hospital conditions is necessary for the protection of the person's own life and health, and public safety.

Although the compulsory detention in a stationary health care institution, without the concerned persons' consent, undoubtedly represents a restriction of the freedom of movement, regardless of the legally prescribed maximum duration of compulsory detention, it still does not contradict the European legal standards observed by the European Court for Human Rights and the provisions of the Law on the Protection of Persons with Mental Disorders which stipulates that no person shall be compelled to undergo medical examination with a view to determining whether or not he/she has a mental disorder, except in the cases and in the procedure authorized by law. In this situation, observing the principle of proportionality between the interests of the society to properly and accurately assess a person's mental health in order to undertake the legally prescribed measure of his/her protection and the right to freedom of movement, the legislator has provided for compulsory detention of limited duration with the objective to assess the mental health status and treatment, so that this court decision does not constitute a violation of the right to privacy, dignity and family life [11].

In case the court decides that the admitted person should be detained in the health care institution, it shall determine the detention period which must not exceed 30 days as counted from the day when the psychiatrist made the decision on detention of the person with mental disorder without the latter's consent.

In more drastic situations, when the health care institution estimates that the detained person needs to remain hospitalized even after the expiry of the period determined by the court decision, it is obliged to propose an extension of detention without consent five days before expiry of the detention period, in compliance with the estimates of the institution's medical consilium regarding the outcome of the treatment. The court may pass a decision to extend the person's detention in the psychiatric institution by up to three months. Any further detention may be extended by a court decision to a six-month period. The psychiatric institution is obliged to deliver to the court regular quarterly reports on the health status of the person detained without consent, or more frequently as requested by the court.

The law has provided for the possibility that the court may, even before the expiry of the determined detention period in a health care institution, *ex officio* or on proposal of the detained person, his/her legal representative or psychiatric institution, decide to discharge the detained person from the health care institution if determined in the proceedings that the medical reasons for further detention for treatment without consent have ceased to exist. The key word here is, naturally, "determined", because it is quite certain that the court has no knowledge of whether or not there has been any improvement in the medical status of a person with a mental disorder, or to which extent his/her medical status has actually improved [12]. Passing of this decision shall depend on obtaining an expert opinion from a psychiatrist listed among expert witnesses.

Extension of parental rights

The need for medical expertise may also arise in proceedings for extension of parental rights instituted before maturity of a person, for reasons stipulated by law [13]. If a person fails to reach the maturity required for acquiring full legal capacity, due to an illness or a disorder in psychophysical development, or when he/she is not capable of protecting his/her own rights and interests, the law provides for the possibility of extension of parental rights. The basis for the extension of parental rights, according to the Family Law, is an illness or disorder in psychophysical development due to which a full-aged person is unable to take care of himself/herself and his/her own interests or actions, thus compromising his/her own rights and interests.

According to the provisions of Article 7 of the Family Law [14], the parental right belongs to the mother and father together, provided that the parents are equal in the exercise of the parental right. For that reason, these proceedings may be instituted either by both parents together, as petitioners, or by only one of them if he/she exercises the parental right on his/her own. Since an adopting parent has the legal status of a parent, he/she also belongs to the group of persons with the right of action. The Supreme Court of Serbia has taken the stand that "a guardian of a person with removed legal capacity who failed to file a petition for restoration of the legal capacity, has no right of appeal against a ruling by which the legal capacity of his/her ward has been restored in proce-

edings where the latter was represented by a special guardian." (Supreme Court of Serbia, rev. 1734/93 of June 2nd 1993).

In these proceedings, the court *ex officio* determines the mental and physical condition of the child, relevant for his/her ability to protect his/her personality, rights and interests. The person over whom the parental right is sought to be extended may have severe health disorders, but still that might not influence rendering of the ruling to extend the parental right (a child who is blind, deaf, mute or paralyzed). The only criterion for the court is whether a person who is about to turn 18 is able, based on his/her psychophysical condition, to take care of himself/herself, and whether the achieved level of mental development is sufficient for an average capability acquired at maturity – to take care of himself/herself and make decisions relevant for one's own self.

The central issue in these proceedings is the mental status and ability of the child, which has to be assessed in a procedure before the court [15]. In these proceedings, the child shall be necessarily examined by at least two doctors of adequate specialty (neuropsychiatrists, psychiatrists), since these proceedings are made equal to the proceedings for removal of legal capacity in terms of legal consequences. In their findings, the expert witnesses need to explain briefly the assignment ordered by court. They need to analyze the opinion and findings of the Center for Social Work and the report of the institution where the child is treated, and specify heterogeneous data. For example, the child's date of birth, the therapy administered, whether the child is conscious, oriented and what is his/her illness, whether he/she is able to protect his/her personality, interests and right.

The opinion of the Center for Social Work on the appropriateness of extension of parental right is particularly important for the court to estimate whether an extension of parental right is in the interest of the "child" as the person concerned. The Center shall not be invited to provide a professional opinion concerning the reasons related or unrelated to the level of mental development of a full age child. Its role is to estimate the appropriateness, in terms of proper attitude of parents to a full-aged child and their capacity to overtake the care of the "child" who shall be actually deprived of legal capacity due to the fact that the parental right shall be extended. The opinion of the Center for Social Work, as an expert witness, must be substantiated from the aspect of its competences. The Center should provide an opinion on the extent of child's capability, the child's attitude to parents or vice versa, and the child's potential living conditions, and the extent of parents' capabilities and motivation for performing these very delicate tasks in the forthcoming period [16].

Once extended, the parental right does not necessarily have to remain permanent. In fact, in case of an improvement in the health status of the person subjected to extended parental right, the court's ruling may be revoked. To rule on cessation of the parental right, the court needs to engage two expert witnesses specialized in neuropsychiatry to testify. The task of the neuropsychiatrists is to verify the allegation that the health status of the person concerned has improved, and to provide reasoning thereof.

Granting permission to conclude marriage

Medical expertise is also necessary in the proceedings for granting a permission to conclude marriage when one or both persons wishing to conclude marriage are minors. The prime task of the court in these proceedings is to rule on whether the minor or both minors are ready to conclude marriage, meaning that it needs to be determined whether they have reached the physical and mental maturity required for the exercise of matrimonial rights and duties. To determine this, the court needs to obtain an opinion from a health care institution on the psychophysical maturity of one or both potential spouses. Besides, if required, the court needs to obtain an opinion on personal faculties of the client if there is a doubt or uncertainty, from a competent person – an expert witness specialized in psychology or psychiatry, or a health care institution.

Proceedings for determination of birth

In the proceedings for determination or proving of birth, when recognition of legal capacity of so called legally invisible persons [17] is concerned (persons who are not registered in the birth registry), the need for medical expertise may arise. The role of the expert witness may be assigned to a doctor of adequate specialty, who shall examine the person concerned and provide findings and opinion on his/her age.

In the wording of the law, the term "a doctor of adequate specialty" is not precisely defined, which might give rise to some concerns in judicial practice. Assessment of age may be performed by pediatricians when children are involved, or gerontologists when old people are involved, and the expertise may be performed by specialists in forensic medicine as well. Besides, a DNA expertise may be performed if required.

Documents

A separate chapter of the Law on Non-Contentious Proceedings [18] regulates the procedures concerning documents. If the court, i.e. notary public is in charge of drawing up a document, the Laws on Public Notary [16] and on Non-Contentious Proceedings stipulate that the documents shall be drawn at the court, i.e. at the notarial premises, and outside the court or notarial premises only when a participant is unable to come to the court or notarial premises or when there are other justified reasons [19, 20]. The legislator has not detailed the reasons for a person's inability to appear before the court, but instead leaves it up to the court to decide [16]. In practice, this situation is normally associated to the health status of a person. In that context, the court may ask for a medical expert's opinion on whether the illness is of such nature that the person is only prevented from coming (immobility, severe disability, etc.) or the medical reasons are of such nature that they disable reasoning and validity of the expression of will of the person who is supposed to make a statemen statement. Depending on this circumstance and the obtained expert opinion, the court shall first decide whet-

her to allow the drawing up of a document, and then whether to have it drawn up outside the court premises. The obtained doctor's opinion must be formulated in writing. If only a certificate is concerned, for example for complete immobility or impaired mobility, it is sufficient to obtain the opinion of a practicing physician, a certificate of a community health center or another common medical documentation confirming the patient's health status.

When drawing up documents on a legal transaction, the court or public notary examines whether the participants possess the legal capacity required for closing of subject transaction and whether there are any impediments in terms of the health status of the person making the statement, or persons making it on his/her behalf. It means that the court or public notary shall use the services of a medical expert, preferably a psychiatrist. Only exceptionally, the court or public notary may obtain the opinion of another doctor who monitors the patient's status on the circumstance that the patient may be currently undergoing extreme pain, strong therapy or alike. These circumstances as well may influence the validity of drawing up of documents from the aspect that such a person, for example, may have been administered morphine or some sedatives, or may be undergoing another medical intervention or therapy which influences the state of mind at the moment of drawing up the document or making an oral statement concerning the document contents.

Provision of evidence in non-contentious proceedings

When there is a reasonable doubt that a piece of evidence shall not be adduced or that its subsequent adducing in a court procedure shall be made difficult, the proceedings for provision of evidence before the non-contentious court or public notary may be instituted. The court practice has supported this, and "it is not allowed to request provision of evidence in non-contentious proceedings for the purpose of DNA expertise to determine whether the petitioner is the biological father of the petitioner's opponent, for the reason that the petitioner has failed to produce evidence that there is a reasonable risk that the proposed evidence could not be adduced in subsequently instituted litigation" (Decision of the Higher Court in Belgrade Gž 1048/2015 of July 18th, 2015).

Besides, the person seeking to draw up a will or a lifelong care agreement, but his/her health is seriously impaired, may request from the court or public notary to adduce evidence in non-contentious proceedings by expert testimony of a neuropsychiatrist on the circumstances of his/her psychological state – accountability. This evidence may be relevant later, in case the legal transaction is contested. The fact that a person's overall health status is poor does not in itself mean that such a person is unable to conclude legal transactions. To prevent any possible subsequent speculations whether the overall health status influenced his/her ability of reasoning and expertise based on medical documents and hearing of witnesses, it is possible to adduce evidence in non-contentious proceedings in advance, showing the person's state of mind and ability of reasoning [21].

If a person has, for example, suffered a severe accident or occupational injury, and the liability of the other driver or employer is disputable, in such cases the person may request a medical examination and adducing of evidence through expert testimony in non-contentious or notarial proceedings, on the following circumstances: kind of injuries, the manner of infliction, consequences of injuries in terms of reduced overall living and working abilities, and maybe an expert testimony on the circumstance of necessary treatment, common therapies, duration of rehabilitation, etc. This way, the person may provide evidence on the kinds and intensity of injuries suffered, and legal consequences of the detrimental event until deliberated whether another person is liable for the damages inflicted. The standard of proof of evidence obtained in proceedings for provision of evidence is relative. It shall be treated as any other proof and evaluated according to the general rules of the standard of proof, by being evaluated in the context of any other proofs, severally and jointly [7].

Provision of evidence shall only make other proceedings easier for the court, if assessment of particular facts is currently difficult due to the time elapsed or other circumstances, such as civil proceedings for compensation of damages, or a labor dispute between the employer and employee for compensation of damages. This is because the court shall avail with a competent impartial opinion of a medical expert who shall confirm the incidence of particular injuries or the mental state of a patient at particular time, relevant for ruling.

Conclusion

The provisions of the Law on Non-Contentious Proceedings which regulate particular non-contentious proceedings regard expert testimony as evidence which is supposed to enable the court to form the factual background for its ruling when the court lacks the necessary professional knowledge. In status non-contentious proceedings, medical expertise is proposed as evidence.

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CASE REPORTS

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Malignant fibrous histiocytoma of the right upper leg – A case report

Maligni fibrozni histiocitom desne natkolenice

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Abstract

Introduction. Malignant fibrous histiocytoma is a fast spreading pleomorphic sarcoma with a high malignant potential. Its spreading is characterized with local invasion and distant metastazes with early onset. Most common localisations of development are extremities, trunk and retroperitoneum. Given the line of rare case and specimen, lack of a clear etiology and mechanisms of this disease, as well as adequate histopathologic findings and intraoperative documentation, we presented current status, discuss putative etiology, histopathology with variant morphology, differential diagnosis and treatment modalities. **Case report.** We presented a 56-years-old female Serbian with tumor in the thigh that clinically resembles incapsulated hematoma. Computed tomography revealed intramuscular tumor with a heterodense structure and compression on surround tissue. *Ex tempore* biopsy specimen showed malignant potential of the tumor. Wide and radical excision of the nodule has been done, and definitive histopathological verification revealed malignant fibrous histiocytoma. **Conclusion.** Malignant fibrous histiocytoma is a most common type of soft tissue sarcomas in adults. Frequent localization is on lower extremities, and every rapidly enlarging nodule in this localization that on computed tomography is like incapsulated hematoma with necrotic zone should alert suspicion on presence of this type of sarcoma.

Key words:
sarcoma; soft tissue neoplasms; diagnosis; histological techniques; surgical procedures, operative.

Apstrakt

Uvod. Maligni fibrozni histiocitom je pleomorfni sarkom visokog malignog potencijala koji se brzo širi. Karakteriše se širenjem lokalnom invazijom i ranom pojavom udaljenih metastaza. Najčešće lokalizacije su ekstremiteti, trup i retroperitoneum. S obzirom na redak preparat, nedovoljno jasnu etiologiju i mehanizme nastanka ove bolesti, kao i adekvatan patohistološki nalaz i intraoperativni prikaz, cilj ovog prikaza je bio da se ukaže na trenutna saznanja o ovoj bolesti, njenoj etiologiji, patohistološkim karakteristikama, diferencijalnoj dijagnozi i lečenju. **Prikaz bolesnika.** Prikazana je bolesnica, stara 56 godina, sa tumorom desne natkolenice koji se klinički prezentovao kao inkapsulirani hematom. Kompjuterizo-vanom tomografijom utvrđeno je da se radilo o intramuskularnom tumoru koji se komprimovao u okolne strukture. *Ex tempore* biopsija je ukazala na maligni potencijal tumora. Urađena je široka i radikalna ekscizija promene, a definitivni patohistološki nalaz pokazao je da se radilo o malignom fibroznom histiocitomu. **Zaključak.** Maligni fibrozni histiocitom predstavlja najčešći tip sarkoma mekih tkiva kod odraslih. Često je lokalizovan na donjim ekstremitetima. Svaki brzorastući tumefakt mekih tkiva donjih ekstremiteta, koji na snimku kompjuterizovane tomografije podseća na inkapsulirani hematom sa zonama nekroze, treba da pobudi sumnju na maligni fibrozni histiocitom.

Ključne reči:
sarkomi; meka tkiva, neoplazme; dijagnoza; histološke tehnike; hirurgija, operativne procedure.

Introduction

Malignant fibrous histiocytoma (MFH) is a most common type of soft tissue sarcomas (STS), that was originally described by Ozzello et al. [1] in 1963 and O'Brien and Stout [2] in 1964 . World Health Organization (WHO) defined MFH as an undifferentiated high grade pleomorphic sarcoma [3]. It is the most common soft tissue sarcoma in adults, arising

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most frequently during the sixth and seventh decades of life [4]. Localisation regarding on the region of the body is as follows: over 70% of cases are located on extremities (50% on lower, and 25% on upper), followed by retroperitoneum (15%), and head and neck in 3–10% [5]. Rare cases include almost every organ in the body – bones, lungs, intestine, greater omentum, scars after surgical incision or even retained gauze [6]. MFH on extremities presents as a slow growing painless mass, while presentation in retroperitoneum is non-specific: appetite and body weight loss, fever and discomfort. It has a great malignant potential, with extensive local spreading and early onset of distant metastases [7]. Regarding on data above, every primary malignant tumor of extremities or retroperitoneum localisation, in people older than 45 years, should be considered as MFH. Recent studies indicate that most probable cells of origin are primitive mesenchimal cells or fibroblastic cells, that have characteristics both of fibroblasts and histiocytes [8]. Given the line of rare case and specimen, lack of a clear etiology, molecular and genetic mechanisms of this disease, we presented literature review, histopathologic findings with variant morphology, intraoperative documentation and modalities of treatment applied to the patient with MFH.

Case report

A 56-year-old female was admitted to our Clinic with the mass in the front of the right thigh. On physical examination firm tumor with positive fluctuation phenomenon was found and initially impressed like an incapsulated hematoma. Incision was done and material was sent to an *ex tempore* biopsy, which confirmed malignant nature of the mass. Standard blood tests and chest x-rays were normal. Preoperative computed tomography of the right thigh revealed intramuscular tumor (size 65 × 64 × 11 mm), that suppressed surrounding structures. It was of a heterodense structure, peripherally with intensive post-contrast opacification and internally with greater zone of necrosis. Ipsilateral inguinal region and bones tomography were normal (Figure 1).

In general anesthesia, wide local excision and Redon drainage of the wound was done (Figure 2). As expected, patient recovered ?uneventfully.

Histopathology

Operating material was sent for histopathologic analysis. Grossly, the tumor at the intersection was of whitish color, vitreous luster, with yellowish areas of necrosis and hemorrhage. Tumor samples were fixed in formalin, embedded in paraffin, cut into the cryotome in 4 μ thick tissue sections and stained with standard hematoxylin and eosine (HE) staining method. Microscopically, the tumor showed a classic image of a giant cell type MFH. It was built out from

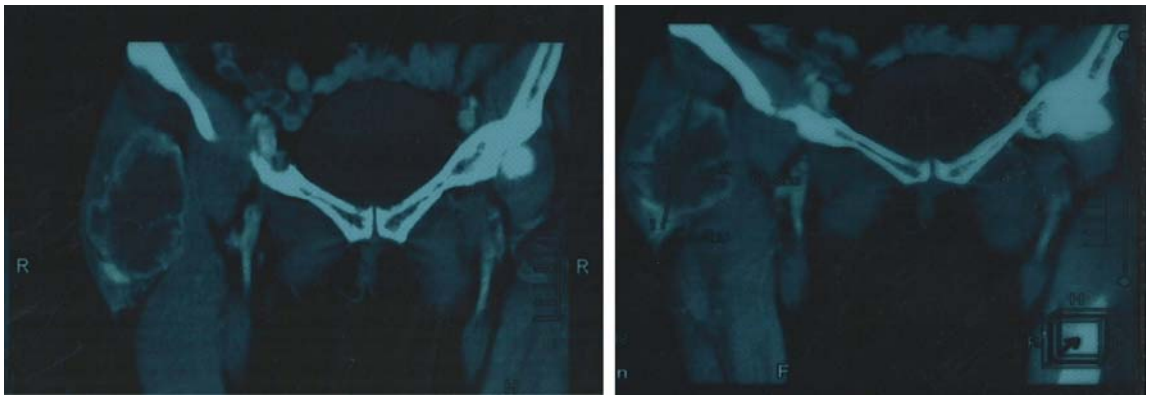

Fig. 1 – Computed tomography (CT) examination of the right femoral region shows an expansive heterodense tumor mass within *musculus tensorfascialatae*, internally in the tumor larger zone of necrosis can be seen.

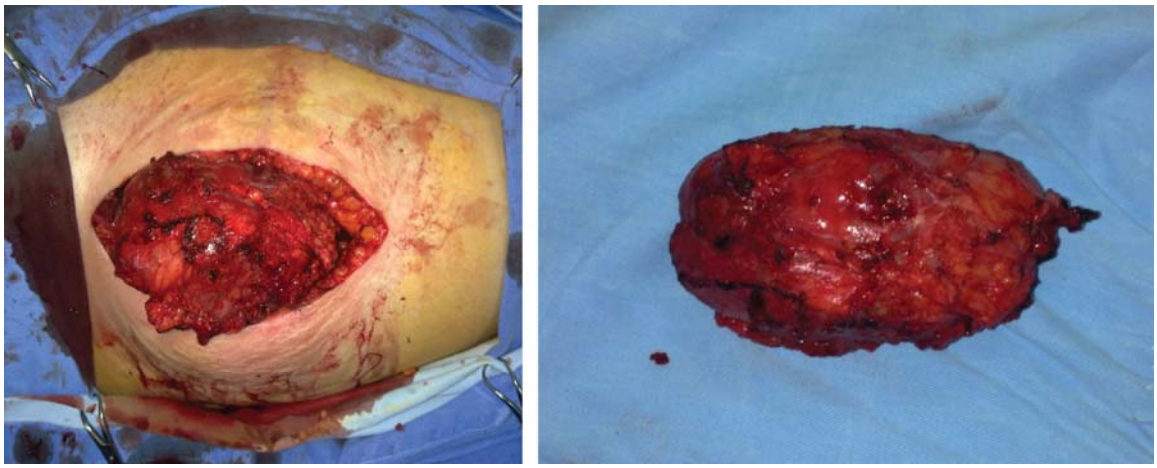

Fig. 2 – Intraoperative findings: large encapsulated tumor of the right thigh with clean resection margins.

the storiform arranged connective cells, along with zones dominated by histiocytes, among which there were numerous multinucleated giant osteoclast type cells (Figure 3).

Discussion

MFH is a group of pleomorphic neoplasm that have similar morphological characteristics. There are many different histopathological images which can be grouped into 4 subtypes, according to the new WHO classification. MFH subtypes are: 1) undifferentiated pleomorphic MFH; the largest part, about 65% of MFH, belongs to this group, which are typically composed of a mixture of spindle, polygonal and round cells found in a storiform matrix; it is usually localized to lower extremities and the retroperitoneum mainly in the elderly; 2) myxoid MFH is also common, occurring in 10–20% of cases. It is characterized by myxoid matrix that can be seen under the microscope, otherwise referred to as myxofibrosarcoma and can occur in two forms: superfitial and deep [9]; 3) MFH with giant cell variant is less common, occurring in 10–15% of cases of this type. It is characterized by the existence of multinucleate giant cells that can be seen under a microscope; 4) inflammatory MFH is the rarest form, occurring in only 5–8% of cases. Its characteristic is the existence of intensive inflammatory infiltrate predominantly consisting of neutrophils, lymphocytes and sparkling or anaplastic histiocytes, mainly in the retroperitoneum [10]. Angiomatoid MFH was considered as the fifth subtype, but no longer because histologically has similarities with blood vessels, low malignant potential and gives rare metastasis [11–14]. In the new WHO classification this type is marked as angiomatoid fibrous histiocytoma. MFH is an aggressive sarcoma, with extensive local spreading and early distant metastases. It has been determined to exhibit high-grade and biological aggressiveness.

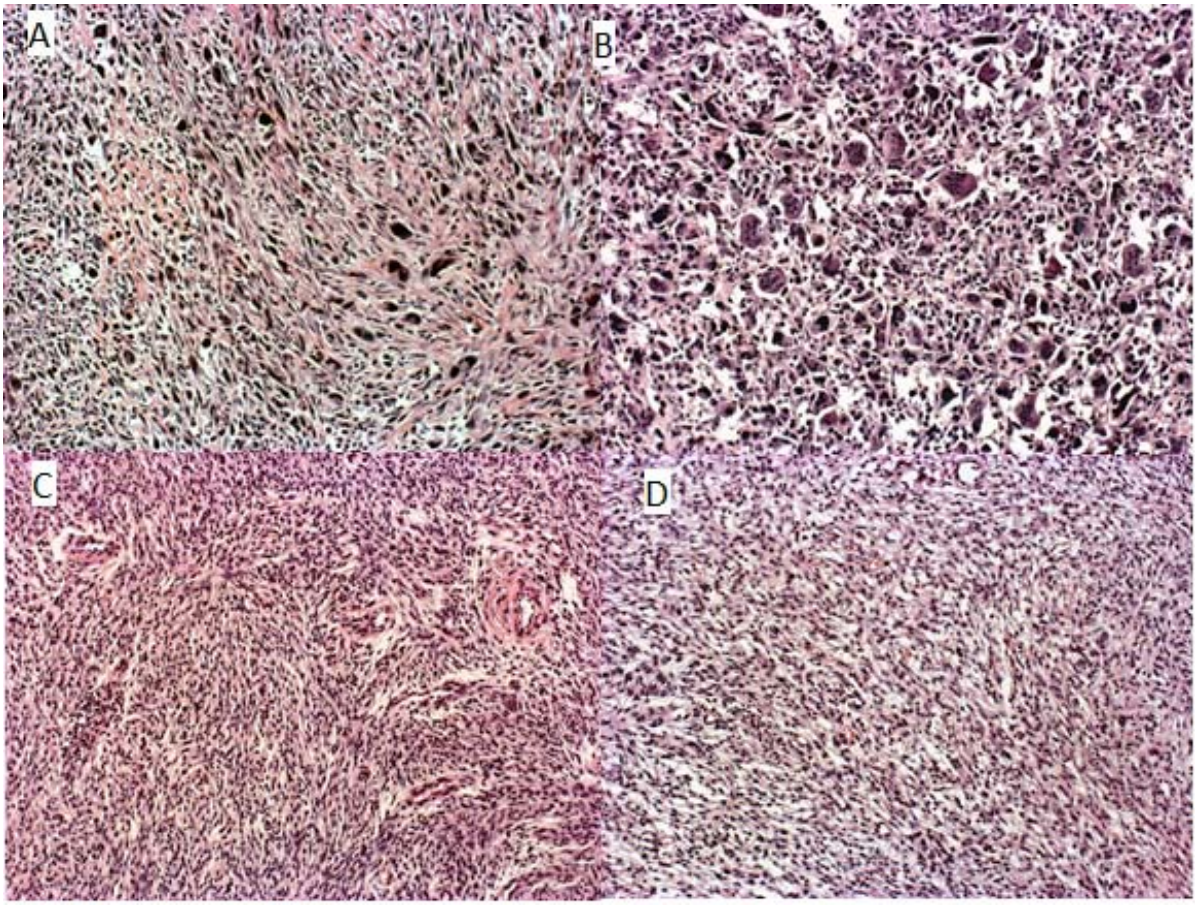

Fig. 3 – The tumor is made up of numerous multinucleate giant cells: A) [hematoxylin eosin (HE), ×200; and B) HE, ×400], which are irregularly scattered in areas storiform arranged connective cells: C) HE, ×100, and D) zones dominated by histiocytes (HE, ×200).

Tumor location, size, and histologic grade directly influence prognosis of MFH. Most commonly metastases occur in the lungs (90%), lymph nodes (12%), bone (8%), and liver (1%) [15]. The incidence of regional lymph node involvement is up to 15% [7, 16].

Risk factors for development of MFH have not been clearly established. Exposure to the ionizing radiation, especially in the MFH of the head and neck, can develop alternative mutations in this tumor. Infarction of the bone is another well-known risk factor [17, 18]. Genetic alterations of the p53 gene is often linked with a poorer prognosis [19], and frequent deletions on

$p16^{INK4A}$ tumor suppressor gene is demonstrated frequently, as well as activation of H- and K- ras gene [19–22].

Diagnosis

The diagnosis of MFH is not easy to establish. The presence of the disease may be suspected and the diagnosis can be set on the basis of the following methods: conventional (native) radiography – MFH is seen as a non-specific calcified tissue mass, or can be seen as compression or erosion of the surrounding tissue [23]; echosonography (EHO) – seen as well-defined mass that has a complex internal scheme, heteroechogenic structures with echogenic areas representing the zone cellularity and hypoechogenic areas representing the zone of necrosis; CT – MFH has mostly muscle density, with hypodense zones representing areas of necrosis; magnetic resonance (MR) – MFH can be visualized as a lobular mass with the intermediate signal on T1 sequences and high signal on T2 sequences [23].

Positron emission tomography/CT scanning is useful on assessing metastases. On angiography scans MFH is seen as a zone of hypervascularisation.

A biopsy has an important place in the diagnosis of MFH. It can be open and needle biopsy. Open biopsy is linked with a higher risk of complications, or less likely diagnoses for non-existence, while in case of the needle biopsy there are opposite results. Sentinel lymph node biopsy is an effective method for evaluating regional disease [24, 25].

For the histologic diagnosis conventional microscopic picture of MFH on standard HE stained tissue sections is usually sufficient. Alternation of storiform arrangements with connective cells and areas dominated by histiocytes, with variations in presence of giant cells, inflammatory infiltrate, fields of mixoid degeneration or proliferation of blood vessels, depending on the histological subtype of MFH, means that MFH has a potential for bilateral differentiation [26]. In atypical cases, as an additional method, immunohistochemistry is used, excluding other types of sarcoma by using a broad-spectrum of antibodies of mesenchymal differentiation. Neoplastic cells are positive on vimentin, in about 50% of the epithelial membrane antigen (EMA) and desmin, smooth muscle actin (SMA) and rarely on calponin, but still negative on cytokeratins and protein S-100. The pre-B cell antigen LN-2 (CD74) is a marker which helps distinguish MFH from atypical fibroxanthoma (AFX). The presence of immunohistochemical marker, bone morphogenic protein 2, gives better prognosis for patients [27]. Focal or weak immunoreactivity to mesenchymal markers such as CD10, CD99, CD68, lysozyme, fascin, and other intermediated filaments like desmin and neurofilaments has already been observed in cases of MFH [5].

Treatment

The goal of treatment is wide surgical resection of the tumor with clear resection margins [28].

The most common form of surgical treatment is the early and complete surgical excision with *en bloc* lymph dissection. In some cases, as a therapeutic option for the solution of MFH, amputation of limb is considered. After tumor resection, as an integral part of the surgical treatment reconstructive procedures are followed [29]. Studies in last two decades have demonstrated that conservative surgery, with or without adjuvant therapy, appears to be an effective treatment for sarcomas, including high-grade sarcomas, with a local recurrence rate of 7–15%, with no significant differences in terms of overall survival and disease-free interval compared with amputation [30–32].

After surgery, chemotherapy is usually applied - doxorubicin, or gemcitabine or a combination of doxorubicin and dacarbazine, and doxorubicin, ifosfamide and mesna. MFH treatment protocols depend on several factors: the size of the primary lesion, metastasis, localization near the vascular or visceral structures, patient's age, general condition. The basic method of treatment is radical surgery: complete removal of tumor and surrounding structures, while in those tumors that are localized near the vascular and nerve elements marginal surgical excision through the fibrous tissue that surrounds sarcoma is performed. Oncology goal of surgery is to achieve clean edges with no tumor cells.

Irradiation is carried out with the aim of reducing the probability of local recurrence and metastasis. It may be preoperative, intraoperative and postoperative. The dose of radiation ranges from 40–65 Gy and depends on the extensiveness of surgical treatment, localization of resection edges and whether they contain or not microscopic or macroscopic tumor cells.

Chemotherapy protocol that is used in the treatment is referred to as mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) [33]. So far, chemotherapy is employed only for widespread disease, but large trials have not shown a significant benefit [34, 35]. Multiple tyrosine kinase inhibitor, sunitinib, for MFH is currently undergoing a phase II trial [36], and phase I trial investigating ipilimumab in the treatment of MFH is in progress [37].

A characteristic of MFH is an increased incidence of local recurrence of the disease. Neoplastic infiltration of the resection margins at the end of surgery appears to be among the major factors affecting the rate of local recurrence. In fact, the local recurrence rate approximates 13% with margins of < 1 cm, while it may be reduced to 0% in cases with margins more than 1 cm. Previous studies have shown that 19–64% of patients with MFH developed local recurrences [16, 38]. The recurrence rate of MFH in extremities was lower than that in other areas. Local recurrence rates in extremities have been reported to be 19–38% [3, 39]. Factors that indicate a poor prognosis are lesions over 5 cm, positive edges and local recurrence, while the most important prediction factor for distant metastasis is the size of the primary lesion, especially over the size of 5 cm [40].

The general outcomes of extremity MFHs are superior to those of head and neck and retroperitoneal MFHs. According to a study conducted by Chen et al. [41] , 5-year survival rate is 76.2%. Clinical outcomes of extremity MFHs are associated with multiple factors. A French multicenter study of 410 patients with soft tissue sarcoma showed that tumor staging, resection margin, tumor location, histology type, and age of the patients are independent predictors of 5-year survival [42]. In regard of the size of the tumor, 5-year

survival for tumors < 5 cm is 82%, then falls to 68% for 5- to 10-cm tumors, and 51% for tumors >10 cm [24, 33].

Conclusion

MFH represents a rare and mysterious type of STS that requires timely diagnosis and aggressive treatment approach. For better survival results it is necessary to re-examine and adopt treatment protocols, especially with new biological agents and molecular – targeted therapy. Adjuvant therapy should be individually based. Understanding etiology, pathogenesis and genetic mechanisms that leads to this disease still remains controversial.

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CASE REPORT

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Transseptal approach to the implantation of cardiac resynchronization therapy

Transseptalni pristup implantacije resinhronizacione terapije srca

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Abstract

Introduction. In patients with cardiac resynchronization therapy left ventricular lead is usually placed through a tributary vein of the coronary sinus. However, when this approach failed, the atrial transseptal approach is mostly used for endovascular left ventricular lead placement, but it is quite difficult to perform. **Case report.** 59-years-old patient, male, was hospitalized due to endovascular left ventricular lead placement by atrial transseptal approach, after failed attempt via coronary sinus vein. Non-ischemic dilated cardiomiopathy was verified 1 year ago. Endoventricular lead was introduced by left subclavian approach and advanced through the previously punctured hole in the left atrium cavity and over mitral valve placed in posterolateral part of left ventricular. Both right ventricular defibrillator lead and atrial electrode were implanted routinely in the right ventricle septum and right atrial appendage. **Conclusion**. Left ventricular endocardial lead implantation by atrial transseptal approach is a feasible and safe in patients with previously failed implantation via tributary vein of the coronary sinus.

Key words:
cardiac resynchronization therapy; cardiac resynchronization therapy devices; treatment outcome.

Apstrakt

Uvod. Kod bolesnika sa resinhronizacionom terapijom srca elektroda za levu komoru se pretezno uvodi preko odgovarajuće grane koronarnog sinusa. Medjutim, u slučaju neuspeha, atrijalni transseptalni pristup je alternativa, ali je prilično zahtevan za izvodjenje. **Prikaz bolesnika.** Bolesnik star 59 godina, muškog pola, hospitalizovan je zbog implantacije srčane resinhronizacione terapije atrijalnim traneseptalnim pristupom zbog nemogućnosti uvodjenja elektrode preko grane koronarnog sinusa. Neishemijska dilatativna kardiomiopatija registrovana je unazad jednu godinu. Aktivno fiksirajuća elektroda je preko vene subklavije, interatrijalnog septuma odnosno mitralnog zaliska implantirana u posterolateralni deo leve komore. Defibrilatorska elektroda za desnu komoru, odnosno elektroda za desnu pretkomoru, su rutinski implantirane u septum desne komore, odnosno aurikulu desne pretkomore. **Zaključak.** Implantacija elektrode za levu komoru atrijalnim transseptalnim pristupom je izvodljiva i sigurna ukoliko se nije uspjelo preko grane koronarnog sinusa.

Ključne reči:
resinhronizaciona terapija srca; resinhronizaciona terapija srca, uređaji; lečenje, ishod.

Introduction

Left ventricular (LV) lead in patients with cardiac resynchronization therapy (CRT) is usually placed through a tributary vein of the coronary sinus (CS) [1]. However, this approach fails in approximately 10% of the cases, so surgical epicardial approach via lateral thoracotomy was used as the first choice [2–4].

In recent years, endocardial LV stimulation has been utilized as an alternative to epicardial approach via lateral thoracotomy due to increased risks, particularly in patients with advanced heart failure [5]. However, atrial transseptal approach is mostly used for endovascular LV lead placement, but it is quite difficult to perform.

We present our technique of LV lead implantation using atrial transseptal approach which is quite simple to perform.

Case report

A 59-years-old patient, male, was hospitalized due to endovascular LV lead placement by atrial transseptal approach, after failed attempt via coronary sinus vein (Figure 1).

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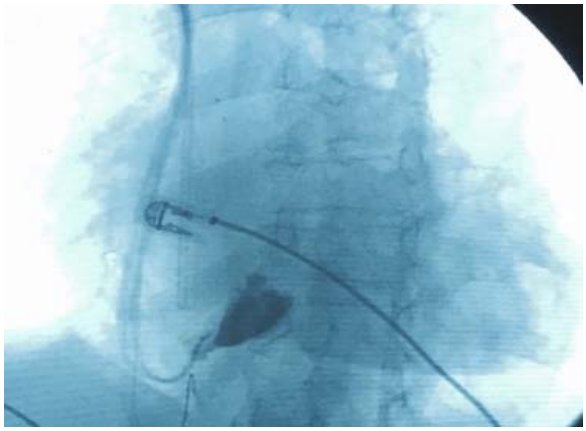

Fig. 1 – Stop the passage of contrast in the coronary sinus.

Non-ischemic dilated cardiomiopathy was verified 1 year ago. He has frequent palpitations during slight efforts accompanied by dyspnea, lightheadedness and syncope at a time. Electrocardiography (ECG) on admission showed sinus rhythm with left bundle branch block with QRS complex width of 180 msec (Figure 2). Echocardiography confirmed an enlarged left ventricle with strongly reduced ejection fraction (EF) of 20% as measured by Simpson method. The patient was categorized as the New York Heart Association (NYHA) functional class III.

After puncture of the right femoral vein were introduced both decapolar maping catheter, placed into the coronary sinus to facilitate the position of *fossa ovalis* and Brockenbrough (BRK) needle inserted via the steerable sheath and dilator was used for transseptal puncture (Figures 3 and 4). The sheath and dilator were withdrawn and exchanged with a tapered dilator. Then deflectable catheter sheath with a tapered dilator was withdrawn. Left subclavian vein was punctured and through the 7F inner lumen, flexible catheter sheath Medtronic 3630-69 active fixation endoventricular deflectable lead was introduced and advanced through the previously punctured hole in the left atrium cavity and over mitral valve implanted in posterolateral part of the left ventricle. Both active fixation right ventricular defibrillator

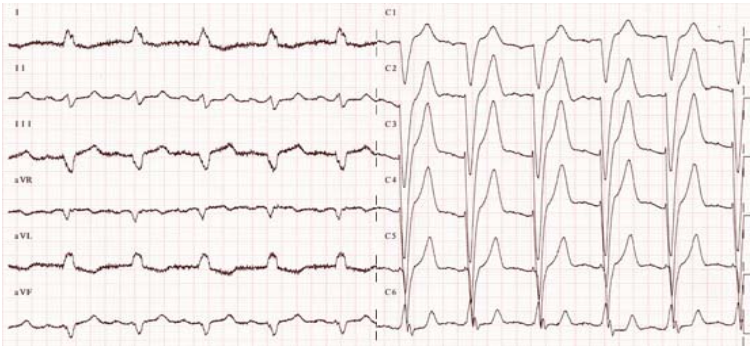

Fig. 2 – Electrocardiogram (ECG) showing the sinus rhythm with left bundle branch block with QRS complex width of 180 msec.

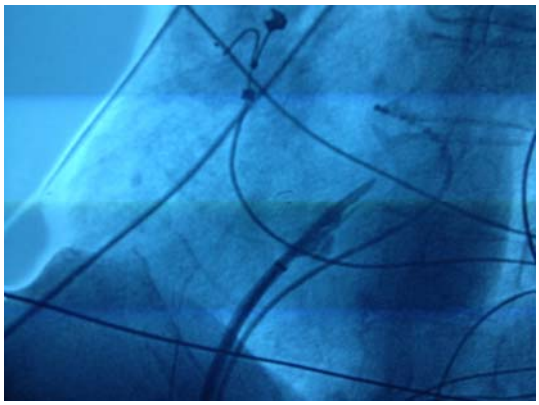

Fig. 3 – Transseptal puncture in left anterior oblique (LAO) view.

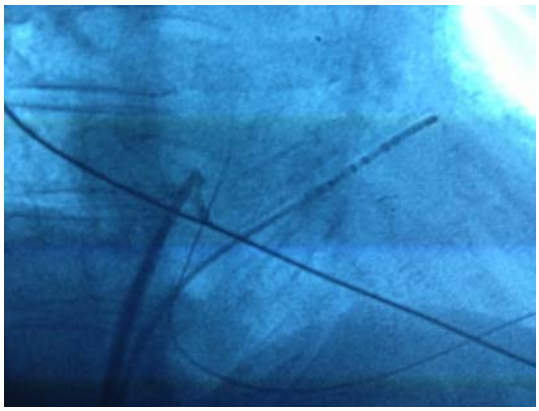

Fig. 4 – Transseptal puncture in right anterior oblique (RAO) view.

lead and non screw-in atrial electode were routinely implanted using also left subclavian approach in the right ventricle septum and right appendage (Figures 5 and 6). Optimal electronic parameters were obtained.

There were no other complications in the course of the procedure. After 1-year of follow- up patient improved NYHA functional class, sensing and capture threshold remained stable and ventricular pacing was more than 98%. ECG showed narrowing of QRS to 120 msec, LVEF was 40%, showing an excellent response to CRT-D (Figure 7).

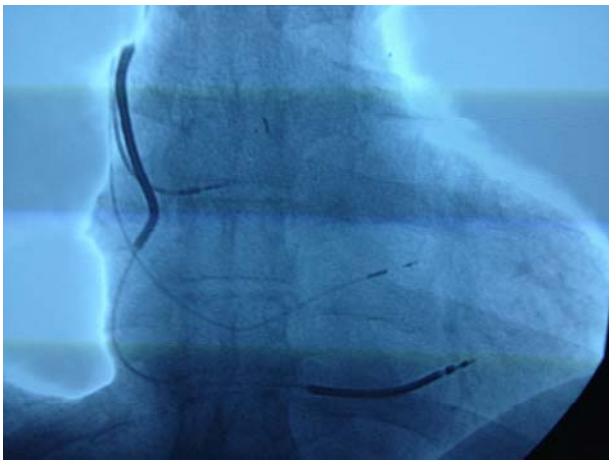

Fig. 5 – Lead position in posterior-anterior (PA) view.

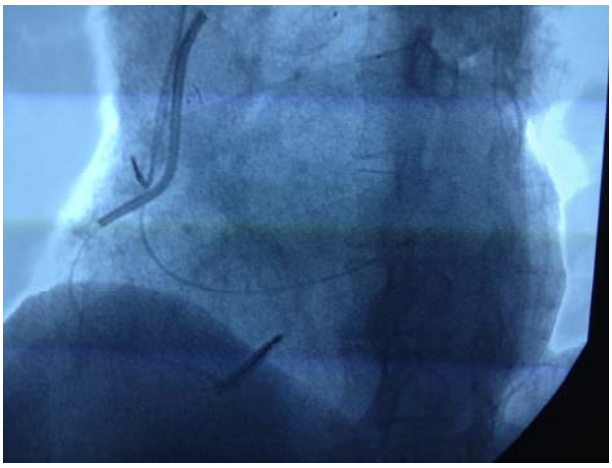

Fig. 6 – Lead position in left anterior oblique (LAO) view.

Discussion

In about 10% of patients, the LV lead cannot be implanted due to difficulties such as obstructing valves or coronary sinus dissection, tortuosities in the venous branches, phrenic nerve stimulation and areas of LV scar [1–4]. Suboptimal anatomical position of LV lead due to difficulties at the ideal site in 20–40% of CRT recipients may contribute to non-response [3, 6–8].

When a lead cannot be successfully delivered through the CS there are alternative routes.

Surgical placement of an epicardial lead can be performed, but it involves higher early morbidity and mortality as well as longer recovery period [5].

The atrial transseptal approach to LV endocardial pacing was initially described by Jaïs et al. [9]. Modifications of the technique have been developed over the past decade but it remains quite complex, with a combined atrial trasseptal puncture from the femoral vein with balloon dilatation of the septum as a prelude to the introduction of LV lead from the subclavian vein [10, 11]. At first, balloon dilatation of the septum carries the risk of splitting the septum as well as hematoma formation with possible surgical intervention to solve this problem. Further, EN Snarew system (Angiotech, Medical Device Technologies Inc., Gainesville, FL, USA) comprising loop shape mechanism necessary for grasping the distal part of the guide wire introduced in the left atrium over the transseptal sheath by femoral vein which is pulled into the superior vena cava and further, out of the subclavian vein [12, 13]. Steerable sheath is advanced over the guide wire and after withdrawal, the guide wire exchanged with electrode.

In our case we performed atrial transseptal punction by femoral vein using BRK 98 cm needle inserted via the steerable sheath and dilator with a pressure line attached to the proximal end of it. An additional curve was added by manually bending the needle. Atrial septum puncture was performed using alternating left anterior oblique (LAO) and right anterior oblique (RAO) fluoroscopic views. The dilator and sheath were then advanced 10–15 mm into the left atrium over the needle. The needle was withdrawn and a 0.032 inch stiff 260 cm J guidewire was advanced through the sheath and dilator in the chamber cavity. The sheath and dilator were withdrawn and exchanged over the stiff guidewire for 91cm deflectable 8.5F inner lumen catheter sheath with a tapered dilator (Agilis©; St Jude Medical Inc, Minessota, USA) passed over a guidewire into the left atrium and it was advan-

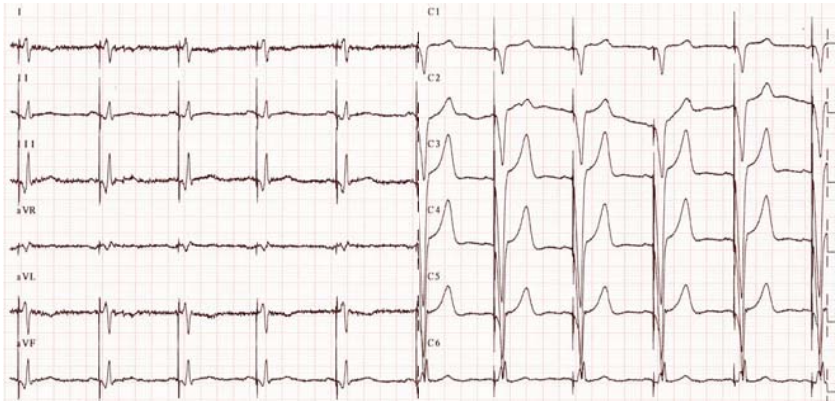

Fig. 7 – Electrocardiogram (ECG) showing biventricular pacing with narrowing of QRS to 120 msec.

ced and withdrawn over the interatrial septum three times to expand the hole of the interatrial septum and facilitate the introduction of the LV electrode. This maneuver is unique and useful to avoid balloon dilatation of the septum, not previously described in literature. Deflectable catheter sheath with a tapered dilator was withdrawn and Stiff J guidewire was left in the left atrium as a guide for the point of the puncture, which is also marked on the monitor by felt pen in both LAO and RAO position. Marked point is very simple but very useful guideline to the determination of the puncture hole. Introduction of Medtronic 3630-69 active fixation endoventricular deflectable lead was guided by described marked point in both LAO and RAO position which is greatly facilitated its introduction in the left atrium cavity and over mitral valve placement in posterolateral part of left ventricular. Movement of electrodes is easily enabled by turning of a rotating lever in a clockwise direction for introduction at left atrium and than in the opposite counterclockwise direction over the mitral valve. We also first described these maneuvers of lead introduction over the interatrial septum as well as mitral valve in the posterolateral part of left ventricule.

Direct puncture of the interventricular septum avoids manipulation across the mitral valve, potentially preventing worsening of mitral regurgitation and reducing the risk of mitral valve endocarditis [12, 13]. It is useful in patients with artificial mitral valve. Direct puncture interventricular septum directs the lead immediately towards the lateral LV, but left ventriculography in a right anterior oblique view is required to identify the LV borders [12, 13]. An angiogram of the left coronary arteries is also used in order to avoid the puncture of the major septal perforator vessel. The LV is a much larger cavity than the left atrium and has thicker muscle walls, potentially reducing the chance of inadvertent perforation and pericardial effusion, but this technique requires operator with experience and described additional procedures.

Conclusion

LV endocardial pacing through a ventricular septal puncture is a feasible and safe in patients with previously failed implantation via tributary vein of the coronary sinus. We present quite simple technique of LV lead implantation using atrial transseptal approach.

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SCIENTIFIC MEETING REPORT

Scientific projects presented at the Serbian Conference on INtERventional cardioloGY and cardiovascular imaging – SINERGY 2017 (September 7–9, 2017, Belgrade, Serbia)

On September 9, 2017, Serbian Conference on INtERventional cardioloGY and cardiovascular imaging (SINERGY 2017) hosted a half-day scientific meeting dedicated to ongoing research in the field of cardiovascular medicine in Serbia. Twenty-four presentations representing different institutions and research groups were delivered - the full list of presentations and authors is available on the conference website: http://sinergy-belgrade.com/#Room3). Starting from 2015, this was the third time that SINERGY organizers have assembled cardiovascular researchers from Serbia from basic to translational and clinical domains, to present and discuss their ongoing projects in an attempt to foster cross-institutional cooperation on the national level. The projects presented here were part of the original presentations during the SINERGY 2017 meeting. For the next SINERGY edition, on September 6-8, 2018, in Belgrade, leading cardiovascular researchers are planned to reconvene and to present the current status of their ongoing projects and discuss potential cooperation agreements.

On the behalf and with permission of the Scientific Committee of the Serbian Conference on INtERventional cardioloGY and cardiovascular imaging – SINERGY 2017 and its director and founder, academician Professor Goran Stankovic, the Vojnosanitetski pregled published some of the cardiovascular scientific projects presented at the Conference.

"CardioNS E1 – multifunctional ECG – application in different clinical scenarios", Project of the Institute of Cardiovascular Diseases Vojvodina, Sremska Kamenica, Serbia

Srđan Sladojević[†,□], Miroslava Sladojević[**], Ilija Srdanović[*,**], Andraš Anderla[†,□], Marko Arsenović[†,□], Velicki Lazar[*,**]

[†]Faculty of Technical Sciences, University of Novi Sad, Novi Sad, Serbia [□]Panonit doo, Novi Sad, Serbia, [*]Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia, [**]Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia

AIM: "CardioNS E1 – multifunctional ECG – application in different clinical scenarios" is a project implemented by a multidisciplinary team comprised of Srđan Sladojević, Miroslava Sladojević, Ilija Srdanović, Andraš Anderla, Marko Arsenović, and Lazar Velicki. CardioNS E1 is simple, but fully featured, precise and reliable 3-channel mobile multifunctional ECG device designed and developed as a dongle to be used as an USB device by on-the-go (OTG) enabled mobile phones or tablets. The purpose of this project was to develop portable and efficient ECG device that could be used in a variety of different clinical scenarios and for the research purposes including resting and stress ECG recorder, Holter monitor, remote monitoring device and Mobile Cardiac Telemetry (MCT) device. We are looking for clinical and biomedical partners interested in CardioNS E1 testing and conceptualization of innovative clinical and research purposes. Detailed presentation of the project is available on the Web - http://panonit.com/cardions. **Corresponding author:** Lazar Velicki, MD, PhD; e-mail: lazar.velicki@mf.uns.ac.rs

Crossing boundaires: from anatomy to surgery and beyond. Cardiovascular anatomy in clinical practice

Prof. dr Milan Milisavljević, prof. dr Branislav Filipović, prof. dr Laslo Puškaš, prof. dr Aleksandar Maliković, prof. dr Zdravko Vitošević

Institute of Anatomy "Niko Miljanić", Faculty of Medicine, University of Belgrade, Belgarde, Serbia

AIMs of our studies are:

1. To examine arteries and veins of the heart, their positions, course, relationships and variations
2. To measure the number, calibers, lengths and branching angles of cardiac arterial vessels
3. To study the coronary branching pattern
4. To compare morphological data obtained from fetal and adult hearts
5. To provide rare learning opportunities where the participants dissect and use human cadavers for themselves and the benefit of the group. The process of doing so is pro-

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found since the participants witness, are engaged in, and experience the whole human anatomy

Methods of our studies are:

1. Traditional anatomical injection of colored liquid latex, fixation in 10% formalin, dissection and measurements under the stereoscopic microscope

2. Histological method of taking parts of tissue, embedding in paraffin and sectioning serially in 5 μm thick slides staining with Masson trichrome method

3. Corrosion cast method using methylmetacrylate injection and immersion in a 30% solution of potassium hydroxide for corrosion. Following washing out and drying, the obtained vascular casts are examined and measured under the stereoscopic microscope in our Laboratory for vascular anatomy

4. *Integral Anatomy Dissection Workshops (unfixed and fixed)* designed primarily for specialists who are hands-on practitioners of some therapeutic modality as well as for surgeons professionals, cardiologists, radiologists, teachers and the like who have prior professional knowledge of anatomy of which they make regular use.

Experimental cardiovascular models for study of the effects of hyperhomocysteinemia (acute and subchronic), hypermethioninemia (acute and subchronic), heart failure and diabetes mellitus in rats

Dragan M. Djurić[1], Vladimir Lj. Jakovljević[2]

[1]Institute of Medical Physiology "Richard Burian", Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [2]Department of Physiology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

Aim: Study of the effects of homocysteine and homocysteine-related compounds on cardiovascular system: role of gaseous transmitters NO, H2S and CO (Research grant no. OI 175043, Ministry of Education, Science and Technological Development, Republic of Serbia, 2011-, principal investigator Dragan M. Djuric)

Ongoing Subprojects/PhD Theses:

1. The effects of subchronic homocysteine overload on coronary hemodynamics and oxidative stress in a rat: the effects of sulfur aminoacids (methionine, L-cysteine and N-acetyl-l-cysteine) and inorganic sodium hydrogen sulfide administration

2. Functional, biochemical and morphohistological changes in a rat cardiovascular system following acutely induced hyperhomocysteinemia or subchronic methionine overload – the effects of sulfur aminoacids (L-cysteine and N-acetyl-l-cysteine) administration

3. Functional, biochemical and immunohistochemical changes in a rat cardiovascular system following monocrotaline-induced heart failure – subchronic effects of vitamin B6 and folic acid administration

4. Functional, biochemical and immunohistochemical changes in a rat cardiovascular system following streptozotocin-induced diabetes mellitus – subchronic effects of vitamin B6 and folic acid administration

5. Mechanisms of cardiodynamic and vasoactive effects of systemic anaesthetic propofol in a rat: the impact of oxidative stress, gasotransmitters and cardiovascular biomarkers

European Research Network

COST Action CA16225, Action Title: Realising the therapeutic potential of novel cardioprotective therapies (2017-2021)

COST Action BM1005, Action Title: Gasotransmitters: from basic science to therapeutic applications (ENOG: European Network on Gasotransmitters) (2011-2015)

Assessment of predictors of mortality, major bleeding and chronic thrombembolic pulmonary hypertension in patients with pulmonary embolism and individualization of therapy

Military Medical Academy, Faculty of Medicine, University of Defence, Belgrade, Serbia

Slobodan Obradović (sloba.d.obradovic@gmail.com), Boris Džudović, Siniša Rusović, Bojana Subotić, Nataša Novičić; *Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia*: Jovan Matijašević (jovanmat99@yahoo.com), Milica Milić, Jadranka Trobok, Sandra Peković, Sovilj. *Zvezdara University Medical Center, Belgrade, Serbia*: Nataša Marković-Nikolić (nmarkovicnikolic@gmail.com). *Clinical Centre Niš, Niš, Serbia*: Dragana Stanojević, Sonja Šalinger (sonja.salinger@gmail.com). *Institute for Cardiovascular Diseases of Vojvodina, Sremska Kamenica,* Serbia: Ilija Sredanović, Aleksandra Vulin, Milana Jaraković (milana.jarakovic@ikvbv.ns.ac.rs). *Clinical Centre Kragujevac*, *Kragujevac, Serbia*: Vladimir Miloradović (vanja.miloradovic@gmail.com), Nikola Jagić. Maja Nikolić.

AIM: The purpose of this project is to create multicenter registry of patients with pulmonary embolism and to study predictors of mortality, major bleeding and development of chronic pulmonary embolic disease. The second goal is to examine efficacy and safety of different thrombolytic protocols and the role of direct oral anticoagulant drugs in the treatment of pulmonary embolism. The participants in the project are form several university clinics, however we will include each hospital which takes part in the management of pulmonary embolism patients.

Effects of remote conditioning on reperfusion injury in patients with acute coronary syndrome

Clinical Centre Kragujevac, Kragujevac, Serbia: Vladimir Miloradović (vanja.miloradovic@gmail.com), Stefan Simovic (simovicst@gmail.com),

The purpose of this project is to evaluate effects of remote conditioning on reperfusion injury in patients with acute myocardial infarction with and without ST segment elevation and unstable angina as well as its effects on markers of oxidative stress and anti-oxidative parameters. One of the purposes will also be to investigate whether different protocols for remote conditioning have different effects. The participants in the project are from single university clinic, however we will include each hospital which take part in the trial, exploring effects of remote conditioning on reperfusion injury.

Ultrasound of extravascular lung water: detection and prognostic value of pulmonary congestion in heart failure patients

Prof. dr Marina Deljanin Ilić [1,2] (corresponding author: Telephone: 018 502 045; e-mail: marinade@mts.rs), Dr Dejan Simonović[2]. *[1]Faculty of Medicine, University of Niš, Niš, Serbia*; *[2]Institute for Treatment and Rehabilitation, Cardiology Clinic, Niška Banja, Serbia*

AIM: Assessment of pulmonary congestion remain challenging without a gold standard, so there is a critical

need for quantitative markers of pulmonary congestion, its correlation with echocardiographic parameters with the aim to increase the speed and accuracy of diagnosis, facilitate early treatment, inform treatment titration and potentially improve risk stratification. Patient population: This is prospective, multi centre, observational study in adults, with the HF hospitalization irrespective of left ventricular ejection fraction. All patients will be divided into three groups according to ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (patients with heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF). Lung ultrasound imaging protocol: Lung ultrasound examinations will be performed on admission to hospital as well as at discharge, evaluating 28 intercostal points on the anterior chest wall with the patient in the supine position (B model; scoring system, 6-15 B-lines mild degree pulmonary congestion, 16-30 moderate degree and > 30 B-lines severe degree pulmonary congestion). All patients will underwent detailed echocardiographic examination on admission and at discharge from hospital. Follow-up and definition of cardiovascular events and primary clinical end-point. Patients will be prospectively followed via phone call, every 3 months for at least 12 months. All hospitalizations and cause of hospitalization, death as well as causes of death should be documented. The primary clinical endpoint will be the time to first heart failure hospitalization or all-cause death.

Multidisciplinary study of diseases of aorta and its branches: pathogenesis, diagnosis and treatment

Prof. Lazar. Davidović, Principle Investigator; Investigators: Prof. Miroslav Marković, Prof. Dušan Kostić, Prof. Slobodan Cvetković, Prof. Dragan Marković, Doc. Marko Dragaš, Asist. Nikola Ilić, Asist. Igor Končar, Asist. Andreja Dimić. *Clinic for Vascular and Endovascular Surgery, Clinical Centre of Serbia, Belgrade, Faculty of Medicine, University of Belgrade, Belgrade, Serbia.* Contact: drmiroslav@gmail.com; davidovic.lazar@gmail.com

AIM: multidiscliplinary and contemporary approach to diseases of aorta and its branches regarding pathogenesis and treatment.

1. Demographic characteristics and ultrasound screening for the patients with increased risk of aneurismatic and atherosclerotic disease of aorta
2. Analysis of biomechanical and biochemical parameters of aortic aneurism (Cooperation with *the Faculty of Mechanical and Civil Engineering, University of Kragujevac, Kragujevac, Serbia)*
3. Determination of genetic and clinical markers of the initial carotid atherosclerosis
4. Participation in BIOLEAK study (Multicenter prospective study of MMP9 in blood as marker of endo-leak after endovascular reconstruction of aortic aneurism). Clinicaltrials.gov, No NCT01965717 (Cooperation with *Universities in Genova, Plzen and Gdansk*)
5. Study of the association between genetic markers and aortic diseases with PCR microarray testing (Cooperation with the *Laboratory for Radiobiology and Molecular Genetics, Institute of Nuclear Sciences Vinca, Belgrade, Serbia*)
6. Study of the methods for the protection of spinal cord during the surgery on thoracic and abdominal aorta
7. Study of the certain circulating markers for the prediction of the progression of aortic aneurism dimeter and rupture
8. Study of the correlation between MRI imaging and biomechanical characteristics of aortic aneurism and relation with the existence of intra-aortic atherosclerosis and thrombus
9. Participation in the Horizon study of the new aortic stent grafts
10. Participation in the multicenter European study "Hernia" for the methods of the closure of laparoscopic wounds and its relation to post-operative hernias after surgery of abdominal aorta * (No NCT02012270, international register of clinical studies – cooperation with *the Clinic for Abdominal Surgery in Gant Belgium*)

Impact of coronary microcirculation dysfunction on the extent of myocardial necrosis in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention

Prof. Goran Stanković (corresponding author), Dr. Dejan Milašinović

Catheterization Laboratory, Department of Cardiology, Clinical Center of Serbia, Belgrade, Serbia

Rationale: Although previous studies have indicated the potential of coronary microvascular resistance to predict outcomes in patients with ST-elevation myocardial infarction (STEMI), treated with primary percutaneous coronary intervention (PCI), several different microcirculatory indices were used, and showed inconsistent results, including thermodilution-derived index of microcirculatory resistance (IMR) and doppler-derived hyperemic microvascular resistance (HMR).

Aim: Our project aims to assess the ability of a novel, doppler-derived index of coronary microvascular resistance, pressure at zero flow (PzF), to predict infarct size in STEMI patients treated with timely primary PCI.

Organization: Coronary microcirculation will be prospectively interrogated using a Doppler wire in STEMI patients after a successful primary PCI. The obtained indices will be correlated with the CMR-assessed infarct size, biomarkers of cardiac injury and echo-derived parameters of left ventricular function.

Cooperation: The study will be primarily conducted in the Department of Cardiology of the Clinical Center of Serbia, with pending inter-institutional cooperation agreements on both the national level (standardized non-invasive imaging protocols and biomarker assessment) and internationally (microcirculatory indices computing).

PRETreatment with Ticagrelor versus clopidogrel in patients undergoing earlY invasive intervention for Non-ST segment Elevation Myocardial Infarction (PRETTY-NSTEMI)

Prof. Milika Ašanin, Assist. Prof. Aleksandra Milošević

Emergency Department, Department of Cardiology, Clinical Center of Serbia, Belgrade, Serbia

Rationale: Ticagrelor has recently been associated with favorable clinical outcomes, when compared with Clopidogrel, in patients with acute coronary syndrome (ACS), including non-ST segment elevation myocardial infarction (NSTEMI), treated with percutaneous coronary intervention (PCI). However, the exact mechanisms of the potentially

beneficial effects of Ticagrelor over Clopidogrel remain unknown.

Aim: Our study was designed to assess the impact of pretreatment with Ticagrelor vs. Clopidogrel on the extent of myocardial injury, expressed by the in-hospital peak and total release of high-sensitivity Troponin T (hsTnT), in patients with NSTEMI referred to early invasive management.

Organization: Patients are randomized to receive either Ticagrelor or Clopidogrel loading dose immediately upon diagnosis of NSTEMI and prior to referral to the catheterization laboratory and the primary endpoint is the extent of in-hospital hsTnT elevation. Afterwards, patients will receive the recommended maintenance doses of Ticagrelor and Clopidogrel and will be clinically followed-up for a year along with the assessment of secondary clinical endpoints including both ischemic and bleeding events.

Cooperation: The study has already commenced and the inclusion is underway in the Department of Cardiology of the Clinical Center of Serbia, with the planned transition to a multicenter randomized trial, pending the cooperation agreements with PCI-capable institutions on the local and national level.

Mechanical dispersion in patients with heart failure and severely depressed left ventricular function with bundle branch blocks*

Investigators: Ivan Stankovic (PI), Aleksandra Janicijevic, Aleksandra Dimic, Milica Stefanovic, Radosav Vidakovic, Biljana Putnikovic, Aleksandar N. Neskovic; *Clinical Hospital Center Zemun, Faculty of Medicine, University of Belgrade, Belgrade, Serbia*

Rationale: Evaluation of bundle branch blocks (BBB)-related mechanical dyssynchrony an dispersion may improve patient selection for device therapy in patients with heart failure and severely depressed left ventricular ejection fraction (LVEF). However, their effect on the natural history in this patient population is unknown. **Methods:** We investigated a total of 155 patients with LVEF□≤□35% and BBB, not treated with device therapy. Mechanical dyssynchrony was defined as the presence of either septal flash or apical rocking on two dimensional echocardiogram. Contraction duration was assessed as a time interval from the electrocardiographic R-(Q-) wave to peak longitudinal strain in each of 17 left ventricular segments. Mechanical dispersion was defined as either the standard deviation of all time intervals ($dispersion_{SD}$) or as the difference between the longest and shortest time intervals ($dispersion_{delta}$). Patients were followed for cardiac mortality during a median period of 33 months. **Main findings:** While mechanical dyssynchrony was not associated with survival, more pronounced mechanical $dispersion_{delta}$ was found in patients with dyssynchrony than in those without it. In the multivariate regression analysis, patients' functional class, diabetes mellitus and $dispersion_{delta}$ were independently associated with mortality. **Conclusions:** Mechanical dispersion measured by deformation imaging (strain), but not dyssynchrony, was associated with poor outcome in patients with severely depressed left ventricular function and bundle branch blocks. Evaluation of mechanical dispersion may have potential to be used for the risk stratification of patients with heart failure and bundle branch blocks.

*presented in part at the ESC Congress in Barcelona 2017; currently *in press* in the Annals of Medicine (*Stankovic I, et al*. Mechanical dispersion is associated with poor outcome in heart failure with a severely depressed left ventricular function and bundle branch block. *Ann Med. 2017 Oct 13:1-11. doi:10.1080/07853890.2017.1387282.)*

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Belgrade, Serbia

E R R A T U M

The article: Psoriasis is independent factor for early atherosclerosis: A prospective study of cardiometabolic risk profile. Vojnosanit Pregl 2016; 73(12): 1094-101.
(DOI: 10.2298/VSP150510134D)

The authors were listed as: Miroslav Ž. Dinić, Radoš D. Zečević, Zoran Hajduković, Mirjana Mijušković, Predrag Djurić, Zoran Jović, Aleksandra Grdinić, **Mirjana Petrović**, Brankica Terzić, Janko Pejović, Lidija Kandolf Sekulović

The list of authors should read as: Miroslav Ž. Dinić, Radoš D. Zečević, Zoran Hajduković, Mirjana Mijušković, Predrag Djurić, Zoran Jović, Aleksandra Grdinić, **Marijana Petrović**, Brankica Terzić, Janko Pejović, Lidija Kandolf Sekulović

The correction has been made to the online version of that issue of the Journal which is available at: www.vma.mod.gov.rs

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Papers should be written on IBM-compatible PC, using 12 pt font, and double spacing, with at least 4 cm left margin. **Bold** and *italic* letters should be avoided as reserved for subtitles. Original articles, reviews, meta-analyses and articles from medical history should not exceed 16 pages; current topics 10; case reports 6; short communications 5; letters to the editor and comments 3, and reports on scientific meetings and book reviews 2.

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MS Word for Windows (97, 2000, XP, 2003) is recommended for word processing; other programs are to be used only exceptionally. Illustrations should be made using standard **Windows** programs, **Microsoft Office** (**Excel**, **Word Graph**)**.** The use of colors and shading in graphs should be avoided.

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a) The title should be concise but informative, while subheadings should be avoided;

b) Full names of the authors signed as follows: ***, †, ‡, §, ||, ¶, **, ††, ...** .

c) Exact names and places of department(s) and institution(s) of affiliation where the studies were performed, city and the state for any authors, clearly marked by standard footnote signs;

d) Conclusion could be a separate chapter or the last paragraph of the discussion;

e) Data on the corresponding author.

2. ***Abstract and key words***

The second page should carry a structured abstract (250-300 words for original articles and meta-analyses) with the title of the article. In short, clear sentences the authors should write the **Background**/**Aim**, major procedures – **Methods** (choice of subjects or laboratory animals; methods for observation and analysis), the obtained findings – **Results** (concrete data and their statistical significance), and the **Conclusion**. It should emphasize new and important aspects of the study or observations. A structured abstract for case reports (up to 250 words) should contain subtitles **Introduction, Case report, Conclusion**). Below the abstract **Key words** should provide 3–10 key words or short phrases that indicate the topic of the article.

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The text of the articles includes: **Introduction**, **Methods**, **Results**, and **Discussion**. Long articles may need subheadings within some sections to clarify their content.

Introduction. After the introductory notes, the aim of the article should be stated in brief (the reasons for the study or observation), only significant data from the literature, but not extensive, detailed consideratuion of the subject, nor data or conclusions from the work being reported.

Methods. The selection of study or experimental subjects (patients or experimental animals, including controls) should be clearly described. The methods, apparatus (manufacturer's name and address in parentheses), and procedures should be identified in sufficient detail to allow other workers to reproduce the results. Also, give references to established methods, including statistical methods. Identify precisely all drugs and chemicals used, with generic name(s), dose(s), and route(s) of administration. State the approval of the Ethnics Committee for the tests in humans and animals.

Results should be presented in logical sequence in the text, tables and illustrations. Emphasize or summarize only important observations.

Discussion is to emphasize the new and significant aspects of the study and the conclusions that result from them. Relate the observations to other relevant studies. Link the conclusions with the goals of the study, but avoid unqualified statements and conclusions not completely supported by your data.

References

References should be superscripted and numerated consecutively in the order of their first mentioning within the text. All the authors should be listed, but if there are more than 6 authors, give the first 6 followed by *et al*. Do not use abstracts, secondary publications, oral communications, unpublished papers, official and classified documents. References to papers accepted but not yet published should be cited as "in press". Information from manuscripts not yet accepted should be cited as "unpublished data". Data from the Internet are cited with the date of citation.

Examples of references:

Jurhar-Pavlova M, Petlichkovski A, TrajkovD, Efinska-Mladenovska O, Arsov T, Strezova A, et al. Influence of the elevated ambient temperature on immunoglobulin G and immunoglobulin G subclasses in sera of Wistar rats. Vojnosanit Pregl 2003; 60(6): 657–612.

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

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

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Each table should be typed double-spaced 1,5 on a separate sheet, numbered in the order of their first citation in the text in the upper right corner and supplied with a brief title each. Explanatory notes are printed under a table. Each table should be mentioned in the text. If data from another source are used, acknowledge fully.

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Any forms of graphic enclosures are considered to bi figures and should be submitted as additional databases in the System of Assistent. Letters, numbers, and symbols should be clear and uniform, of sufficient size that when reduced for publication, each item will still be legible. Each figure should have a label on its back indicating the number of the figure, author's name, and top of the figure (**Figure 1**, **Figure 2** and so on). If a figure has been published, state the original source.

Legends for illustrations are typed on a separate page, with Arabic numbers corresponding to the illustrations. If used to identify parts of the illustrations, the symbols, arrows, numbers, or letters should be identified and explained clearly in the legend. Explain the method of staining in photomicrographs.

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Authors are encouraged to use abbreviations and acronyms in the manuscript in the following manner: abbreviations and acronyms must be defined the first time they are used in the text consistently throughout the whole manuscript, tables, and graphics; abbreviations should be used only for terms that appear more than three times in text; abbreviations should be sparingly used.

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Rukopis se piše sa proredom 1,5 sa levom marginom od **4 cm**. Koristiti font veličine 12, a načelno izbegavati upotrebu **bold** i *italic* slova, koja su rezervisana za podnaslove. Originalni članci, opšti pregledi i metaanalize i članci iz istorije medicine ne smeju prelaziti 16 stranica (bez priloga); aktuelne teme – deset, seminar praktičnog lekara – osam, kazuistika – šest, prethodna saopštenja – pet, a komentari i pisma uredniku – tri, izveštaji sa skupova i prikazi knjiga – dve stranice.

U celom radu obavezno je korišćenje međunarodnog sistema mera (SI) i standardnih međunarodno prihvaćenih termina (sem mm Hg i °C).

Za obradu teksta koristiti program **Word for Windows** verzije 97, 2000, XP ili 2003. Za izradu grafičkih priloga koristiti standardne grafičke programe za **Windows**, poželjno iz programskog paketa **Microsoft Office** (**Excel, Word Graph**). Kod kompjuterske izrade grafika izbegavati upotrebu boja i senčenja pozadine.

Radovi se pripremaju u skladu sa **Vankuverskim dogovorom**.

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Delovi rada su: **naslovna strana, apstrakt sa ključnim rečima, tekst** rada, zahvalnost (po želji), literatura, prilozi.

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a) Poželjno je da naslov bude kratak, jasan i informativan i da odgovara sadržaju, podnaslove izbegavati.

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2. ***Apstrakt i ključne reči***

Na drugoj stranici nalazi se strukturisani apstrakt (250-300 reči za originalne članke i meta-analize) sa naslovom rada. Kratkim rečenicama na srpskom i engleskom jeziku iznosi se **Uvod/Cilj** rada, osnovne procedure **– Metode** (izbor ispitanika ili laboratorijskih životinja; metode posmatranja i analize), glavni nalazi **– Rezultati** (konkretni podaci i njihova statistička značajnost) i glavni **Zaključak**. Naglasiti nove i značajne aspekte studije ili zapažanja. Strukturisani apstrakt za kazuistiku (do 250 reči), sadrži podnaslove **Uvod, Prikaz bolesnika** i **Zaključak**). Ispod apstrakta, „Ključne reči“ sadrže 3–10 ključnih reči ili kratkih izraza koje ukazuju na sadržinu članka.

3. ***Tekst članka***

Tekst sadrži sledeća poglavlja: **uvod**, **metode**, **rezultate** i **diskusiju**. **Uvod.** Posle uvodnih napomena, navesti cilj rada. Ukratko izneti razloge za studiju ili posmatranje. Navesti samo važne podatke iz literature a ne opširna razmatranja o predmetu rada, kao ni podatke ili zaključke iz rada o kome se izveštava.

Metode. Jasno opisati izbor metoda posmatranja ili eksperimentnih metoda (ispitanici ili eksperimentne životinje, uključujući kontrolne). Identifikovati metode, aparaturu (ime i adresa proizvođača u zagradi) i proceduru, dovoljno detaljno da se drugim autorima omogući reprodukcija rezultata. Navesti podatke iz literature za uhodane metode, uključujući i statističke. Tačno identifikovati sve primenjene lekove i hemikalije, uključujući generičko ime, doze i načine davanja. Za ispitivanja na ljudima i životinjama navesti saglasnost nadležnog etičkog komiteta.

Rezultate prikazati logičkim redosledom u tekstu, tabelama i ilustracijama. U tekstu naglasiti ili sumirati samo značajna zapažanja.

U **diskusiji** naglasiti nove i značajne aspekte studije i izvedene zaključke. Posmatranja dovesti u vezu sa drugim relevantnim studijama, u načelu iz poslednje tri godine, a samo izuzetno i starijim. Povezati zaključke sa ciljevima rada, ali izbegavati nesumnjive tvrdnje i one zaključke koje podaci iz rada ne podržavaju u potpunosti.

Literatura

U radu literatura se citira kao superskript, a popisuje rednim brojevima pod kojima se citat pojavljuje u tekstu. Navode se svi autori, ali ako broj prelazi šest, navodi se prvih šest i *et al*. Svi podaci o citiranoj literaturi moraju biti tačni. Literatura se u celini citira na engleskom jeziku, a iza naslova se navodi jezik članka u zagradi. Ne prihvata se citiranje apstrakata, sekundarnih publikacija, usmenih saopštenja, neobjavljenih radova, službenih i poverljivih dokumenata. Radovi koji su prihvaćeni za štampu, ali još nisu objavljeni, navode se uz dodatak „u štampi“. Rukopisi koji su predati, ali još nisu prihvaćeni za štampu, u tekstu se citiraju kao „neobjavljeni podaci“ (u zagradi). Podaci sa *Interneta* citiraju se uz navođenje datuma pristupa tim podacima.

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Tabele

Sve tabele pripremaju se sa proredom 1,5 na posebnom listu. Obeležavaju se arapskim brojevima, redosledom pojavljivanja, u desnom uglu (**Tabela 1**), a svakoj se daje kratak naslov. Objašnjenja se daju u fus-noti, ne u zaglavlju. Svaka tabela mora da se pomene u tekstu. Ako se koriste tuđi podaci, obavezno ih navesti kao i svaki drugi podatak iz literature.

Ilustracije

Slikama se zovu svi oblici grafičkih priloga i predaju se kao dopunske datoteke u sistemu **aseestant**. Slova, brojevi i simboli treba da su jasni i ujednačeni, a dovoljne veličine da prilikom umanjivanja budu čitljivi. Slike treba da budu jasne i obeležene brojevima, onim redom kojim se navode u tekstu (**Sl. 1; Sl. 2** itd.). Ukoliko je slika već negde objavljena, obavezno citirati izvor.

Legende za ilustracije pisati na posebnom listu, koristeći arapske brojeve. Ukoliko se koriste simboli, strelice, brojevi ili slova za objašnjavanje pojedinog dela ilustracije, svaki pojedinačno treba objasniti u legendi. Za fotomikrografije navesti metod bojenja i podatak o uvećanju.

Skraćenice i akronimi

Skraćenice i akronimi u rukopisu treba da budu korišćeni na sledeći način: definisati skraćenice i akronime pri njihovom prvom pojavljivanju u tekstu i koristiti ih konzistentno kroz čitav tekst, tabele i slike; koristiti ih samo za termine koji se pominju više od tri puta u tekstu; da bi se olakšalo čitaocu, skraćenice i aktinome treba štedljivo koristiti.

Abecedni popis svih skraćenica i akronima sa objašnjenjima treba dostaviti pri predaji rukopisa.

Detaljno uputstvo može se dobiti u redakciji ili na sajtu: www.vma.mod.gov.rs/vsp