Publishing Sector of the Society of Physicians of Vojvodina of the Medical Society of Serbia, Novi Sad, Vase Stajica 9,

MEDICAL REVIEW

JOURNAL OF THE SOCIETY OF PHYSICIANS OF VOJVODINA OF THE MEDICAL SOCIETY OF SERBIA

THE FIRST ISSUE WAS PUBLISHED IN 1948

MEDICAL REVIEW is published two-monthly (six double issues per a year) in the circulation of 1000 copies. Payment for individuals from the territory of Serbia for the year 2015 is 3,000.00 dinars (the VAT being calculated in) and 4,000.00 dinars for the individuals outside the territory of Serbia, and 8,000.00 dinars (+ the VAT) for institutions. The payments are to be made to the account number 340-1861-70 or 115-13858-06, with the remark "Additional membership fee for the Medical Review".

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Printed by: Department for Joint Affairs of Provincial Authorities - Sector for Printing

Izdavačka delatnost Društva lekara Vojvodine Srpskog lekarskog društva, Novi Sad, Vase Stajića 9

MEDICINSKI PREGLED

ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA
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Štamparija: Uprava za zajedničke poslove pokrajinskih organa - Odsek za poslove štamparije

M E D I C A L R E V I E W
JOURNAL OF THE SOCIETY OF PHYSICIANS OF VOJVODINA OF THE MEDICAL SOCIETY OF SERBIA
Novi Sad Vase Stajića 9 Serbia

Med Pregl 2015; LXVIII (11-12): 363-432. Novi Sad: November-December.

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Med Pregl 2015; LXVIII (11-12): 363-432. Novi Sad: novembar-decembar.

SADRŽAJ

EDITORIAL
UVODNIK

University of Novi Sad, Faculty of Medicine
Clinical Centre of Vojvodina, Novi Sad
Department of Orthopaedic Surgery and Traumatology

Editorial
Uvodnik
UDK 616.728.3-089.844 i 616.728.3-089.28

IMPLANTATION OF THE KNEE JOINT ENDOPROSTHESIS

IMPLANTACIJA ENDOPROTEZE ZGLOBA KOLENA

Zoran GOJKOVIĆ

Although the primary osteoarthritic changes in the knee joint are found more often than at any other joint, only in the last years of this century the number of interventions for the knee replacement has taken the leading position in modern orthopaedic surgery [1]. It is considered that in developed countries over 1% of the population owes their quality of life to knee endoprostheses. Every year over 700,000 these interventions are done in the United States of America. If this trend continues, it is expected that over 3.48 million citizens of the United States will be operated annually by 2030 [2]. In former Yugoslavia, the first procedure of the knee joint replacement with endoprosthesis was performed at the former provincial hospital in Novi Sad, and continuing that trend the first contemporary Insall-Burstein posterior-stabilized (IBPS) knee endoprosthesis was implanted at the Department of Orthopaedic Surgery and Traumatology in Novi Sad in 1989. Today, about 2000 patients are operated per year in the Republic of Serbia, while in Vojvodina over 500 operations of this kind are performed. It is prevalent in females and increases linearly with age [3]. Surgical operation, methods of fixation, biological responses of bone tissue and mechanical stability and support of a single complex system have simultaneously developed and improved through the long history of technological progress, improvements in characteristics of prosthetic components, as well as selection of materials and their design. Today, the knowledge gained from this approach provides excellent postoperative results in over 90% of treated patients [4].

Implantation of knee endoprosthesis is indicated in terminal stages of degenerative knee diseases resulting from either the primary or secondary osteoarthritis, avascular necrosis, or various inflammatory arthropathies. Since this is a chronic disease, these patients lead a life of poor quality, suffer form a lot of pain and have difficulty in movement, and therefore use various drugs and undergo various surgical or rehabilitation procedures [5]. The main goal of a successful surgical treatment is to eliminate pain, restore the function, correct a possible deformity, ensure the joint stability and provide a long-term reconstruction effect. Surgery is contraindicated in patients with poor general health condition, the presence of active joint infection and rare diseases such as neuropathic arthropathy [6].

Depending on the degree of damage of the knee joint surfaces, it is nowadays possible to implant unicompartmental, bicompartmental or tricompartmental knee joint endoprostheses. Unicompartmental endoprostheses replace medial or lateral femoraltibial compartment enabling the quick recovery, significantly less postoperative pain and blood loss. The fact that the knee joint disease is present only on medial or lateral side in less than 15% of cases significantly reduces the indication for this type of prosthetics. Additionally, a disadvantage of these prostheses is a very demanding surgical procedure that often requires a new surgery due to the development of osteoarthritic changes in the knee joint not having been replaced. Nevertheless, a qualitative preoperative selection of patients with relatively good mobility of the knee joint and adequate ligamentous stability gives good results for a longer period [7]. Bicompartmental and tricompartmental prostheses can be called total knee endoprostheses. The difference is in the fact that whether during the surgical procedure there is a patellar knee joint replacement or not. This is one of the greatest controversies in prosthetic knee surgery, and there are numerous studies for and against it. A good long-term result of the implantation of total knee endoprosthesis is closely and reciprocally associated with adequate position, function and mobility of the kneecap. Nowadays, it is observed on an individual level (case by case) and most often depending on the affinity, experience and careful preoperative

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preparation, the final decision is up to the surgeon [4]. Those who advocate patellar replacement, although in the minority, even claim that the bicompartmental approach cannot represent the total knee joint replacement anatomically [8].

According to the method of fixation endoprosthesis components to the bone, total endoprotheses can be: cement, non-cement and hybrid (non-cement femoral component and cement tibial component) one. While in prosthetic hip surgery a limit has moved towards non-cement fixation method, the dominant fixation in prosthetic knee surgery is the cement one. Articulation method of the prosthetic components classifies total prostheses into three groups: knuckled (hinge, constrained), partially knuckled (semi constrained) and non-articular prosthesis (free or condylar, unconstrained). Today, condylar prostheses represent the gold standard of knee arthroplasty [9]. Implantation of fully or partially articulated prosthetic components increases the stability of the knee joint; however, biomechanics and statics are seriously disturbed, motions in the knee are restricted and the stress on both the prosthetic components and the bone-cement interconnection is increased, which reduced the lifespan of the prosthesis [4, 7]. Therefore, this type of prostheses is used exclusively in the revision and demanding primary surgery where there are large bone defects and axial deformities followed by extensive ligament deficiency [10].

Modern total endoprostheses differ in whether the posterior cruciate ligament (PCL) is sacrificed or preserved during implantation. However, today there are both mobile and fixed tibial polyethylene platforms. Current technological development and progress in the design and structural geometry of prosthetic components attempt to simulate the normal anatomic knee kinematics true-to-life [11]. However, an orthopaedic surgeon is the one who still plays the leading role in the knee reconstruction. Good knowledge and understanding of anatomy and knee biomechanics, precise operational techniques and full respect to neurovascular and soft-tissue structures are essential factors for placing the prosthesis component in the optimal position and the consequent stability and mobility of the joint. A clear indication for surgical treatment with adequate preoperative preparation is the gold standard for the good final outcome [6, 12]. Different scoring systems are of great help for this purpose. Their application helps the surgeon to examine both the general health condition of the patient and the local status of the diseased knee joint precisely and systematically [13]. Prior to operation, it is very important to evaluate ligamentous stability and knee mobility, the presence of articular or extra-articular deformities, muscle strength and neurovascular support, with careful analysis of the main, and additional diagnostic radiographic procedures, if necessary.

Not only the surgical techniques but also the accompanying surgical instruments have been evolved and improved through decades of applying these procedures, and even computer-assisted navigation is applied today [14]. The surgical approach to the knee joint from the front gives the adequate possibility of the knee joint visualization, antero-medial arthrotomy being the mostly used. One of the most important aims of operational procedure is to establish the normal mechanical axis of the leg both in the frontal and in the sagittal plane. This is achieved by the adequate resection of the articular surfaces of distal femur and proximal lower-leg. After preparation of the bone ends of femur and tibia, fixation is done by placing the metal implants appropriately to the bone tissue [6]. Mistakes made in the inadequate assessment of the mechanical axis and the inadequate resection set the prosthetic components in the unsatisfactory position consequently resulting in poor postoperative outcome. It is often necessary to make the adequate soft tissue balance in a more or less pronounced knee deformity and take it to the full knee stability and mobility, regarding both flexion and extension.

Surgical technique of total knee endoprosthesis implantation is highly demanding, it tolerates neither compromises nor the smallest mistakes. It must be performed only by experienced and well trained orthopaedic surgeons effectively and appropriately [15]. When all these principles and requirements are fulfilled, the complication rate is minimal [16]. Primarily, it is reflected in post-operative infection that occurs in about 2% of cases [17]. Systemic complications, pulmonary thromboembolism being the most common one, are very rare [16]. Nowadays, the focus is on prevention of surgical site infections, eradication of the focus of infection (teeth, urogenital system, skin), as well as preventive preoperative use of single-dose of antibiotics and increased hygienic epidemiological surveillance. Moreover, anticoagulants are of high importance in prevention of serious vascular complications [18]. Imprecise surgery results in serious problems with the implant, chronic pain and limitation of motions in the knee, which requires re-intervention and surgical revision of the knee [19].

Other specialist, mainly anaesthesiologists and physiotherapists, are of upmost importance for successful surgical procedures, which indicates a multidisciplinary approach to this intervention [20, 21]. Adequate anaesthesia, blood transfusion and circulating liquid transfusion, treatment of postoperative pain and early rehabilitation undoubtedly have a great significance and role in the final outcome of the treatment [22, 23].

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Rad je primljen 18. X 2015.
Prihvaćen za štampu 18. X 2015.
BIBLID.0025-8105:(2015):LXVIII:11-12:367-369.

ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

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Original study
Originalni naučni rad
UDK 616.728.3-089.84:617.3
DOI: 10.2298/MPNS1512371M

BONE-PATELLAR TENDON-BONE GRAFT PREPARATION TECHNIQUE TO INCREASE CROSS-SECTIONAL AREA OF THE GRAFT IN ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

TEHNIKA OBRADE KOST-LIGAMENT ČAŠICE-KOST KALEMA ZA POVEĆANJE POVRŠINE POPREČNOG PRESEKA KALEMA KOD REKONSTRUKCIJE PREDNJEG UKRŠTENOG LIGAMENTA KOLENA

Miroslav MILANKOV[1,2], Mirko OBRADOVIĆ[1,2], Miodrag VRANJEŠ[1,2] and Zlatko BUDINSKI[1,2]

Summary

Introduction. Not much has changed in the way the bone-patellar tendon-bone graft is prepared before implantation. We present a modified bone-patellar tendon-bone graft preparation technique by implying the increased cross-sectional area. **Material and Methods.** Measurements of bone-patellar tendon-bone graft were made during the reconstruction of the anterior cruciate ligament in 93 male patients. The bone part of bone-patellar tendon-bone graft 10 mm wide and the tendon part 12-14 mm wide was placed on the holder with a handle in a way which allowed sewing the edges of the patellar tendon in a shape of a tube. The circumference of the central part of the graft was measured using a suture tightened around the graft. The diameters of the circle and cross-sectional areas were then calculated using geometrical calculation. **Results.** After preparation of the bone-patellar tendon-bone graft, the following measures were recorded: the circumference of 30 mm, the diameter of 9.55 mm, and the cross-sectional area of 72 mm^2 in 9 patients; the circumference of 31mm, the diameter of 9.87 mm, and the cross-sectional area of 76 mm^2 in 15 patients, and the circumference of 32 mm, the diameter of 10.19 mm, and the cross-sectional area of 82 mm^2 in 69 patients. **Conclusion**. For the average thickness (3-5 mm) and width (10 mm) of the patellar tendon graft, the cross-sectional area will be 30-50 mm^2. The modified bone-patellar tendon-bone graft preparation technique made it possible to increase its cross-sectional area to 71-81 mm^2.

Key words: Anterior Cruciate Ligament Reconstruction; Orthopedic Procedures; Bone-Patellar Tendon-Bone Grafting; Bone-Patellar Tendon-Bone Grafts; Tendon Injuries; Patellar Ligament; Reconstructive Surgical Procedures; Recovery of Function

Sažetak

Uvod. Tokom vremena nije se mnogo toga promenilo u načinu pripreme kost–ligament čašice–kost kalema za rekonstrukciju prednjeg ukrštenog ligamenta kolena. Predstavljena je naša tehnika pripreme kalema kojom smo povećali površinu poprečnog preseka kost–ligament čašice–kost kalema. **Materijal i metode.** Kod 93 muškarca za vreme rekonstrukcije prednjeg ukrštenog ligamenta izvršeno je merenje kost–ligament čašice–kost (K-L-K) kalema. Kalem kod koga je koštani deo bio širok 10 mm a tetivni 12-14 mm, stavljen je u držač koji je omogućio šivenje ivica tetiva tako da on dobije oblik cevi. Koncem obavijenim oko centralnog dela kalema je meren njegov obim. Na osnovu ovog podataka izračunat je prečnik i površina poročnog preseka kalema. **Rezultat.** Posle pripreme kalema kod 9 pacijenata obim je bio 30 mm, prečnik 9,55 mm i površina poprečnog preseka 72 mm^2; kod 15 pacijenta obim je bio 31 mm, prečnik 9,87 mm i površina poprečnog preseka 76 mm^2, a kod 69 pacijenta obim je bio 32 mm, prečnik 10,19 mm i površina poprečnog preseka 82 mm^2. **Zaključak.** Kod prosečne debljine tetive čašice kolena (3-5 mm) i širine (10 mm), poprečni presek kost–ligament čašice–kost kalema iznosi 30-50 mm^2. Našom modifikacijom povećana je površina poprečnog preseka kost–ligament čašice–kost kalema na 71-81 mm^2.

Ključne reči: Rekonstrukcija prednjeg ukrštenog ligamenta; Ortopedske procedure; Kost-ligament čašice-kost kalemljenje; Kost-ligament čašice-kost kalemi; Povrede tetiva; Patelarna tetiva; Rekonstruktivne hirurške procedure; Oporavak funkcije

Introduction

Patellar tendon autografts are used daily by orthopedic surgeons for anterior cruciate ligament (ACL) reconstruction because they are known to give good and easily reproducible clinical results. The first surgeon who used a part of patellar ligament for ACL replacement was Langworthy in 1930s [1]. Thirty years later, Jones [2] and Brückner [3] refined the initial technique by using the

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Abbreviations

BTB – bone-patellar tendon-bone
ACL – anterior cruciate ligament
CSA – corss-sectional area

central third of the patellar tendon. Following Franke's [4] publication, bone-patellar tendon-bone (BTB) became one of the most popular graft sources and gained further popularity both in Europe and the United States through the work of Eriksson [5] and Clancy [6].

The use of BTB graft is associated with excellent clinical results in 80-90% of cases, as well as some complications of the knee extensor mechanism, including BTB harvest site morbidity [7] and disruption of the knee extensor apparatus [8]. Bone-patellar tendon-bone graft ensures strong initial graft fixation using interference screws, allowing direct bone-bone healing and consecutive bony integration at the fixation points of the reconstruction [7]. The main disadvantage of BTB is a graft–tunnel mismatch [9] due to a smaller cross-section area and incomplete filling of the tunnel compared to hamstring tendon graft [10, 11].

Not much has changed in the way the BTB graft is prepared before implantation. Pujil et al. [12] described arthroscopic double-bundle ACL reconstruction technique using a rectangular patellar bone block, a double stranded patellar tendon, and a double tibial bone block. By simulating anatomical ACL reconstruction, Shino et al. [13] and Herbort et al. [14] tried to improve the BTB SB technique, creating a rectangular tunnel and bony part of the graft, neglecting the importance of the cross-sectional area of the classic BTB graft, with a width of 10 mm and the thickness of 3-5 mm, which ultimately depends on the individual patient's characteristics [15–17].

The aim of this study was to present the modified BTB graft preparation technique. We hypothesized that modified BTB graft preparation technique would increase the cross-sectional area of the graft, thus getting closer to the characteristics of the native ACL and/or hamstring tendon graft.

Material and Methods

The procedure of the study was approved by the Local Human Research Ethical Committee. A prospective study, conducted from July 1 to December 31, 2013, included 93 male patients of the average age 26 (15-44) in whom measurements of the patellar tendon and BTB graft were performed during the anterior cruciate ligament reconstruction. Only men were included in the study due to a small number of women operated in that period. The knee was approached through a vertical skin incision made from the middle of the patella to the inferior portion of the tibial tubercle, with the knee flexed. The skin flaps were created and the incision was sharply carried down through the transverse

Figure 1. BTB graft after preparing bone parts to circumference of 10 mm and tendon part width 14 mm
Slika 1. *Kalem posle uzimanja gde je koštani deo 10 mm a tetivni deo 14 mm širine*

fibres of the paratenon. The paratenon was incised at its midpoint to expose the entire width of the patellar tendon. Next, while maintaining the tendon in a stretched position by flexing the knee, it was incised first on one side of the graft followed by the other side, obtaining 12-14 mm wide patellar tendon. Then, a chisel was used to create the tibial bone plug, approximately 25 mm long and 10mm wide, by scoring the tibial cortex and removing an equilateral triangle of bone with the saw. An osteotome was used to lift the tibial bone plug carefully from its bed onto a lap pad. The patellar tendon with a tibial bone plug was lifted up and cleaned off the remaining soft tissue attachments with the scissors. Using an oscillating saw, a patellar plug of trapezoidal shape, 25 mm long and 10 mm wide, was created and gently removed. The tendinous part of the BTB graft was measured (its width and thickness) and prepared on a side table by an assistant **(Figure 1)**. The graft was then placed on the holder with a handle in a way which allowed sewing the edges of the patellar tendon in the shape of a tube **(Figure 2)**. The diameter of the graft was determined by passing the folded graft through the sizing cylinders with incremental size changes of 1 mm. The circumference of the central part of the BTB graft was manually measured using a suture tightened around the graft. The suture was then cut and its length was measured in mm [14]. The diameters of the circle and the cross-sectional areas were then calculated using a geometrical calculation ($O=2r\pi$ and $P=r^2\pi$) **(Figure 3).**

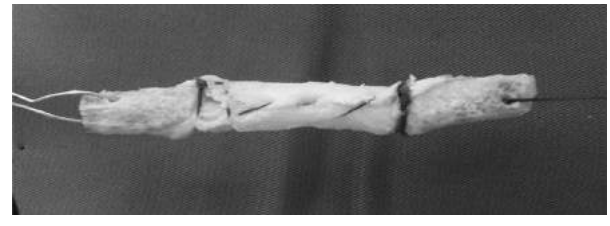

Figure 2. The BTB graft was prepared on a side table, on the holder, so as to have the edges of the patellar tendon sewn together at the end in order to obtain a tube
Slika 2. *Kalem je pripremljen na stolu u držaču tako da su ivice spojene da naprave tubus*

Figure 3. Example: The cross-sectional area of a classic rectangular shape BTB allograft (right) 10 mm wide and 4 mm thick (P=ab) is 40 mm^2, and a modified BTB allograft of a circular shape (left), 10 mm in diameter and ($P=r^2\pi$) is 81 mm^2.
Slika 3. *Primer: poprečni presek klasičnog četvorougaonog alografta (desno) širine 10 mm i debljine 4 mm (P = ab) je 40 mm^2 a modifikovanog kalema (levo) kružnog oblika, prečnika 10 mm i poprečnog preseka ($P = r^2\pi$) je 81 mm^2*

The standard anterolateral portal was used as a viewing portal and the anteromedial one as a working portal. The ACL stump was debrided. The femoral tunnel was created through the anteromedial portal to avoid excess fluid loss. The knee was placed at 110-120 degrees of flexion. The femoral guide with an appropriate offset was introduced into the joint through the anteromedial portal. With the help of a femoral guide, a drill-wire was placed into the centre of the anatomic ACL insertion which was then overdrilled with a 10-mm diameter reamer. A suture was retrieved after the guide pin had been drilled into the joint. Afterwards, a cannulated reamer with an equal diameter to the graft created the tibial tunnel. A grasper was then placed through the tibial tunnel to retrieve the suture. Then the graft was passed through the tibia into the femoral socket, and once the graft was properly positioned in the tunnel, it was fixed with round cannulated interference screws (RCI). Firm traction was applied to the tibial bone block while putting the knee through the full range of knee motion in order to pretense the graft and make sure that there is no impingement in full extension. The graft was then tensioned using 80 N force and the screws were additionally tightened if needed. Lachman test was used to check the knee stability. A drain was placed in the knee and the operative wound was closed in the usual fashion.

Results

The width and the thickness of patellar tendon was 33 mm (28-43) and 4.05 mm (3-5), respectively. The width of the taken patellar tendon was 13.62 mm (12-14). After the preparation of the BTB grafts **(Table 1)**, the following measures were recorded: the circumference of 30 mm, the diameter of 9.55, and the cross-sectional area of 71.59 mm^2 in 9 patients; the circumference of 31 mm, the diameter of 9.87 mm, and the cross-sectional area of 76.50 mm^2 in 15 patients, and the circumference of 32 mm, the diameter of 10.19 mm, and the cross-sectional area of 81.51 mm^2 in 69 patients.

Discussion

The patellar tendon is the most distal part of the extensor mechanism which connects the inferior pole of the patella and the tibial tubercle. Technically, it is a ligament (connecting a bone to a bone), but it has often been referred to as a tendon because the patella is a sesamoid bone. The average length of the patellar tendon is 40-53 mm [15, 16, 18, 19]. The patellar tendon is wider proximally than distally because the fascicles tend to converge toward the midline [20]. Yoo et al. [15] measured the width of the proximal and distal part of the tendon and they were 30 mm and 24 mm, respectively. In our study, the mean patellar tendon width measured in the middle of the tendon was 33 mm (28-43 mm). Regarding the thickness of the patellar tendon, it has been shown that the central third of the patellar tendon is significantly thicker than the medial and lateral thirds [18], and may be affected by long-term sports activity [21]. The average patellar tendon thickness in our study ranged from 3 to 5 mm, similar to the average

Table 1. Geometric characteristics of the modified BTB graft
Tabela 1. *Geometrijske karakterisitke modifikovanog kalema*

No of patients *Broj pacijenata*	BTB graft circumference in mm (measured at the central part) (O=2rπ)/*Obim kalema u mm (mereno u središnjem delu)*	Diameter in mm *Prečnik u mm*	Half-diameter in mm *Poluprečnik u mm*	Cross-sectional area in mm^2 ($P=r^2\pi$). *Poprečni pesek u mm^2*
9	30	9.55	4.77	71.59
15	31	9.87	4.93	76.50
69	32	10.19	5.09	81.51

O circumference/*obim*; P surface/*površina*, r half-diameter/*poluprečnik*, π = 3,14

tendon thickness described in other studies using either magnetic resonance imaging (MRI) [19], or cadaveric [16, 17] knee measurements.

The goal of the anatomical ACL reconstruction is to restore the natural anatomy. The reconstructed ACL size is determined by the harvested graft size, not by the size of the native ACL insertion site[13]. It is important to know the geometric characteristics of the graft including the length, cross-sectional area, and surface attachment of ACL in order to determine the optimal mechanical graft properties and obtain optimal ACL reconstruction results. The ACL has a "band-like" shape and does not have the same dimensions throughout its whole length [22]. Harner et al. [23] measured the cross-sectional area of the ACL mid-substance in older cadavers, and found that cross-sectional ACL mid-substance area was approximately 3.5 times smaller than the ACL tibial and femoral insertions. The tibial insertion area in 2D (projected on the tibial plateau) ranged from 114 mm^2 to 229 mm^2 [17, 24, 25], while the calculated cross-section area of the native ACL ranged from 32 to 65 mm^2, also confirmed in cadaveric studies [12, 16, 25].

If a BTB graft has the thickness of 3 mm, the width of 10 mm and the cross-sectional area (CSA) of 30 mm^2, it is still significantly smaller than a cross-sectional area of the native ACL and/or 8 mm diameter hamstring tendon graft (with 50 mm^2 of cross-sectional area) [17]. Shimizu et al. [26] and Yoshiya et al. [27] have reported that a 10-mm wide patellar tendon graft has an average CSA of 33 mm^2, while Staubli et al. [28] reported the average CSA of 36 mm^2 in a cadaveric study. For the patellar tendon graft of the average thickness (3-5 mm) [16–18] and the width of 10 mm, the CSA will be 30-50 mm^2. Our modified BTB graft preparation technique made it possible to increase its cross-sectional area to 71-81 mm^2, and come close to the CSA of the native ACL and hamstring tendon graft **(Table 2).**

Regardless of whether the anatomic tunnel placement in the native footprint may be more important than a complete filling of the footprints [29], we believe that our modified BTB graft preparation allows better reconstruction of native ACL and/or hamstring tendon graft geometric characteristics. Geometric characteristics of the patellar tendon directly affect the BTB graft and the results of ACL reconstruction, and in an ideal anatomical ACL reconstruction, the geometry of the ACL graft should resemble that of the original ACL [30]. The major finding in the present study is that the modified BTB graft preparation technique made it possible to increase its CSA.

One of the possible complications associated with our modified BTB graft preparation is a rupture of the patellar tendon. We have been using this modified BTB graft preparation technique since 2006, and out of 1750 ACL reconstructions we performed during this period, only two patients developed a patellar tendon rupture 8 months after surgery associated with an intense jump [31].

The main weakness of this study is the lack of mechanical and biological testing of our graft, which is going to be addressed in our future research.

Conclusion

For the average thickness (3-5 mm) and width (10 mm) of the patellar tendon graft, the cross-sectional area will be 30-50 mm^2. The modified bone-patellar tendon-bone graft preparation technique made it possible to increase its cross-sectional area to 71-81 mm^2.

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Rad je primljen 20. VI 2015.
Recenziran 29. VI 2015.
Prihvaćen za štampu 30. VI 2015.
BIBLID.0025-8105:(2015):LXVIII:11-12:371-375.

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Original study
Originalni naučni rad
UDK 616.348/.35-006.6-073.7
DOI: 10.2298/MPNS1512376M

DIAGNOSTIC ROLE OF FLUORINE-18 (^{18}F) FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY COMPUTED TOMOGRAPHY IN DETECTING RECURRENT DISEASE IN PATIENTS WITH COLORECTAL CANCER AND ELEVATED CARCINOEMBRYONIC ANTIGEN

DIJAGNOSTIČKA ULOGA POZITRON EMISIONE TOMOGRAFIJE/KOMPJUTERIZOVANE TOMOGRAFIJE FLUOR–18 FLUORODEZOKSI GLUKOZOM U OTKRIVANJU RECIDIVA KOD PACIJENATA SA KOLOREKTALNIM KARCINOMOM I POVIŠENIM KARCINOEMBRIONSKIM ANTIGENOM

Emil MATOVINA, Jasna MIHAILOVIĆ, Katarina NIKOLETIĆ and Dolores SRBOVAN

Summary

Introduction. Early detection of recurrence is an important factor for long term survival of patients with colorectal cancer. Measurement of serum levels of carcinoembryonic antigen has been commonly used in the postoperative surveillance of colorectal cancer. The purpose of this study was to evaluate the ability of positron emission tomography–computed tomography to detect pathological substrate of elevated serum carcinoembryonic antigen in patients with colorectal cancer. **Material and Methods**. The patients with colorectal cancer who underwent curative surgical resection and/or chemotherapy, who were found in our database, were analyzed retrospectively. Forty-eight ^{18}F- fluorodeoxyglucose positron emission tomography–computed tomography studies including 45 patients (14 women, 31 men; mean age: 62.93 years) with elevated serum, carcinoembryonic antigen levels, which had been performed between January 2011 and January 2014, were evaluated. Serum levels of carcinoembryonic antigen were measured within 3 months after positron emission tomography–computed tomography examination. Final diagnosis of recurrence was made by histopathological findings, radiology studies or clinical follow-up. **Results.** Recurrences were diagnosed in 37 patients, the prevalence being 77.1%. Liver metastases were found in 18 patients, abdominal, pelvic and/or mediastinal lymph nodes were positive in 19 patients, 11 patients had loco regional recurrences and 4 patients had pulmonary metastasis, and bone metastases were found in one patient. One patient was diagnosed with metastasis in scar tissue. The overall sensitivity and specificity of positron emission tomography–computed tomography was 90.24% and 71.42%, respectively. The positive and negative predictive values were 94.87% and 55.56%, respectively. **Conclusion.** ^{18}F- fluorodeoxyglucose positron emission tomography–computed tomography is a powerful tool that could be used in determining colorectal cancer recurrence in patients with elevated carcinoembryonic antigen levels and could have an important clinical impact on the management in patients with suspected recurrent colorectal cancer.

Key words: Colorectal Neoplasms; Carcinoembrionic Antigen; Recurrence; Early Diagnosis; Fluorodeoxyglucose F18; Positron Emission Tomography; Tomography, X-Ray Computed; Sensitivity and Specificity; Predicitive Value of Tests

Sažetak

Uvod. Rano otkrivanje recidiva je važan činilac za dugoročno preživljavanje bolesnika sa kolorektalnim karcinomom. Merenje serumske koncentracije karcinoembrionskog antigena uobičajeno se koristi u postoperativnom praćenju ovih pacijenata. Cilj istraživanja bio je proceniti sposobnosti pozitron emisione tomografije/kompjuterizovane tomografije za otkrivanje patološkog supstrata povišenog karcinoembrionskog antigena kod bolesnika sa kolorektalnim karcinomom. **Materijal i metode.** Bolesnici sa kolorektalnim karcinomom koji su bili podvrgnuti kurativnoj hirurškoj resekciji kao i eventualnoj hemioterapiji su retroaktivno pretraživani u našoj bazi podataka. Ukupno je evaluirano 48 pozitron emisionih tomografija/kompjuterizovanih tomografija F^{18} fluorodezoksi glukozom studija načinjenih u periodu između januara 2011. i januara 2014. godine 45 bolesnika (14 žena, 31 muškarac, prosečne starosti: 62,93 godine) s povišenim koncentracijama karcinoembrionskog antigena. Merenje serumskih koncentracija karcinoembrionskog antigena sprovedeno je unutar 3 meseca od pozitron emisione tomografije/kompjuterizovane tomografije. Konačna dijagnoza recidiva je potvrđena na osnovu histopatološkog nalaza, radioloških studija ili kliničkog praćenja. **Rezultati.** Recidiv bolesti registrovan je kod 37 bolesnika (prevalencija 77,1%). Hepatične metastaze pronađene su kod 18 pacijenata, limfni čvorovi abdomena, karlicei/ili medijastinuma bili su pozitivni kod 19 pacijenata, lokoregionalni recidivi pronađeni su kod 11 pacijenata, plućne metastaze kod 4 pacijenta, a dok su koštane metastaze pronađene kod samo jednog pacijenta. Takođe kod jednog pacijenta metastaza je registrovana unutar postoperativnog ožiljka kože. Sveukupna osjetljivost, specifičnost pozitron emisione tomografije/kompjuterizovane tomografije je 90,24% i 71,42%, respektivno. Pozitivne i negativne prediktivne vrednosti bile su 94,87% i 55,56% respektivno. **Zaključak.** Pozitron emisiona tomografija/kompjuterizovana tomografija ^{18}F-fluorodezoksi glukozom je moćan "alat" koji bi se mogao koristiti u određivanju recidiva kolorektalnog karcinoma kod bolesnika sa povišenim koncentracijama karcinoembrionskog antigena i takođe bi mogao imati važan uticaj na klinički tretman pacijenata sa suspektnim recidivom ove bolesti.

Ključne reči: Kolorektalne neoplazme; Karcinoembrionički antigen; Rekurencija; Rana dijagnoza; Fluorodeoksiglukoza F18; PET; CT; Senzitivnost i specifičnost; Prediktivna vrednost testova

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Abbreviations

CEA – serum carcinoembryonic antigen
PET/CT – positron emission tomography–computed tomography
CRC – colorectal cancer recurrence
FDG – fluorodeoxyglucose
SUV – standardizen uptake values

Introduction

Colorectal carcinoma account for 13% of all malignancies in the United States and the Western Europe and in 2008 it was the third most common cancer in men and women. It is the third leading cause of cancer-related deaths in the United States. The 5-year survival rate is about 66% [1]. Advances in treatment strategies include laparoscopic colon resection and the local excision of small tumors, followed by radiation and chemotherapy. However, approximately 40% of patients who undergo first curative surgery for colorectal carcinoma present with suspected recurrence at the first year follow-up [2].

Serum carcinoembryonic antigen (CEA) is a well established method for the detection of local tumor recurrence and metastases in the postoperative surveillance of colorectal carcinoma patients [3–8]. Circulating CEA levels provide a very sensitive measure of recurrence. In addition, preoperative serum levels of CEA correlate more or less with tumor stage and prognosis [9].

During the postoperative follow-up, computed tomography (CT) has been shown to be insufficiently accurate for early detection of local recurrence of colorectal carcinoma. Selzner et al. reported 53% sensitivity for CT [10].

18F-fluorodeoxyglucose positron emission tomography (FDG PET) is an advanced imaging technique. It allows the whole body search for malignant foci, which are detected by their increased glucose uptake. Successful FDG PET scanning has been performed in a wide variety of cancers. Several studies have demonstrated the value of FDG PET in terms of detecting recurrent colorectal cancer [11–13].

The purpose of this study was to evaluate the ability of PET/CT to detect pathological substrate of elevated CEA in patients with recurrent colorectal cancer.

Material and Methods

The FDG PET/CT images of patients with treated colorectal cancer and elevated CEA levels, scanned between January 2011 and January 2014, were retrospectively reviewed. All patients had been previously treated by surgical resection, irradiation and/or chemotherapy. Measurements of serum levels of CEA were performed within 3 months after PET/CT examination. No medical interventions were performed between CEA measurements and PET/CT examination. Fifty-one ^{18}F-FDG PET/CT studies of 45 patients (14 women, 31 men) with elevated CEA levels were evaluated. The mean age of patients who underwent imaging was 62.93 years (ranging from 36 to 79 years).

Figure 1. Lesion sites in PET/CT
Slika 1. *Lokalizacija lezije na PET/CT-u*

The presence or absence of recurrent disease was confirmed histopathologically or by clinical follow-up for at least 6 months.

The patients were imaged using a whole-body PET/CT scanner (Biograph True64, Siemens Medical Solutions). PET images were obtained 60-90 min after intravenous injection of 3.7 MBq/kg (0.1 mCi/kg) of ^{18}F-FDG. Minimal fasting period before injection was 6 hours. The plasma-glucose level at the time of FDG injection was measured in all patients. The patients rested during the 60-90 minute of uptake period. During the uptake phase the patients were asked to drink 1 L of oral contrast dispersion. CT scan was performed for topographic localization and attenuation correction, with 40 mAs and 120 kV, and 5 mm slice thickness. This was followed with PET scanning, with the time of emission data acquisition of 3min/bed position in 3-dimensional mode. Scans were performed from the skull base to the middle part of the thighs. Attenuation-corrected images were reconstructed in axial, coronal and sagittal projection, and maximum intensity projection (MIP) images were obtained.

PET/CT images were interpreted by at least two experienced nuclear physicians. In some cases radiologists were consulted. The standardized uptake values (SUV) were calculated automatically by software in the selected regions of attenuation corrected images. The positive FDG PET findings were defined as focal accumulation of FDG with SUV value over 2.5. A physiologically increased uptake was excluded. The analyses were based on the comparisons between FDG PET/CT findings and histopathology findings (n = 18) or radiological and clinical follow-up for at least 6 months after PET/CT (n = 27) according to the following criteria:

True positive - PET/CT positive lesion that increased during follow-up period in association with CEA elevation.

False positive - PET/CT positive lesion that decreased or remained unchanged during the follow-up period without treatment.

True negative – negative PET/CT and no recurrence on follow-up radiological and clinical findings.

False negative - no abnormal findings on PET/CT, but with recurrence identified by follow up in radiological and clinical findings.

Table 1. Patients, CEA levels and lesion sites
Tabela 1. *Pacijenti, nivo karcinoembrionskog antigena (CEA) i mesto lezije*

Scan number *Broj studije*	Patient's Age *Godište pacijenta*	Gender *Pol*	CEA *CEA*	Lesion sites in PET *Mesto lezije na PET/CT-u*	PET findings *PET nalaz*	Confirmed by *Potvrđen putem*
1	57	f	5, 4	Liver/*Jetra*	TP	Histology/*Histološki*
2	63	m	22,2	Abdominal lymph nodes/*Abdominalni limfni čvorovi*	TP	Follow-up/*Praćenjem*
3	58	m	8,65	Lung/*Pluća*	TP	Histology/*Histološki*
4	75	m	11,9	Abdominal lymph nodes/*Abdominalni limfni čvorovi*	TP	Follow-up/*Praćenjem*
5	60	m	4,7	Liver/*Jetra*	TP	Histology/*Histološki*
6	63	f	937	Liver/*Jetra*	TP	Follow-up/*Praćenjem*
7	61	m	15,2	Negative/*Negativan*	TN	Follow-up/*Praćenjem*
8	66	m	9,6	Abdominal lymph nodes/*Abdominalni limfni čvorovi*	TP	Histology/*Histološki*
9	67	f	58.5	Mediastinal lymph nodes and lung *Medijastinalni limfni čvorovi i pluća*	TP	Follow-up/*Praćenjem*
10	61	m	6,4	Negative/*Negativan*	TN	Follow-up/*Praćenjem*
11	65	m	476	Mediastinal lymph nodes and liver *Medijastinalni limfni čvorovi i jetra*	TP	Follow-up/*Praćenjem*
12	70	f	12	Skin (in scar tissue)/*Koža (u ožiljnom tkivu)*	TP	Histology/*Histološki*
13	76	m	18,7	Liver, loco regional, pelvic lymph nodes *Jetra, lokoregionalno, karlični limfni čvorovi*	TP	Follow-up/*Praćenjem*
14	70	f	26,1	Negative/*Negativan*	FN	Follow-up - loco regional by MR/*Praćenjem*
15	65	m	212	Liver and abdominal lymph nodes *Jetra i abdominalni limfni čvorovi*	TP	Follow-up/*Praćenjem*
16	67	f	8, 2	Parotid gland/*Parotidna žlezda*	FP	Histology-granulomatosis *Histološki*
17	71	m	92.8	Liver and abdominal lymph nodes *Jetra i abdominalni limfni čvorovi*	TP	Follow-up/*Praćenjem*
18	66	m	6,4	Negative/*Negativan*	TN	Follow-up/*Praćenjem*
19	64	m	32,7	Liver/*Jetra*	TP	Histology/*Histološki*
20	58	f	5,3	Loco regional/*Lokoregionalno*	TP	Histology/*Histološki*
21	60	m	107,6	Loco regional/*Lokoregionalno*	TP	Follow-up/*Praćenjem*
22	52	m	↑	Loco regional, abdominal and mediastinal lymph nodes, bone/*Lokoregionalno, abdominalni i medijastinalni limfni čvorovi, kosti*	TP	Follow-up/*Praćenjem*
23	75	m	↑	Mediastinal, abdominal and pelvical lymph nodes/ *Medijastinalni, abdominalni i karlični limfni čvorovi*	TP	Follow-up/*Praćenjem*
24	73	m	10,9 (bio 62,7)	Liver, peritoneum, loco regional, abdominal and pelvical lymph nodes/*Jetra, peritoneum, lokoregionalno, abdominalni i karlični limfni čvorovi*	TP	Follow-up/*Praćenjem*
25	49	m	5	Liver/*Jetra*	TP	Histology/*Histološki*
26	69	m	29	Supraclavicular, mediastinal and abdominal lymph nodes/*Supraklavikularni, medijastinalni i abdominalni limfni čvorovi*	TP	Follow-up/*Praćenjem*
27	66	m	10,8	Liver, mediastinal lymph nodes and loco regional/*Jetra, mediastinalni limfni čvorovi i lokoregionalno*	TP	Follow-up *Praćenjem*
28	57	f	9.1	Negative/*Negativan*	FN	Follow-up by CT lung metastasis/*Praćenjem CT plućne metastaze*
29	58	m	7,6	Negative/*Negativan*	TN	Follow-up/*Praćenjem*
30	55	m	8,4	Abdominal and pelvic lymph nodes *Abdominalni i karlični limfni čvorovi*	TP	Follow-up/*Praćenjem*
31	51	m	7,9	Liver/*Jetra*	TP	Histology/*Histološki*

32	74	m	↑	Amdominal lymph nodes, loco regional *Amdominalni limfni čvorovi, lokoregionalno*	TP	Follow-up/*Praćenjem*
33	66	m	↑	Negative/*Negativan*	TN	Follow-up/*Praćenjem*
34	75	m	9	Liver, abdominal lymph nodes *Jetra, abdominalni limfni čvorovi*	TP	Histology/*Histološki*
35	64	f	10.4	Negative/*Negativan*	FN	Follow-up, locoregional *Praćenjem, lokoregionalno*
36	61	f	67	Abdominal, pelvic lymph nodes, loco regional *Abdominalni, karlični limfni čvorovi, lokoregionalno*	TP	Follow-up/*Praćenjem*
37	73	m	40	Mediastinal lymph nodes/*Medijastinalni limfni čvorovi*	TP	Follow-up/*Praćenjem*
38	79	m	8,6	Liver and loco regional/*Jetra i lokoregionalno*	TP	Follow-up/*Praćenjem*
39	74	m	6,8	Liver/*Jetra*	TP	Follow-up/*Praćenjem*
40	54	m	↑	Loco regional/*Lokoregionalno*	TP	Histology/*Histološki*
41	58	f	↑	Loco regional/*Lokoregionalno*	FP	Follow-up/*praćenjem*
42	50	f	19,83	Lung/*Pluća*	TP	Histology/*Histološki*
43	60	f	233,5	Abdominal lymph nodes/*Abdominalni limfni čvorovi*	TP	Histology/*Histološki*
44	36	m	↑	Liver, lung/*Jetra, pluća*	TP	Histology/*Histološki*
45	68	m	↑	Liver/*Jetra*	TP	Histology/*Histološki*
46	51	m	18,46	Negative/*Negativan*	FN	Follow-up by MR and histology loco regional *Praćenjem MR i histološki lokoregionalno*
47	52	f	320	Liver/*Jetra*	TP	Follow-up/*Praćenjem*
48	58	f	80	Lung/*Pluća*	TP	Follow-up/*Praćenjem*

The patients with multiple lesions were defined as being true positive when at least one lesion was proved to be positive. The patient with a combination of false positive and false negative was defined as false negative according to a previous study [14].

Results

Forty-eight FDG-PET scans were performed in 45 patients **(Table 1)**. The scans were repeated in 3 patients at least a year after the initial scan. A lesion was defined as a site of suspected recurrence when identified by FDG-PET. The total number of lesions in 48 patients was 69 **(Figure 1)**. Liver metastases were found in 18 patients; abdominal, pelvic and/or mediastinal lymph nodes were positive in 19 patients, loco regional recurrences were found in 11 patients, 4 patients had pulmonary metastasis, and bone metastases were found in one patient. One patient was diagnosed with metastases in scar tissue **(Figures 2 and 3)**. Of 69 lesions, 67 were malignant and 2 were benign. We analyzed the sensitivity and specificity of FDG-PET. The overall sensitivity and specificity of FDG-PET were 90.24% and 71.42%, respectively.

Two false-positive lesions and four false-negative lesions were detected by FDG-PET. Three of four false-negative lesions were loco regional recurrences masked by a bowl activity or interpreted as a postoperative inflammation. One false-negative lesion was a solitary lung nodule too small for metabolic evaluation. One false positive lesion was a normal bowl activity interpreted as a loco regional recurrent disease, and the other one was an increased activity due to granulomatous lymphadenitis.

The positive and negative predictive values were 94.87% and 55.56%, respectively.

Discussion

The results hereby presented show that FDG PET/CT could diagnose a recurrent colorectal cancer recurrence (CRC) disease with high precision. However, false negative and false positive results can be obtained. The false positive results were obtained in 2 out of 48 cases (4.17%). These can arise due to physiological, infective or inflammatory processes regardless of serum CEA concentrations. Among the false-positive results, serum CEA values remained unchanged after PET/CT.

The false negative results were obtained in 4 out of 48 cases (8.33%). In all false negative findings, the serum CEA concentration continued to increase after PET/CT. In one case of false-negative results, PET/CT scan was repeated after 4 months and the recurrence was detected. In other three cases of false-negative results, the recurrences were detected during follow-up by other imagining modalities which were performed at least 3 months after the initial PET/CT scans, therefore we could not be sure if PET/CT scans would be negative at the moment of recurrence detection. An increase in CEA during follow-up might be an important indicator of recurrent disease even when FDG PET/CT findings are negative and repeated PET/CT scans should be considered.

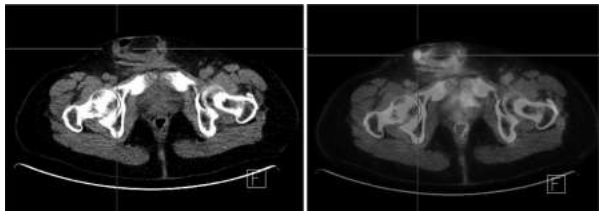

Figure 2. Recurrence in scar tissue of abdominal wall
Slika 2. *Rekurentna bolest u ožiljnom tkivu prednjeg abdominalnog zida*

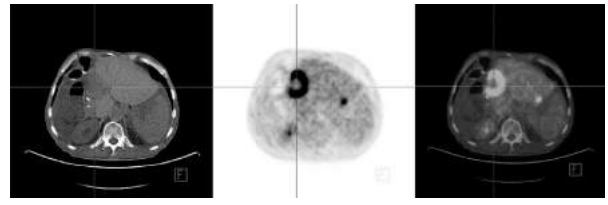

Figure 3. Two liver lesions, only the larger one was seen on CT
Slika 3. *Dve lezije unutar jetre, samo je veća viđena na kompjuterizovanoj tomografiji*

The results obtained in this study are similar to those from previous ones. In the study performed in 2010, Yukishige et al. reported that the sensitivity and specificity of PET/CT in patients with colorectal carcinoma and elevated CEA were 93% and 74%, respectively [14]. These results were very close to the sensitivity and specificity in our study, which were 90.24% and 71.42%, respectively. In the study done by Sarikaya et al., the performance of PET/CT was tested in the patients with suspected recurrence disease but with normal CEA levels, where the specificity and sensitivity were 81.4% and 66.6%, respectively [15], that being significantly lower and indicated that positive PET/CT in combination with elevated CEA could have higher probability for the presence of recurrent disease. However, in the study done by Tomoharu et al. the sensitivity of PET alone in a patient with recurrent colorectal carcinoma was 95% (16), which was slightly higher than 90.24% as reported in our study, even though not all patients included in the study done by Tomoharu et al. had elevated CEA level.

Whiteford et al. pointed out that the sensitivity of FDG-PET/CT imaging for detection of mucinous adenocarcinoma was significantly lower than in non-mucinous adenocarcinoma (58% and 92%, respectively), most likely due to the hypocellularity of these tumors [17]. Similar findings with sensitivity of 41% in mucinous adenocarcinoma have been reported by Capirci et al. [18]. Although this histological subtype of colorectal carcinoma is relatively rare, accounting for 6-20% of all colorectal carcinomas [19–21], it affects the overall sensitivity of PET/CT.

A difference in the sensitivity when evaluating different localizations of recurrent disease could also affect the overall PET/CT performance in colorectal carcinoma. Abdel-Nabi et al. evaluated the usefulness of FDG-PET for staging the patients with the known or suspected primary colorectal carcinomas. They found that FDG was poorly sensitive in detecting local lymph nodes involvement with the sensitivity of 29%, but much more efficient in detecting hepatic metastases, with the sensitivity and specificity of 88% and 100%, respectively [22].

Our study was retrospective with relatively small number of patients. A significant number of patients who had been scanned could not be included because of chemotherapy and/or radiotherapy applied between PET/CT and CEA measurement. Another group was excluded because of the long period between PET/CT and CEA measurement. Histopathological finding was not available for all detected lesions. This problem was in part overcome by clinical and radiological follow-up. CEA levels were measured in different laboratories at different moments, and they were elevated in all patients in comparison to reference values for each individual laboratory. The measurements were performed within three months before or after PET/CT scan.

Conclusion

Our results indicate that ^{18}F- fluorodeoxyglucose positron emission tomography–computed tomography could be a powerful diagnostic tool that could be used in the determination of colorectal cancer recurrence in the patients with elevated serum carcinoembryonic antigen levels and could have an important clinical impact on the management of the patients with suspected recurrent colorectal cancer.

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Rad je primljen 30. XII 2014.
Recenziran 29. VI 2015.
Prihvaćen za štampu 6. VII 2015.
BIBLID.0025-8105:(2015):LXVIII:11-12:376-381.

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Original study
Originalni naučni rad
UDK 616-053.9-083 i 613.98:616-057.875
DOI: 10.2298/MPNS1512382M

KNOWLEDGE AND ATTITUDES OF HEALTH CARE SCIENCE STUDENTS TOWARD OLDER PEOPLE

ZNANJA I STAVOVI STUDENATA ZDRAVSTVENIH NAUKA PREMA STARIM OSOBAMA

Dragana MILUTINOVIĆ[1], Dragana SIMIN[1,2], Jelena KAČAVENDIĆ[1] and Vesna TURKULOV[1,3]

Summary

Introduction. Education of health science students in geriatrics is important in order to provide optimal care for the growing number of elderly people because it is the attitudes of health professionals toward the elderly that play the key role in the quality of care provided. Therefore, the aim of this study was to assess the knowledge and attitudes of health care science students towards ageing and care for the elderly. **Material and Methods.** The present cross-sectional study was carried out on a sample of 130 students (medical, nursing and special education and rehabilitation) of the Faculty of Medicine, University of Novi Sad. The students were divided into two groups. The first group (E) included students having been taught geriatrics and nursing older adults and the other group (C) included students who had not been trained in this subject. The authors used Palmore's facts on Ageing Quiz for the knowledge evaluation and Kogan's Attitude toward Older People Scale for the attitude evaluation. **Results.** The results of Facts on Aging Quiz showed the average level of students' knowledge and statistically significant difference between E and C group. The analysis of Kogan's Attitudes toward Old People Scale showed that both groups had neutral attitudes toward older people. Furthermore, a positive correlation between students' knowledge and attitudes was found. **Conclusion.** There is increasing evidence on the correlation between education, knowledge and attitudes toward older people which suggests that by acquiring better insights into all aspects of ageing through their education the students develop more positive attitudes and interest in working with older adults.

Key words: Health Knowledge, Attitudes, Practice; Students, Nursing; Aged; Aged, 80 and over; Nursing Care; Geriatric Nursing; Quality of Health Care; Ageism; Questionnaires

Sažetak

Uvod. Obrazovanje studenata zdravstvenih nauka iz gerijatrije je važno za pružanje optimalne zdravstvene zaštite rastućoj populaciji starih jer upravo stavovi zdravstvenih radnika prema starima imaju ključnu ulogu u kvalitetu nege koja se pruža. Stoga je cilj ove studije bio da proceni znanja i stavove studenata zdravstvenih nauka prema starenju i brizi o starima. **Materijal i metode.** Istraživanje je sprovedeno u obliku studije preseka na uzorku od 130 studenata medicine, zdravstvene nege i specijalne edukacije i rehabilitacije Medicinskog fakulteta Univerziteta u Novom Sadu podeljenih u dve grupe. U prvoj grupi (E) bili su studenti - njih 61, koji je su imali edukaciju iz Gerijatrije i nege starih lica, dok je drugu grupu (K) činilo 69 studenata koji nisu imali edukaciju. Za procenu znanja studenata koristio se kviz Činjenice o starenju (*Facts on Aging Quiz*), a za procenu stavova Koganova skala stavova o starenju (*Kogan's Attitude toward Older People Scale*). **Rezultati.** Rezultat kviza Činjenica o starenju pokazao je statistički značajnu razliku između E i K-grupe ($t = -2{,}407$ $df = 128$ $p<0{,}01$). Studenti obe grupe su najviše znanja pokazali u oblasti fizičkog zdravlja. Najmanje znanja u oblasti socijalnog položaja starih pokazali su studenti E-grupe, dok su studenti iz K-grupe imali najniže znanje u oblasti mentalnog zdravlja starih. Analiza Koganove skale pokazala je da studenti obe grupe imaju neutralne stavove prema starima. Utvrđeno je i da između znanja i stavova studenta postoji pozitivna korelacija. **Zakjučak.** Dokaza o povezanosti obrazovanja, znanja i stavova prema starima sve je više, što ukazuje na to da ako studenti imaju bolje obrazovanje o svim aspektima starenja, njihovi stavovi će biti pozitivniji, a interesovanje za rad sa starima veće.

Ključne reči: Znanje o zdravlju, stavovi i praksa; Studenti zdravstvene nege; Stari ljudi; Stari ljudi, 80 i više godina; Zdravstvena nega; Nega u gerijatriji; Kvalitet zdravstvene nege; Predrasude o starim osobama; Upitnici

Introduction

Current demographic changes and global population ageing signify that greater attention should be paid to nursing older adults [1].

By 2030, the proportion of the population aged ≥65 years is projected to increase to approximately 28% in Western Europe and to 21% in the United States [2], whereas the percentage of persons over 65 in the Republic of Serbia will be at least 22%. In addition, Serbia is among the countries with the oldest population in the world with the median age of 41.6 [3]. Thus, the projected increase in the number of people aged 65 and older will result in a larger number of persons with chronic non-communicable diseases, functional dependency, and higher rates of multimorbidity [4–6].

In addition to having health problems, older people are also increasingly exposed to ageism, which is defined as "the process of systematic stereotyping and discrimination against people because they are

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Abbreviations
FAQ – Facts of Aging Quiz

old" [7]. Ageism reinforces the view of older people as unproductive, depressed, ill or even ugly and poor, and creates the perception that cognitive limitations and sexual inactivity are a natural consequence of the ageing process [8]. Unfortunately, health professionals are among those who are also susceptible to this type of stereotyping because of more frequent contact with older and disabled persons [9].

Given the projected increase in older population who will need care, it is clear that most nurses and other health professionals will predominantly care for them, regardless of their attitudes. Therefore, there is a strong need for education and fostering positive attitudes of future health professionals toward elderly persons and the ageing process [1]. Attitudes of the future health care providers toward the older people can affect behavior and care given, and have a direct impact on the quality of diagnosis, treatment and care provided to the older people [10].

Consequently, various studies have been conducted over the last two decades in order to evaluate attitudes among health care science students, especially among medical and nursing students, toward older people. However, these studies produced conflicting results: while some studies showed negative attitudes of students [11, 12], others demonstrated that students' attitudes toward older people were positive [13 17]. Hence, recent research among health care science students has confirmed an increase in positive perceptions regarding the ability of the elderly, the aging process, as well as toward older people in general. This progress in attitudes has been the result of a number of changes in education since major universities and colleges that educate health professionals have included geriatric specific education in the compulsory and optional subjects [18].

This research has also examined factors that may affect students' attitudes including: gender, age, place of residence, economic status of the family and family type, having a family member aged ≥ 65, or living with a person aged ≥ 65 and the year of study. However, none of them was singled out as the dominant predictor of positive attitudes. Such inconsistent results highlight the need to use qualitative research design for more sophisticated analysis of variables. Although only a small number of studies have investigated this issue, students' interest in working with older people and knowledge of the elderly have been identified as the factors significantly related to students' positive attitudes [1, 15, 17, 19, 20]. These results indicate that students, who received training in the care of elderly patients and appropriate clinical practices during their formal education, have become interested in the problems that develop during older age, and showed more interest in further study of ageing and working with older people, thus significantly improving positive attitudes [1, 14, 21].

Therefore, the aim of the present study was to assess knowledge and attitudes of health care science students toward ageing and nursing older people.

Material and Methods

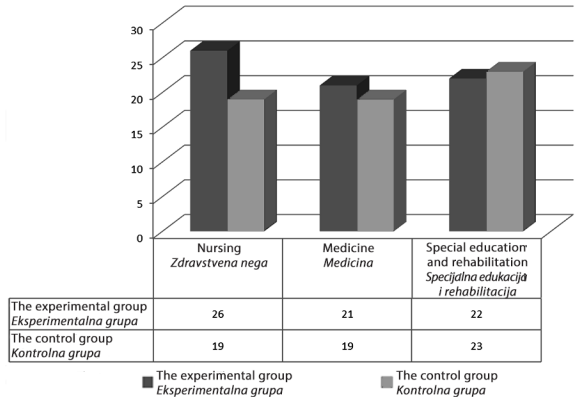
The present cross-sectional study was carried out on the sample of 130 medical, nursing and special education and rehabilitation students of the Faculty of Medicine, University of Novi Sad. The students were divided into two groups. The first group (E) consisted of 61 students with training in geriatric medicine and nursing older adults, while the other group (C) consisted of 69 students who had no training in these subjects. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Novi Sad.

Palmore's Facts on Aging Quiz (FAQ) and Kogan's Attitudes toward Old People Scale were used to measure factual knowledge and to evaluate attitudes toward older people, respectively.

The Facts on Aging Quiz was originally compiled by Erdman Palmore (1977) to help people, particularly students, confront their prejudices about older people. Approximately half of the items were retained from Palmore's original test (in total 50). The other half of the items represented issues that later became the focus of attention or considered relevant by the authors. The items of this questionnaire can be conditionally divided into the following four categories: the facts about physical health, the facts about mental health, the facts about social position of the elderly and the facts related to most common misconceptions about ageing. Knowledge is defined on the following three levels: low (0-17 points), average (18-35 points) and high (36-50 points) level of knowledge. According to previous research, the reliability of Cronbach's alpha value was limited from 0.45 to 0.70 due to „true/false" version [1, 22]. The Serbian version of the FAQ was also found to possess low reliability with (α) = 0.41.

Kogan's Attitude toward Older People Scale consists of one set of 17 statements expressing positive statements and one set of 17 negative statements. The quantitative measure of attitudes was obtained using six-point Likert scale. In order not to diminish the positive attitudes by the negative ones, the specific values were assigned to all the statements, so the possible score ranged from 34 to 204. The attitudes ranging from 34 to 101 represent the negative attitudes, whereas the neutral and the positive attitudes ranged from 102 to 136 and from 137 to 204, respectively. According to previous research regarding reliability, Cronbach's alpha values for this test ranged from 0.70 to 0.81 [23]. The Serbian version also had adequate reliability with (α) = 0.76 for the total scale.

The Statistical Package for the Social Sciences for Windows, version 19.00 was used for descriptive and inferential analysis (SPSS, Inc., Chicago, IL, USA). The following methods of descriptive statistics were used in this study: measures of central tendency (arithmetic mean) and variability measures (standard deviation) for numerical characteristics and frequency determination (proportion) for attribute characteristics. The authors used independent-samples t-test as a method of inferential statistics for numerical parameters, and Pearson's



Graph 1. Distribution of the experimental (E) and control (C) group respondents
Grafikon 1. *Distribucija ispitanika eksperimentalne (E) i kontrolne (K) grupe*

correlation coefficient to assess the relation between knowledge and attitudes of students. P-values of < 0.05 were taken as statistically significant.

Results

Of 180 students who were eligible to participate in the study, 130 (71.2%) completed the questionnaire. Of the total number of students (N = 130), 61 (46.9%) were included in the experimental group, while 69 (53.1%) were in the control group. Each group consisted of nursing students (second and fourth year of study), medicine (fourth and sixth year of study) and special education and rehabilitation (third and fourth year of study) **(Graph 1).**

Analysis of Students' Knowledge about Ageing

The FAQ total average score for experimental group was M = 30.52, SD = 3.61, which indicated the average level of students' knowledge, where the students of nursing had the lowest total average score M = 29.53, SD= 3.87, and the medical students had the highest score M = 31.11, SD = 3.68. Further descriptive analysis of FAQ for the experimental group revealed that the students showed the highest level of knowledge in the most common misconceptions about ageing M = 10.13, SD = 2.41, followed by physical health M = 7.49, SD = 1.18, while the lowest level of knowledge was related with the social position of older people M = 6.25, SD = 1.46 **(Table 1).**

The control group students also showed the average level of knowledge M = 29.07, SD = 3.26 with the highest level of knowledge also related with the most common misconceptions about aging M = 9.33, SD = 1.73, followed by physical health M = 7.84, SD = 1.30, while the lowest level of knowledge was about mental health M = 5.61, SD = 1.60 **(Table 2)**. In the control group, the students of nursing had the lowest total average score of M = 27.96, SD = 3.26, but this time the students of special education and rehabilitation had the highest score of M = 30.14, SD = 3.14.

The total average score on the FAQ showed a statistically significant difference between the control and experimental group (t = -2.407; df = 128; p < 0.01). The students in the control group with no training in geriatrics and nursing older adults showed less knowledge in the test than the students of the experimental group who underwent training in geriatrics and nursing older adults.

The Analysis of Students' Attitudes toward Older People

The students from both groups, that is the experimental and the control one, had the neutral attitude toward older people M=123; SD=15.61 and M = 119.25, SD = 14.82, respectively.

Attitudes toward older people among the students from the control and experimental groups were significantly different (t = -1.602; df = 128; p

Table 1. Descriptive analysis of responses of experimental group students (E) to Palmore's Facts on Ageing Quiz
Tabela 1. *Deskriptivna analiza odgovora studenata eksperimentalne grupe (E) na Palmorovom kvizu činjenica o starenju FAQ*

Questions/*Pitanja*	Mean/*AS*	SD/*SD*
Facts on mental health/*Činjenice o mentalnom zdravlju*	6.66	1.25
Facts on physical health/*Činjenice o fizičkom zdravlju*	7.49	1.18
Facts on the social position/*Činjenice u vezi sa socijalnim položajem*	6.25	1.46
The most common misconceptions about ageing/*Najčešće zablude u vezi sa starenjem*	10.13	2.41
The total score on the FAQ/*Ukupan skor za FAQ*	30.52	3.61

Table 2. Descriptive analysis of the responses of the control group students (C) to Palmore's Facts on Ageing Quiz
Tabela 2. *Deskriptivna analiza odgovora studenata kontrolne grupe (K) na Palmorovom kvizu činjenica o starenju FAQ*

Questions/*Pitanja*	Mean/*AS*	SD/*SD*
Facts on mental health/*Činjenice o mentalnom zdravlju*	5.61	1.60
Facts on physical health/*Činjenice o fizičkom zdravlju*	7.84	1.30
Facts on the social position/*Činjenice u vezi sa socijalnim položajem*	6.29	1.34
The most common misconceptions about ageing/*Najčešće zablude u vezi sa starenjem*	9.33	1.73
The total score on the FAQ/Ukupan skor za FAQ	29.07	3.26

Table 3. Correlation between the students' knowledge and attitudes toward ageing (the control (C) and the experimental (E) group)
Tabela 3. *Povezanost znanja i stavova studenata o starenju (kontrolna (K) i eksperimentalna* (E) *grupa)*

Group/*Grupa*		N	r	p
The experimental group *Eksperimentalna grupa*	Nursing (4th year)/*Zdravstvena nega (4. godina*)	19	0.590**	0.008
	Medicine (6th year)/*Medicina (6. godina)*	19	0.649**	0.003
	Special education and rehabilitation (4th year) *Specijalna edukacija i rehabilitacija (4. godina)*	23	0.532**	0.009
	The whole (E) group/*Ukupno (E) grupa*	6	0.563**	0.000
The control group *Kontrolna grupa*	Nursing (2nd year)/*Zdravstvena nega (2. godina)*	26	0.420*	0.033
	Medicine (4th year)/*Medicina (4. godina)*	21	-0.028	0.905
	Special education and rehabilitation (3 rd year) *Specijalna edukacija i rehabilitacija (3. godina)*	22	0.274	0.217
	The whole (C) group/*Ukupno (K) grupa*	69	0.334**	0.005

* Correlations significant at the 0.05 level
* *Značajna povezanost na nivou 0,05*
**Correlations significant at the 0,01 level
** *Značajna povezanost na nivou 0,01 level*

< 0.01). The students from the experimental group scored closer to moderately positive attitudes compared with the students from the control group.

Correlation between Students' Knowledge and Attitudes toward Ageing

Pearson's correlation coefficient was used to measure the correlation between the students' knowledge and attitudes toward the care for older people. The results showed a statistically significant positive correlation (r = 0.563; N = 61, p = 0.000 for the experimental group and r = 0334; N = 69, p = 0.005 for the control group). The analysis was performed for each profile separately. The test results are shown in the **Table 3.**

A weak negative correlation was observed between knowledge and attitudes of medical students in the control group, but this correlation was not significant.

Discussion

Ageing population is one of the most complex issues in the modern society and its impact on health and social care services creates a greater demand for the services of all health care professions, particularly nurses. Due to these current demographic changes, a growing number of studies have recently examined students' attitudes and knowledge in almost all countries.

This study was perhaps the first of its kind in this country and the region which focused on determining knowledge and attitudes of health science students (with and without training in geriatric and nursing older adults) toward ageing and care for older people. Sampling included a sufficient number of responses for the appropriate data analysis and the metric properties of the questionnaire were acceptable.

In both groups, the average scores of FAQ (60% of correctness) correlated with the average scores of students in the study on the FAQ conducted in China [22], but they were higher than those revealed in other studies [1, 15]. Since the lowest level of knowledge in our study was demonstrated by the nursing students, it is important to evaluate and improve the program of nursing study because nurses play a distinct role in ensuring quality care for older people. Namely, the significant role of nurses in providing care to older adults is widely recognized, nurses are responsible not only for providing direct physical care, but also emotional support to older people in a variety of settings, such as hospitals, respite care units, as well as in care recipient's home [20]. For this reason, the nursing students who completed a course on the care of older people at university should get 80% of the questions right.

The results of the present study have shown that students have positive attitudes toward older people after attending lectures on geriatrics, which correlates with the results obtained by Baumbusch et al. [18]. Unlike students from the Netherlands who had neutral to slightly positive attitudes although they had not been given lectures on geriatrics (M = 130.6, SD = 9), the students from the control group attending the Faculty of Medicine in Novi Sad had neutral to slightly negative attitudes toward older people [1]. In this study, it was found that the medical students had more positive attitudes than the nursing students. The same results were obtained in the study performed by Ayoğlu et al [17]. However, other previous studies evaluating attitudes of medical and nursing students toward older people have reported conflicting results. In the study conducted in Taiwan during 2009, the nursing students showed more positive attitudes [24], while in the study conducted among Malawian students, there was no difference between the students' attitudes [25].

Furthermore, there is increasing evidence for the correlation between education, namely knowledge and attitudes toward older people. Numerous authors such as Lambrinou et al. [15] and others believe that students with a higher level of knowledge have more positive attitudes.

Finally, a strong correlation between the students' knowledge and attitudes was found among all the students who participated in the study. The results indicated more positive attitudes of students with better education in all aspects of ageing, and an increase

in their interest in working with older adults. Thus, these results can be used to guide changes and modifications to study programs in order to improve students' knowledge, promote positive attitudes and dispel misconceptions about ageing and older adults through practical experience.

Caring of the elderly will become increasingly important for all health professionals, especially nurses. Therefore, educating and training future health professionals for working with older people should be considered significant and necessary. The present study did not include demographic data (gender, age), the previous contacts with the elderly, or the experience in working with them, which can be considered limitations of this study.

Conclusion

There is increasing evidence on the correlation between education, knowledge and attitudes toward older people which suggests that by acquiring better insights into all aspects of ageing through their education the students develop more positive attitudes and interest in working with older adults.

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Rad je primljen 3. VI 2015.
Recenziran 19. VI 2015.
Prihvaćen za štampu 9. VII 2015.
BIBLID.0025-8105:(2015):LXVIII:11-12:382-386.

REVIEW ARTICLES
PREGLEDNI ČLANCI

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Review article
Pregledni rad
UDK 616.314-002-084:613.2]-055.26
DOI: 10.2298/MPNS1512387J

THE ROLE OF NUTRITION IN CARIES PREVENTION AND MAINTENANCE OF ORAL HEALTH DURING PREGNANCY

ULOGA ISHRANE U PREVENCIJI KARIJESA I OČUVANJU ORALNOG ZDRAVLJA U TRUDNOĆI

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Summary

Introduction. Pregnancy may pose an increased risk for the development of caries and other oral health problems. Continuous screening of oral health status, implementing appropriate preventive measures (particularly oral hygiene, healthy diet plans and education) is of paramount importance not only for oral health but also for the general health status of the future mother and her offspring. **Effects of Food on Caries Development.** Caries prevention through healthy diet implicates the reduction in frequency and amount of intake of cariogenic food, above all of refined carbohydrates, i.e. sugars and sweets. Foods known to have caries-prophylactic effects should predominate in healthy diet plans. They mainly include solid foods, which have mechanical effects on teeth cleaning, as well as foods providing sufficient amounts of vitamins (A, C, D) and a variety of elements and compounds (calcium, phosphates, fluorides) favoring the preservation and remineralization of tooth structures. **Education of Pregnant Women on Healhy Deit.** In accomplishing these goals, education and direct positive communication between the educator and the pregnant woman play a crucial role. Educative approach is always individual and determined by the patient's specific cultural and socioeconomic features and status, as well as her habits, motivation and willingness to accept relevant recommendations. Accomplishing the aforementioned goals requires the appropriate organization and professional competence within the preventive dental service and its close cooperation with the relevant medical institutions and social support in the framework of public health protection. **Conclusion.** Preserving of oral health during pregnancy is predominantly influenced by the following factors: 1) healthy diet, 2) oral hygiene, 3) patients' education, 4) regular control of oral health, 5) appropriate organization of dental services and 6) community engagement.

Keywords: Dental Caries; Preventive Dentistry; Oral Health; Pregnancy; Mass Screening; Diet; Nutrition Policy; Public Health, Dentistry; Tooth Remineralization; Oral Hygiene; Diet, Cariogenic; Food Habits; Health Education, Dental

Sažetak

Uvod. Tokom trudnoće rizik za nastanak karijesa zuba i drugih poremećaja oralnog zdravlja je povećan. Redovni skrining stanja oralnog zdravlja, sprovođenje odgovarajućih preventivnih mera (prvenstveno oralne higijene, zdrave ishrane i edukacije) veoma su značajni ne samo za oralno zdravlje nego i za opšte zdravstveno stanje buduće majke i njenog potomstva. **Uticaj hrane na razvoj karijesa.** U prevenciji karijesa zdravim načinom ishrane treba redukovati učestalost i količinu unosa kariogene hrane, prvenstveno rafinisanih ugljenih hidrata, odnosno šećera i slatkiša. U zdravoj ishrani prednost ima hrana sa profilaktičkim dejstvom na karijes. Ovde spada čvršća hrana, koja ima mehanički efekat u odnosu na čišćenje zuba, kao i hrana koja obezbeđuje dovoljan unos vitamina (A, C, D) i određenih elemenata i jedinjenja (kalcijuma, fosfata, fluorida) koji pomažu u očuvanju i remineralizaciji građe zuba. **Edukacija trudnica o zdravoj ishrani.** U postizanju ovih ciljeva pomaže edukacija uz direktnu i pozitivnu komunikaciju između edukatora i trudnice. Edukativni pristup je individualan jer svaka trudnica ima specifična kulturološka i socioekonomska obeležja i status, uz različite navike, motivisanost i spremnost za prihvatanje datih preporuka. Za ostvarivanje pomenutih ciljeva potrebna je odgovarajuća organizacija i stručnost stomatološke preventivne službe i njena saradnja sa drugim medicinskim službama, uz društvenu podršku u okviru javnog zdravlja. **Zaključak**. U očuvanju oralnog zdravlja tokom trudnoće važne uloge imaju: 1. zdrav način ishrane, 2. oralna higijena, 3. edukacija trudnica, 4. redovne stomatološke kontrole, 5. organizacija stomatološke službe i 6. društveno angažovanje.

Ključne reči: Karijes; Preventivna stomatologija; Oralno zdravlje; Trudnoća; Skrining; Ishrana; Pravila ishrane; Javno zdravlje, stomatologija; Remineralizacija zuba; Oralna higijena; Kariogena ishrana; Navike u ishrani; Zdravstveno obrazovanje, stomatologija

Acknowledgments. This paper was supported by the grant No. TR31095 of the Ministry of Education, Science and Technological Development of the Republic of Serbia.

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Introduction

Pregnancy is associated with an increased risk for development of dental caries and other oral health problems [1–5]. Specific alterations of hormonal status in pregnant women such as the increase and change in progesterone and estrogen levels as the most prominent ones stimulate fluid retention in the body that may result in gingival swelling (edema). These changes are responsible for the increased sensitivity of the gums, hyperemia and tendency for bleeding, gingivitis, periodontitis, pyogenic granuloma, increased tooth mobility, plaque formation as well as substantial colonization of bacteria involved in caries pathogenesis [2, 4, 6–8].

Minozzi et al. [9] have identified the following major etiologic factors which play a role in caries development during pregnancy: 1) modified saliva composition (elevated acidity and mucin levels) that favors the formation of bacterial plaque; 2) changes in dietary habits (smaller but more frequent meals to prevent nausea, vomiting and hypoglycemia); 3) inadequate dietary intake of minerals, vitamins and other protective compounds; 4) erosive effects of gastric acid (frequent vomiting and regurgitation); 5) poor oral hygiene, and 6) inadequate dental surveillance and monitoring.

Dental caries is a change of multifactorial etiology defined as the demineralization of the inorganic portion and destruction of the organic structure of the tooth [10]. Demineralization of the enamel and dentin, which make a solid inorganic portion of the tooth, is caused by organic acids produced in dental plaque as a by-product of anaerobic sugar degradation by bacteria from the diet of the host. Besides the sugar and specific bacteria, the caries development is determined by bacterial species, tooth resistance, quality of the saliva and salivary secretion rate. The saliva contains substantial amounts of calcium and phosphates, and the pH range of pH7 (neutral) promotes the enamel remineralization process. However, the acid environment resulting from the elevated acidity of the saliva during pregnancy enhances the demineralization, which then predominates over remineralization process, thus stimulating the caries development [1, 2, 4, 6]. The tooth demineralization is attributed to organic acids, which increase the solubility of calcium hydroxyapatite in the dental hard tissues. Furthermore, the factors that may contribute to the development of caries during pregnancy include poor quality (composition) of food and inadequate dietary regimen as well as inadequate oral hygiene [1, 2, 6, 9, 11].

It is of vital importance to preserve and improve oral health in pregnancy not only because of the pregnant woman herself, but for the outcome of pregnancy, health and development of the newborn baby. In that respect, periodontitis in pregnant women can be associated with premature birth, low birth weight of the newborn [2, 9, 12–15] as well as preeclampsia [15, 16]. Furthermore, cariogenic bacteria (including *Streptococcus mutans*) from the oral cavity of the mother with caries can be transmitted to her baby's mouth, which is significantly related to the prevalence or incidence of caries in the child [1, 2, 9]. Adequate dental health protection in pregnant women is indispensable and it should encompass the implementation of preventive and therapeutic measures and regular check-ups during pregnancy, as well as the active involvement of pregnant woman in preserving and maintenance of her oral health. The aforementioned practices are of multiple benefits for both oral health of the woman and pregnancy outcome, prenatal health and reduced incidence of caries in her child [9, 17–20]. The active involvement of the pregnant woman and her close cooperation with the dentist, gynecologist and other specialists are of crucial importance for the accomplishment of these goals [3–5, 9]. The abovementioned measures and activities contribute to the improvement of health status among the general population. To reach the final positive outcome in this sphere, interdisciplinary health care practices and cooperation should be linked with identifying the role of the existing environmental risk factors and novel approaches and new aspects in dentistry, medicine, pharmacy and other fields related to public health [21–24].

The integrated prenatal health care and protection should encompass preventive measures and control of oral health of a pregnant woman; however, it is often neglected in everyday practice [2]. Solving of this problem is supported and improved by a range of relevant handbooks and guidelines offering recommendations on the preservation and improvement of oral health during pregnancy [3, 6, 7, 11, 19, 25].

Effects of Food on Caries Development in Pregnant Women

"Cariogenic" Food and its Impact

Some foods may increase the risk of caries formation during pregnancy, which should be taken into consideration when planning the diets for pregnant woman.

Easily digestible carbohydrates (mainly sugars) are considered potential factors that may provoke caries formation because acid by-products of their bacterial decomposition attack and damage the dental enamel and tooth structure. Monosaccharides, glucose, and disaccharides (including saccharose and lactose) are direct substrates in this process. Maltodextrin, broken down by salivary amylase into the aforementioned "aggressive" mono- and disaccharides, also plays a role in caries formation [1, 11]. Frequent and abundant intake of standard sugar (saccharose) and products containing substantial amounts of sugar and honey (sweets) are considered important risk factors in the caries development [6]. Other risk factors encompass prolonged keeping of carbohydrates in the mouth, especially when taking sticky candies that tend to adhere to the teeth. Some food of plant origin such as corn flakes and similar

processed cereals mostly used for breakfast demonstrate similar properties. Such products are rich in polysaccharides, thus easily decomposed by bacteria into acid compounds.

Restriction of concentrated carbohydrates in the diet has positive effects on not only oral health, but also on the prevention of overweight/obesity and diabetes and related health conditions and complications, which nowadays represent critical healthcare issues in both pregnant women and general populations [26–28].

Consuming abundant amounts of *foods containing organic acids*, such as fruit juice, yoghurt, fermented milk and cream may contribute to caries formation. Harmful effects of these foods manifest as direct demineralization of tooth surface and consequent erosion of dental enamel. Fruit juices have particularly high cariogenic potential as they contain both acids and carbohydrates (glucose, fructose, saccharose). To that end, fruit juices should not be consumed between meals. Taking fruit juices and beverages at mealtime (immediately before/after or during the meal) is recommendable because their cariogenic effects are less pronounced. Lemonade has the highest cariogenic potential of all fruit juices since it contains both sugar and citric acid. Due to their cariogenic nature, some dairy products (yoghurt, fermented milk, cream and sour milk cheese) are strongly recommended to be consumed during meals in order to reduce their own cariogenic effects [3–5].

The increased acidity in the mouth during pregnancy is commonly due to the presence of gastric acid produced by frequent vomiting at the initial stage of pregnancy and gastric reflux during the later pregnancy stages. Acute acid reflux into the mouth results from a decreased esophageal sphincter tone and movement of the acid contents of the stomach because of the increased abdominal pressure caused by the enlarged uterus [3–5, 7]. The presence of gastric acid in the mouth can provoke erosion of dental enamel; therefore, immediate rinsing of the mouth with water is highly recommendable. After vomiting, the acid neutralization can be accomplished by rinsing the mouth with sodium bicarbonate solution (1 teaspoon of baking soda in a glass of water) [3–5]. Some pregnant women avoid frequent tooth brushing because of nausea and vomiting tendency as well as because of vulnerable gums prone to bleeding and pain in contact with the toothbrush, which adds to the persistent acidity of the mouth and its negative effects [3–5]. Some pregnant women tend to take frequent smaller meals (because of nausea), yet without teeth brushing after the meal, thus promoting intensive bacterial activity and carbohydrate decomposition and consequent increase of mouth acidity [7].

Frequent Intake of Foods Contributing to Development of Caries

Besides consuming large amounts of sugar in one meal, frequent intake of sugar, i.e. carbohydrates throughout the day puts pregnant women at a substantial risk. The practice of taking sweet snacks between the main meals causes prolonged retention of carbohydrate in the mouth for a long period. Thus, besides the type and amount of dietary carbohydrates, one should take into consideration the frequency of their intake as well as the duration of retention of food in the mouth [6]. Some authors recommend to reduce the number of high-sugar meals to fewer than four, with a maximum sugar amount of less than 60 g/day [20]. Moynihan P and Petersen PE from the *WHO Collaborating Centre for Nutrition and Oral Health* recommend that the frequency of consumption of foods containing free sugars should be limited to a maximum of 4 times per day along with tooth brushing with fluoride toothpaste at least twice a day. These authors also encourage the production of sugar-free products and candies containing artificial sweeteners as an alternative to the products rich in concentrated and free sugars [29]. Such strategy may prevent both dental and other health problems, such as overweight, which is quite a common condition during pregnancy. Promoting healthy food and dietary habits needs to be appropriately addressed through adequate marketing strategies [26, 27].

Caries-Prophylactic Effects of Some Foods

Cariogenic food, i.e. food rich in carbohydrates and acids, should be avoided while encouraging caries-preventive diets in order to reduce the risk of caries development. Prophylactic effects on dental caries is best accomplished with diets providing sufficient amounts of vitamins, minerals and specific elements and compounds such as vitamins A, C, D, calcium, phosphate and fluoride. Furthermore, some foods exert a positive mechanical cleansing action on teeth, thus representing a potential protective factor in caries prevention [6].

Indispensable vitamins are primarily provided by the adequate intake of fruits and vegetables and related foods. Fresh fruits and some vegetables (though to a somewhat lesser extent) contain carbohydrates that may undergo bacterial fermentation and convert to acidic products; however, high water contents in such foods dilute the concentration and effects of carbohydrates while their fiber contents helps mechanical teeth cleaning thus reducing the risk of caries development.

Vitamin A plays an important role in the development of healthy bones and teeth and in the regeneration of mucosa, skin and other tissues as well. Major natural sources of vitamin A are orange-colored foods, melon, peach and some vegetables such as carrot, courgette, savoy cabbage (kale), spinach and red peppers. Milk and dairy products and eggs are also a good source of vitamin A [6].

Vitamin C offers a range of health benefits. Besides its role in collagen synthesis, vitamin C prevents gum bleeding, promotes iron and calcium resorption and has a powerful antioxidative potential. High vitamin C foods include rose hip, red currant, bilberry, lemon, orange, tangerine, grapefruit,

kiwi, papaya, raspberry, strawberry, sour cherry, melon, watermelon, paprika, tomatoes, cabbage and other leafy vegetables, broccoli, cauliflower, kohlrabi, parsley, potatoes and other fruits and vegetables [6].

Vitamin D is essential for the adequate absorption and metabolism of calcium and phosphates, and it is of particular importance for the maintenance of bone and teeth density during pregnancy as well as for the proper development of the bones and teeth of the fetus. Good sources of vitamin D are milk and dairy products, fatty saltwater fish (salmon, tuna, sardines, herring, mackerel, and swordfish), fish oil and eggs. The human body is capable of synthesizing vitamin D in the skin cells through the sunlight-mediated pathway; however, only moderate and controlled exposure to sunlight is advisable during pregnancy [6].

Calcium, along with phosphorus and vitamin D, is an important component in the bone and teeth mineralization. The best food sources of calcium are milk and dairy products (cheese, yoghurt), sardines, salmon, leafy greens, beans, lentil, sesame seed, soybean, figs, fruit juices (strawberry), dried fruits, almond, hazelnut and grains [6].

Phosphorus is an integrative component of teeth and bones, and it is contained in milk, cheese, eggs (egg yolk), peanut butter, meat, fish and fish oil, barley, legumes, walnut, fruit juices (red currant and raspberry) and brown bread [6].

Liver, which is rich in vitamin D and vitamin A, calcium and phosphorus, has not been listed in the aforementioned sources because of its particularly high vitamin A content that (if consumed frequently) could negatively affect the development of the fetus [6].

Foods containing substantial amounts of dietary fibers (roughage) are of solid consistency and their mechanical mincing during chewing process enables mechanical cleansing of teeth, promotes blood circulation in the gums, improves defense capacity of periodontal tissues, improves the keratinization and tonus of gingival tissue and stimulates salivary secretion. This group of foods includes some vegetables (carrot, cucumber, radish, celery, cabbage, lettuce, etc.) and nuts. The major benefit of such foods is that they provide adequate intake of vitamins and minerals without an increased bacterial production of acid compounds in the oral cavity [6]. The mechanical effects of teeth cleansing can be attributed to some fruits of solid consistency (e.g. some apple varieties, pears, etc.).

Meat and fish are an important source of proteins as the major building block, so the adequate intake of these foods during pregnancy is essential. Meat and fish consumption does not induce acidity in the oral cavity, and thus it may help to prevent dental caries [6].

Hard cheese, as a good source of calcium and phosphates, manifests caries-prevention properties through its positive effects on mineralization and remineralization of teeth. Cheese is also a strong sialogogue [1, 29]. It does not increase the acidity in the oral cavity, on the contrary – it inhibits the acidification process in the mouth thus acting as a preventive agent against caries. Such positive effects are characteristic mainly for hard (mature) cheeses, whereas fresh and sour milk cheeses as well as yoghurt increase the acidity of the mouth; therefore their consumption should be limited to mealtime [12].

Mobley C et al. recommend chewing sugar-free gum to protect and maintain oral health. The beneficial effects of chewing gum are manifested by mechanical teeth cleansing, improvement of gum tonus, stimulation of salivary secretion and reduction of acidity and bacterial count in the mouth [12]. Chour VG and Chour GR identified some leading factors contributing to caries development. Besides the refined carbohydrates and cariogenic bacteria, they emphasized the role of xerostomia (dry mouth), i.e. reduced secretion of the saliva, which can occur during pregnancy [30].

Education of Pregnant Women on Healthy Diet

Nutrition during pregnancy and its effects on caries development among the population of pregnant women and consequent caries in children is determined by a wide range of factors, including cultural and socio-economic ones [1–3, 12, 19]. Individual determinants such as behavioral orientation (characteristics, habits and education about nutrition), bad habits (smoking, repeated consumption of sweets and alcohol), actual oral health status, willingness and motivation of a pregnant woman to accept the recommendations are of great importance for preserving oral health during pregnancy. Furthermore, dietary recommendations should be tailored and adapted to the objective circumstances and family and social conditions of the pregnant woman's life [1, 2, 11, 20, 30].

The first step in creating healthy diet during pregnancy is to identify potential current nutritional imbalance. The subsequent step includes the correction and modification of dietary habits, that is, eliminating bad and promoting good eating habits. Having in mind specific cultural and socio-economic characteristics of pregnant women, their different habits, motivation and willingness to accept relevant recommendations, an individualized, patient-centered approach is of vital importance [1, 2, 11, 20, 30, 31].

In regard to individual educational approach, the direct contact between the counselor and pregnant woman and their adequate verbal and non-verbal positive communication are the most important moments. These methods should motivate the pregnant woman to participate actively in the education program and to accept the recommended routine. The counselor should show a certain degree of empathy and take the perspective of the patient, i.e. pregnant woman [19, 32].

Besides the personal contact, nutrition counseling of pregnant women may include a range of informative and educational materials as a useful education tool [19, 32, 33].

Education process is highly complex, encompassing initial assessment of the type and model of nutrition as well as recording of particular eating habits of the pregnant woman (in workshops, pregnancy cours-

es, and specially designed questionnaires for statistical processing). The assessment and, if necessary, correction and modification of eating pattern including meal composition and number of meals taken per day play a major role in caries-prevention procedures. The strategy of healthy diet and nutrition education focus on reducing the amount and rate of consumed carbohydrates, i.e. sugars [1–3, 7, 11, 20, 30]. Whenever possible, adequate oral hygiene should be practiced after each meal containing sugars [1–3, 7, 11, 20, 32–34]. Besides the harmful effects of refined carbohydrates (sugars) on oral health, they pose a substantial risk of overweight in pregnant women, which is known to be related to the development of periodontitis [35].

In addition to the restricted consumption of refined carbohydrates as harmful factors, a sufficient intake of beneficial food ingredients that promote teeth remineralization (vitamins A, C, D, calcium, phosphates and fluorides) plays an important role in caries prevention. Substantial amounts of such elements are provided from organic milk and dairy products made using natural and healthy processing methods [36]. Education process should emphasize that healthy eating is of importance not only for oral health of pregnant woman but also for her general health condition, pregnancy course and health status of her baby, which will give her motivation to accept the recommendations and advice [11, 20].

Though not directly related to nutrition yet in the aspect of general healthcare, pregnant women are strongly encouraged to avoid alcohol and smoking. Negative and harmful effects of smoking on oral health of general population are well established, and they can contribute to the development of periodontitis, tooth loss, carcinoma, etc. In pregnant women, such harmful effects are even more aggravated [20, 37].

Highly complex nature of oral health issue in pregnant women and its relation to her overall health status, quality of life, pregnancy outcome and health of her baby requires a multidisciplinary approach and involvement of health professionals and specialists of different profiles, i.e. dentists, general practitioners and gynecologists. Such an approach is useful in all communities, and particularly among populations of lower cultural and educational status and poorer economical status characterized by higher incidence of the aforementioned morbidities. In that respect, the style and methods of promotion of oral health and education should be adapted to the relevant population [7, 38]. Establishing preventive prenatal oral health institutions with educated and professional staff, assessment and control of oral health status of the pregnant women and referring them to relevant health centers, adequate and successful education programs as well as broader community engagement and social support to such programs and activities are highly valuable [39–42]. The importance of social and financial support for oral health, particularly among the populations of poorer cultural, educational and economical status, was demonstrated in 2005 in Serbia through the Law on Health Insurance, which restricted the rights of adult population to oral health care. The consequence of this Law was a substantially reduced access to oral health protection and dental services that were formerly covered by mandatory social security funds, which consequently lead to drastic deterioration of oral health status within adult population [43–45] including women before pregnancy.

Conclusion

The importance of following factors in preserving oral health during pregnancy should be emphasized: 1) healthy diet, 2) oral hygiene (regular teeth brushing), 3) education and motivation of pregnant women to practice appropriate procedures actively, 4) regular control of oral health status and potential introduction of relevant therapeutic measures, 5) appropriate organization and competence of preventive dental services and their cooperation with other medical care departments, and 6) community engagement and social support.

The aforementioned factors play an important role in the field of both dental health care (particularly preventive dentistry) and the healthcare system as a whole. They significantly affect and contribute to overall health status of the population. Evidently, systematic activities and initiatives undertaken by relevant decision makers in this field are of utmost importance for the improvement of both oral and general health status of the population.

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Rad je primljen 3. VII 2015.
Recenziran 7. VII 2015.
Prihvaćen za štampu 17. VII 2015.
BIBLID.0025-8105:(2015):LXVIII:11-12:387-393.

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Review article
Pregledni rad
UDK 616-089
DOI: 10.2298/MPNS1512394P

ENERGY SYSTEMS IN SURGERY

ENERGETSKI SISTEMI U HIRURGIJI

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Summary

Introduction. The systems of energy in surgery are applied in order to achieve better and more effective performing of procedures. Whereas various energy sources, including electricity, ultrasound, laser and argon gas, may be used, the fundamental principle involves tissue necrosis and hemostasis by heating. **Electro Surgery.** Electro Surgery is a surgical technique by which surgical procedures are performed by focused heating of the tissue using devices based on high-frequency currents. It represents one of the most frequently used energy systems in laparoscopy. **Ultrasound Energy.** The basic principle of operation of the ultrasound surgical instruments is the usage of low-frequency mechanic vibrations (ultrasound energy within the range of 20-60 kHz) for cutting and coagulation of tissue. **Laser.** Laser is the abbreviation for **L**ight **A**mplification by **S**timulated Emission of Radiation, aimed at increasing light by stimulated emission of radiation and it is the name of the instrument which generates coherent beam of light. **Argon Plasma Coagulation.** It has been in use since 1991 for endoscopic hemostasis. It uses high-frequency electric current and ionized gas argon. The successful application of devices depends on the type of surgical procedure, training of the surgeon and his knowledge about the device. Surgeons do not agree on the choice of device which would be optimal for a certain procedure. **Conclusion.** The whole team in the operating room must have the basic knowledge of the way an energy system works so as to provide a safe and effective treatment of patients. The advantages and shortcomings of different systems of energy have to be taken into account while we use a special mode.

Key words: Gastrointestinal Stromal Tumors; Leiomyosarcoma; Diagnosis, Differential; Diagnosis; Immunohistochemistry; Morphological and Microscopic Findings; Signs and Symptoms; Combined Modality Therapy; Tumor Markers, Biological; Actins; Desmin; Proto-Oncogene Proteins c-kit

Sažetak

Uvod. Energetski sistemi u hirurgiji se primenjuju radi boljeg i efikasnijeg izvođenja hirurških procedura. Bez obzira na različit energetski izvor koji se koristi, uključujući elektricitet, ultrazvuk, laser, argon gas, osnovni princip podrazumeva tkivnu nekrozu i hemostazu zagrevanjem. **Elektrohirurgija.** Elektrohirurgija je hirurška tehnika kojom se hirurške operacije izvode fokusiranim zagrevanjem tkiva pomoću elektronskih uređaja na bazi visoko frekvencijskih struja. Predstavlja jedan od najčešće korišćenih energetskih sistema u laparoskopskoj hirurgiji. **Ultrazvučna energija.** Osnovni princip rada ultrazvučnih hirurških instrumenata je da koriste niske frekvencije mehaničke vibracije (ultrazvučne energije u opsegu 20-60 kHz) za sečenje i koagulaciju tkiva. **Laser**. Laser je skraćenica od engleskog *"**L**ight **A**mplification by **S**timulatet **E**mission of **R**adiation"* što znači pojačanje svetla pomoću stimulisane emisije zračenja i naziv je za uređaj koji generiše koherentni svetlosni zrak. **Argon plazma koagulacija.** U upotrebi je od 1991. godine za endoskopsku hemostazu. Koristi visokofrekventnu električnu struju i jonizovani argon gas. Uspešnost primene energetskih uređaja zavisi od vrste hirurške procedure, obučenosti hirurga, poznavanja uređaja. Ne postoji konsenzus o tome koji uređaj je optimalan za datu proceduru. **Zaključak.** Ceo tim u operacionoj sali mora da poznaje osnovne principe rada energetskih izvora za bezbednu i efikasnu primenu u nezi pacijenta. Prednosti i nedostaci različitih energetskih sistema moraju da se imaju na umu dok se koristi poseban modalitet.

Ključne reči: Gastrointestinalni stromalni tumori; Lejomiosarkom; Diferencijalna dijagnoza; Dijagnoza; Imunohistohemija; Morfološki i mikroskopski nalazi; Znaci i simptomi; Kombinovana terapija; Tumor markeri; Aktin; Desmin; Proto-onkogen c-kit

Introduction

A large number of surgical procedures is performed by the application of different devices whose energy is used for coagulation or cutting in the operating field. Surgical procedures can be performed by focused heating of the tissue, by using electronic devices based on the high-frequency currents, laserbeams, argon(gas) and microwaves. Regardless of the source of energy, the basic principle is the tissue necrosis and hemostasis by heating [1]. The concept of electro surgery was created in the first half of the 19th century when the French physicist Henry Becquerel used electro cauterization. To perform hemostasis, he used a wire through which he distributed alternating current. The first model of an electrosurgical device was developed in 1926 by physicist William T. Bowie and neurosurgeon Harvey Cushing. This model had been used until 1968 when Valleylab created the core of modern electrosurgical unit [2].

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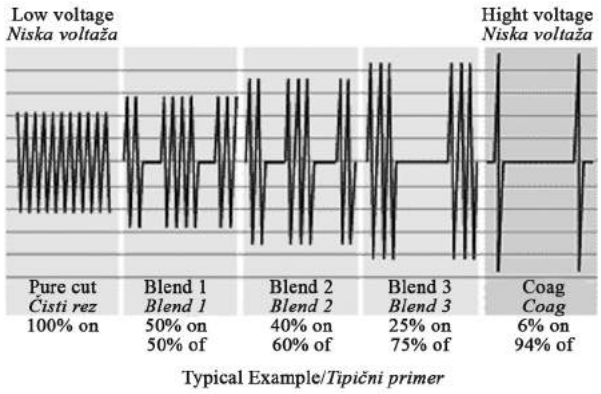
Electro Surgery

Electro surgery is a surgical technique by which surgical procedures are performed by focused heating of the tissue using devices based on high-frequency currents. It represents one of most frequently used energy systems in laparoscopy. It is usually wrongly identified with electrocautery. Cautery uses the heat conductibility of the test probe which heats directly using alternating current, while electro surgery uses high-frequency current which directly heats the tissue itself. Electrocautery is an electro surgical instrument which heats the focused tissue and cuts it by the high-frequency generator with the frequency of 2MHz, the output power from several tenths to several hundred Watts and voltage of 15 kV [3, 4]. Electro surgery shortens the duration of surgical procedures, reduces hemorrhage and destruction of the tissue, has a good cosmetic outcome, and alleviates the postoperative pain when compared to the conventional surgeries performed by scalpels. At the same time, it provides the comparable postoperative healing of wounds and percentage of infections [5–7]. When electricity flows through the biological tissue, one of the three effects appears depending on the type of electricity and its frequency: electrolytic, Faraday's or heat effect. *Electrolytic effect:* when we use the direct current or the low frequencies of alternating current, the electrolytic effect will dominate, which means that the ions in the tissue will move. The positive ions will move towards the negative electrode (cathode) and the negative ions move towards the positive electrode. This effect is used in ionosphere which is used to introduce different types of medicines to an organism. However, the electrolytic effect is not desirable in electro surgery because it may cause the damage of the tissue. *Faraday's effect:* it is created when alternating current with the frequency of 20 MHz flows through a human body. With this frequency level, electricity stimulates the nerve and the muscle cells and, for example, it can cause muscle contractions. The maximum of excitation will happen at the frequencies from 10 to 100 Hz. The Faraday's is successfully used in a form of electric stimulation in diagnostics and therapy [8]. As well as the electrolytic effect, the Faraday's effect is not desirable in electro surgery because muscle contractions are unpleasant, problematic for doctors and can even be dangerous for the patient. *Thermal effect:* The application of high-frequency direct current in human tissue prevents the appearance of the electrolytic and Faraday's effect to a great extent and makes the thermal effect dominant. The frequency of direct current is usually at least 300 kHz and that is why it is called the high–frequency surgery, radio frequency surgery or generally, electro surgery [9, 10] **(Table 1).** The basic principle for all electro surgeries is the thermal effect which is caused by the electric current flowing through a body. The thermal destruction of the tissue is used for cutting or coagulation in the area of the operation. If the tissue is heated long enough to the temperature of 100˚C using the high-frequency direct current, the evaporation of the internal and external cellular fluid will be caused with the resulting coagulation and decreasing of the tissue. There are several types of coagulation: soft, urgent, draining, and spray coagulation [11]. The high-frequency direct current can also be used for quick heating of the target tissue by temperatures higher than 100˚C, so the pressure of the vapor causes the explosive rapture of the membrane. The large number of these small 'cell explosions' create an incision, i.e. cause the cutting. There is a difference between the auto cut, dry cut and high cut. The electric current flows only though a closed system. That means that both active and neutral electrode, if connected correctly, create the electro surgical unit when the monopolar mode of operation is applied [12]. The neutral electrode, which is larger, must be correctly placed on the patient's thigh. When the doctor touches the tissue with the active electrode, the electro surgical unit is on and high-frequency electricity flows through the patient. Electricity flows through the patient and then it returns to the electro surgical unit through the neutral electrode. In bipolar surgery, the active and neutral electrodes are on the place of operation, inside the instrument. These are, actually, the forceps with the tweezers or scissors. The flow of electricity is limited between these two poles which are very close one to another, so the neutral electrode on the patient's body is not needed. Since the poles are very close one to another, the low voltages are used to achieve the tissue effect. Bipolar mode is very safe for electro surgery. Maximum thermal lateral span is less than 5 mm [13]. The shortcomings of bipolar electro surgery are the longer periods needed for coagulation because of low electricity, carbonization and unpredictable

Table 1. The heat effect on the tissue
Tabela 1. *Toplotni efekat na tkivo*

Temperature/*Temperatura*	Process/*Proces*
42˚C	Reversible tissue damage/*Reverzibilna ćelijska trauma*
49˚C	Irreversible tissue damage/*Ireverzibilna ćelijska trauma*
70˚C	Coagulation/*Koagulacija*
100˚C	Dessication/*Isušivanje*
200˚C	Carbonization/*Karbonizacija*
500˚C	Vaporization/*Vaporizacija*



Graph 1. Waveforms of an electro surgical unit with different tissue effects. Blend 1 (80% cutting, 20% coagulation); Blend 2 (60% cutting, 40% coagulation); Blend 3(50% of cutting, 50% coagulation)

Grafikon 1. *Talasni oblici elektrohirurške jedinice sa različitim tkivnim efektima. Blend 1 (80% sečenje, 20% koagulacija); Blend 2 (60% sečenje, 40% koagulacija); Blend 3 (50%, 50% sečenje, koagulacija).*

breaking of neighboring blood vessels. Three tissue effects are possible when using modern electro surgical units: cutting, draining and coagulation (fulguration). The achievement of these effects is influenced by the following factors: density of electricity, time, size of an electrode, tissue conductibility and the waveform of electricity. The clean cut (evaporating) uses the waveform of electricity which is continuous, non-modulated and unamortized. The blend waveform is a modification of cutting waveform and it is used when we need the hemostasis during cutting. It is a combination of cutting waveform and coagulation [11, 14] **(Graph 1)**. The devices for obturation of blood vessels caused a revolution in modern laparoscopy. They can be divided into two categories: advanced bipolar and ultrasound instruments. The advanced bipolar devices for obturation/cutting blood vessels use adaptive technology, which is a part of modern electro surgical units, to deliver the controlled energy of low voltage with minimal lateral thermal span. The most important element of this technology is usage of bipolar electro surgery which is based on generators of tissue response. To be more precise, electricity of great strength and low voltage causes denaturation of collagen and elastin in the walls of blood vessel by treating target tissue and the mechanical pressure of the instrument enables denatured proteins to form coagulum [15]. Blood vessels not wider than 7 mm and large tissue strings can be surgically ligated. Moreover, heat distribution decreases when compared to traditional bipolar surgical systems. Nowadays there are several types of advanced bipolar devices on the market: Plasma Kinetics system, LigaSure, EnSeal and Cayman. Each of these types is licensed to be used for obliteration of the tissue not more than 7 mm wide. Some of these include the Thanderbeat platform by Olympus which integrates both ultrasound and advanced bipolar technologies. LigaSure includes both advanced bipolar and monopolar technologies. Cayman 12 offers articulated 12 mm instrument [16]. Binding (ligating) of veins is very difficult because of very thin walls and that is why the so-called thermo fusion can sometimes be useful. When thermo fusion is applied, veins do not have to be separated from the surrounding tissue. They are coagulated together with the connecting tissue around the blood vessel. Shrinking of tissue helps ligation of a blood vessel to form the natural ring (collar).Thermo fusion must not be used near the important structures such as the ureter [17]. The number of reported electro thermal injuries is 1-5 injuries per 1000 cases. The majority of electro thermal injuries of intestine (75%) are not recognized when they happen [18]. The consequences of these unnoticed injuries are usually very serious and often cause long-term complications. The organ which is injured most is the small intestine (ileum), but these injuries can neither be noticed clearly and immediately nor cause the abnormal laboratory values. Generally speaking, the symptoms of the intestine perforation are usually noticed 4 to 10 days after the procedure. The symptoms of direct traumatic perforation of intestine usually appear within 12 to 36 hours, although there have been a few cases when they appeared in the period of 11 days. The electric injuries are caused by surface coagulation necrosis [11, 19]. Electro thermal injuries often appear in the following situations: direct application, direct coupling, weakening of the isolation and capacitive coupling. Direct application appears as a consequence of the unintended activation of the electro-surgical probes when the probe is, for example, moved from the operating field to the thigh artery. Direct coupling ensues when the electro surgical unit is activated unintentionally, while the active electrode is very close to another metal instrument. Electricity in the active electrode flows through the neighboring instruments following the path of the least resistance and it potentially damages the organs which are out of the field of view, but which are in the direct contact with the instrument. It can be prevented by visualization of the electrodes when they are in contact with the target tissue and by avoiding contact with any other conductible instrument before activating the electrodes. Unsuccessful isolation (weakening of the isolation) is considered to be the main cause of electro surgical injuries. It is defined as an interruption or a defect in isolation which covers the instrument. It is caused by extended, long time use of the instrument, especially by its multiple passing through the trocar and by its repeated sterilization. The instruments for one use only have lower frequency of isolation damage when compared to the instrument for multiple usage. The distal third of the laparoscopy instruments is the part which is the most problematic. Capacitive coupling is the electric current which flows through the tissue or in metal instruments which are parallel, but not in the direct contact with the active electrode. This happens when electric

current is transferred from one conductor (the active electrode) through untouched isolation to the neighboring conducting material, for example the intestine, without direct contact. In monopolar mode, the alternating current flows through the active monopolar electrodes and then flows back to the electro surgical generator through the patient and the return plate induces undesirable electricity in all the conductors in the vicinity. The strength of induced electricity will depend on how far the conductor is. It will also depend on the voltage and isolation. Every conductor in the operating room is in danger of the electricity which flows in the wrong direction because it can become capacitively coupled with the electricity which comes from the active electrode. If an injury appears, it is usually out of the field of view of the surgeon and includes body structures. Ironically, the use of metal trocars can actually decrease this risk, enabling the stored energy from capacitors to discharge through the large surface of the patient's skin, which makes electric energy less concentrated and less dangerous. The problems connected to the capacitive coupling can be eliminated by using the active system to monitor the electrodes and limit the time during which high voltage can be used [9, 20, 21]. To prevent electro surgical complications the following protective measures are used: the thorough checkup of isolation, application of the weakest possible strength, usage of short, interrupted activation, usage of low-voltage waveform (cutting out), avoiding usage in either closed circuit or in the vicinity or direct contact with another instrument, using bipolar electro surgery when it is appropriate. Choose completely metal canile system as the safest choice. Apply the available technology (generator of tissue response, active monitoring of electrodes) to eliminate problems which are caused by weakening of isolation and capacitive coupling. For the effective electrosurgery, the surgeon must be able to check the equipment and settings at first sight [1, 4].

Ultrasound Energy

Ultrasound energy in medicine was first applied in 1960 to cure the Meniere's disease and then in the late 1980s it was used for coagulation and cutting the tissue. The basic principle of operation of ultrasound surgical instruments is the usage of low-frequency mechanic vibrations (ultrasound energy within the range of 20-60 kHz) for cutting and coagulation of tissue. A harmonic scalpel is an ultrasound instrument for cutting and coagulation of tissue and it uses the frequency of 55.5 kHz. It has no electro surgically generated energy. The combination of mechanical energy and heat which is generated causes the denaturation of proteins and forming of coagulum which seals small blood vessels. Vibrating of the top of the blade makes large changes of pressure and causes cellular liquid to evaporate on low temperatures which causes cells to rupture and it is used for highly precise cutting and dissection. Another mechanism of cutting by harmonic scalpel is the real cutting power coming from a relatively large knife which vibrates at the frequency of 55.5 kHz. The friction temperature of the tissue is usually about 80˚C, which decreases the tissue carbonization, and causes drying and reduction of the zone of the wound. It is characterized by the lateral thermal spreading from 1 – 4 mm, the ability for obturation (ligation) of the blood vessels not wider than 5 mm. The shortcoming of this technology is the appearance of small, greasy drops from the tissue being treated and this can disturb the visualization through the laparoscope [22].

Laser

Laser is the abbreviation from **L**ight **A**mplification by **S**timulated **E**mission of **R**adiation, which means to increase light by stimulated emission of radiation and it is the name of the instrument which generates coherent beam of light. It is a ray, actually a wave, which transfers oscillation of light photons of certain frequency at a certain wavelength and in a certain direction of polarization. In a small space, laser beams enable big amount of energy to focus in one point which potentiate a large quantity of radiation energy to focus and thus the temperature could reach 7000˚C in a very small space. In the area effected by laser beams, any substance can evaporate. As all other forms of light therapy, the effect of laser beams depends on their absorption. The absorption of radiation is different with different kinds of tissue. Differences in tissue absorption ability are closely related to the wavelength and content of fluid in the tissue [23]. The usual laser system in gynecological practice includes carbon-dioxide laser as well as Nd YAG laser. Both types of beams are invisible. There are four categories of lasers. The majority of medical lasers belong to categories 3B or 4, which require protection. Radiation of laser which penetrates the eye is focused on the retina, so that the strength of energy can dramatically decrease which can damage retina. Fire also represents threat when laser of category 4 is used. The retina of the eye is very sensitive to the effect of laser beams, therefore the eyes of both patients and doctors who work with it must be protected when this kind of beams is applied. Special protective glasses having a special optic filter are usually worn. Under any circumstances, protection must be complete, which means laterally as well, because otherwise the retina and sclera can be damaged. An eye can be damaged at the temperature of 0.24 –7 J/cm^2. The eye must be protected when laser beams are used. Surgical effect produced by laser and electro surgery is the result of generating heat in the tissue. Since water heats to the extreme temperatures, inter-cellular pressure rises, which results in the cell explosion. In the situation like this, vapor has to be released and spread in the air. At the same time, microscopic particle is released into the air. That particle represents biological, contaminating substance in smoke which consists of oxidized tissue, blood and possibly contagious viruses and bacteria. Infection risk exists and is caused by exposure to the

living viruses of the infected deoxyribonucleic acid (DNA) and bacterial contaminates. Moreover, chronic irritation caused by surgical smoke can cause skin problems (dryness and rushes) as well as inflammation of respiratory tract (bronchitis). Mucosa along the nasal-pharyngeal area can be irritated. Those who wear contact lenses should be informed that small lenses absorb the contents of surgical smoke. In addition to biological substances, there are also the chemical contaminating substances which include toxins (carcinogens) such as Acroleyn, Benzene, Formaldehyde and Toluene, together with polycyclic aromatic carbon-hydrogen (PAH). It is necessary to provide effective elimination of smoke close to the surface on which surgery is performed in order to remove the vapor before operating room stuff (doctors and nurses) inhale it. Filtrating is only used for particles [24]. Masks do not filtrate gases which are chemical contaminating substances. Standard masks have the range of effective filtrating from 0.6 to 5 microns. Masks with a wide range of filtrating (when used properly) can filtrate 0.1–0.5 microns. These masks make breathing difficult. Integral system of *approach,* AirSeal(R) has sensors for flow of gases and pressure. It combines trocar and pipe system with a filter which enables fixed pneumo-peritoneum with the constant discharging of smoke, as well as the approach to venter without a vent hole [25]. Its holders can be 5, 8 and 12 mm wide in diameter. By the system of automatic and constant elimination of smoke, surgical smoke is prevented to get out. Constant filtering has been carried out and it provides circulation of CO_2.

Argon Plasma Coagulation

It has been in use since 1991 for endoscopic hemostasis. It uses high-frequency electric current and ionized gas argon. Besides lasers, this is noncontact method in which argon, being a good conductor of electricity, is used to transfer electricity from an instrument to the tissue. The result is quicker coagulation when compared with conventional devices and it provides coagulation on a wide surface and shallower coagulation of treated tissue, which results in quicker dispersion, decreasing the damage of tissue. Moreover, it produces less smoke than conventional systems. It is applied in hemostasis of the surface diffusion hemorrhages from parenchyma organs [26]. The most significant limitation of the usage of argon plasma system is a possible danger of emboly by argon [27].

In spite of the advances, search for the ideal energetic device which will result in perfect hemostasis with minimal damage of the surrounding tissue in the most effective way with minimal possibility of complications has not been completely successful.

Every energetic system has its advantages and shortcomings. It is necessary to be very well acquainted with every device in order to be able to decide which source of energy will be used. Generally speaking, the majority of studies suggest that the effect of any procedure depends on skillfulness of the surgeons and their ability to use a certain device.

Conclusion

The whole team in the operating room must know basic information on how to apply sources of energy which represents the crucial point for the safety of patients. In addition, it helps to notice and prevent potential complications. The advantages and the shortcomings of different systems of energy have to be taken into account while we use a special mode. We have to use the most modern technologies with effective haemostatic characteristics whenever it is possible.

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Rad je primljen 15. VI 2015.
Recenziran 2. IX 2015.
Prihvaćen za štampu 13. IX 2015.
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CASE REPORTS
PRIKAZI SLUČAJEVA

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Case report
Prikaz slučaja
UDK 616.317-005.9:616.313]-079.4 i 616.833.17
DOI: 10.2298/MPNS1512401R

CLINICAL CHARACTERISTICS AND TREATMENT OF MELKERSSON-ROSENTHAL SYNDROME – OVERVIEW OF SIX PATIENTS

KLINIČKA PREZENTACIJA I TRETMAN KOD MELKERSON-ROZENTALOVOG SINDROMA − PREGLED ŠEST PACIJENATA

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Summary

Introduction. Melkersson-Rosenthal syndrome is a rare disease of unknown etiology. Histopathologically, it presents as granulomatous cheilitis. From laboratory aspect, it is a nonspecific, differential diagnostically and therapeutically complex condition. **Case Report.** This is a report of six cases treated at the Department of Allergology and Immunology of the Clinical Center of Serbia, who had presented with the referral diagnosis of recurring or persistent lip edema, and who were diagnosed with Melkersson-Rosenthal syndrome upon detailed evaluation. Three patients had complete triad of symptoms, two had the oligosymptomatic form and one manifested the monosymptomatic form of the disease. Histopathological findings of the oral mucosa specimens verified the presence of non-necrotic epithelioid granulomas in all patients. The patients were treated with the H1 and H2 antihistamines, corticosteroids, followed by anabolic drugs and antibiotics, resulting in transient and unfavorable effects. **Conclusion.** In differential diagnosis, Melkersson-Rosenthal syndrome diagnosis primarily refers to conditions of angioneurotic edema and hereditary angioedema, as well as granulomatous diseases such as sarcoidosis, tuberculosis and Chron's disease. It is necessary to follow-up these patients in view of monitoring the effects of the therapy and possible development of systemic granulomatous diseases.

Key words: Melkersson-Rosenthal Syndrome; Morphological and Microscopic Findings; Signs and Symptoms; Diagnosis; Treatment Outcome; Lip; Edema; Cheilitis; Tongue, Fissured; Facial Paralysis; Angioedema

Sažetak

Uvod. Melkerson-Rozentalov sindrom je retko oboljenje, nepoznate etiologije. Patohistološki se prezentuje kao granulomatozni heilitis. Laboratorijski je nespecifičan, diferencijalno-dijagnostički i terapijski kompleksan. Lečenje ovih bolesnika je kompleksno i često zahteva upotrebu različitih terapijskih modaliteta. **Prikaz slučaja.** Prikazano je šest bolesnika koji su ispitivani na Klinici za alergologiju i imunologiju Kliničkog centra Srbije, pod uputnom dijagnozom angioedema usana, a kod kojih je nakon detaljne evaluacije postavljena dijagnoza Melkerson-Rozentalov sindroma. Tri bolesnika su imali kompletan trijas simptoma, dva oligosimptomatsku i jedan monosimptomatsku formu. Kod svih pacijenata patohistološki nalaz biopsije mukoze usana potvrdio je postojanje nenekrotičnih epiteloidnih granuloma. Pacijenti su lečeni H1 i H2 antihistaminicima, kortikosteroidima, uz antibiotike i anaboličke lekove, sa promenljivim uspehom. **Zaključak.** Dijagnoza Melkerson-Rozentalov sindrom se diferencijalno-dijagnostički odnosi pre svega na stanja rekuretnog i hereditarnog angioedema, kao i granulomatozne bolesti kao što su sarkoidoza, tuberkuloza i Kronova bolest. Neophodno je praćenje ovih bolesnika zbog efekta primenjene terapije i mogućnosti razvoja sistemskih granulomatoznih bolesti.

Ključne reči: Melkersson-Rosenthal Sindrom; Morfološki i mikroskopski nalazi; Znaci i simptomi; Dijagnoza; Ishod lečenja; Usna; Edem; Heilitis; Fisure jezika; Facijalna paraliza; Angioedem

Introduction

In 1928, Melkersson first described the clinical syndrome as an edema of the orofacial region with the facial nerve palsy [1], and in 1931, Rosenthal added fissured tongue as a part of the clinical picture of this syndrome [2]. This was the way of Melkersson/Rosenthal syndrome (MRS) development, which is characterized by a triad of symptoms: lip and face swelling, fissured tongue and peripheral type paresis and/or paralysis of the facial nerve. When it is presented in classical form, it is not difficult to be diagnosed, but oligo- and monosymptomatic forms represent a problem in making the differential diagnosis. Given that lip edema is predominant in the clinical picture, these patients are referred to an allergologist because of a suspected allergic reaction.

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Abbreviations

MRS – Melkersson-Rosenthal syndrome
SPEC – serum protein electrophoresis
IFX – immunofixation
PPD – purified protein derivative
ACE – angiotensin-converting enzyme

Case Report

The patients, who had presented with the referral diagnosis of recurring or persistent lip edema, were examined at the Department of Allergology and Immunology of the Clinical Center of Serbia, during the period 1994-2012 and were finally diagnosed with MRS.

There were four females and two males, whose mean age was 50.5 years and the average length of symptoms was 6.4 years. **Table 1** shows the age, symptom duration and clinical picture of each case.

The patients could not associate occurrence of their lip edemas with some of the incriminating factors such as food and medicaments. In addition, all patients denied having difficulties associated with any organic systems, in the first place the respiratory system or gastrointestinal tract. Three patients reported migraine-type headache and facial nerve paresis.

The complete triad including lip edema, fissured tongue and facial nerve paresis was manifested in three patients, oligosymptomatic form with lip edema and fissured tongue was diagnosed in two patients and one patient had only lip edema (monosymptomatic form). Lip edema, presented in all patients, was clinically manifested differently. It affected either the upper or the lower lip or both lips **(Figure 1).** A patient with characteristically fissured tongue (lingua plicata s. geographica) is presented in **Figure 2**.

All patients underwent the following analysis:

Laboratory analyses (erythrocyte sedimentation rate, complete blood count with leucocyte formula, biochemistry analyses, serum protein electrophoresis (SPEP) with immunofixation (IFX), serum angiotensin-converting enzyme (ACE));

Immunoloserological analysis (serum immunoglobulins, chamber count of eosinophils, antinuclear antibodies, complement components - C1q, C3, C4 and C1s inhibitor – qualitative and quantitative analyses, antineutrophil cytoplasmic antibodies, cryoglobulins);

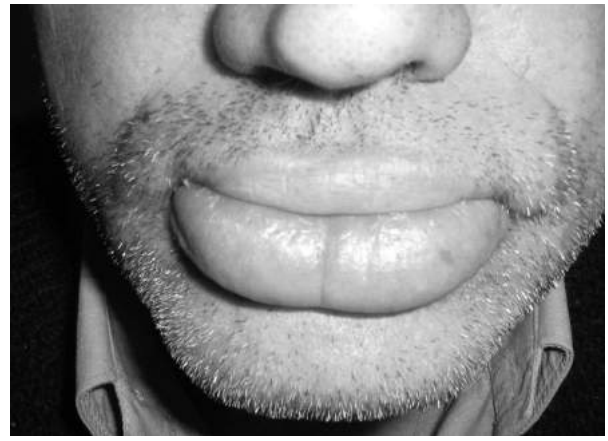

Figure 1. Edema of the lower lip was firm on palpation. There was edema of the upper lip and above it as well, which was of softer consistency on palpation.
Slika 1. *Edem donje usne je tvrd pri palpaciji. Postoji otok gornje usne koji zahvata i region iznad usne, a koji je meke konzistencije pri palpaciji.*

Skin prick tests with standard inhalation and nutrition allergens, X-ray of the lungs, purified protein derivative (PPD) test, throat, nasal and sputum swabs for bacterial and fungal culture isolation;

Neurological and dental examination;

Examination by a maxillofacial surgeon with the biopsy of oral mucosa.

Inflammatory syndrome was absent in all patients, blood count and biohumoral findings including SPEP and IFX and ACE were within limits. The results of immunoserological analyses were regular in all patients. However, lowered C1 inhibitor function and normal quantitative C1 inhibitor, C4, C1q and C3 complement components values were recorded in one patient. Skin prick tests including the inhalation and nutritional allergens, lung X-ray and PPD test findings, the results of throat, nasal and sputum swabs were all negative. Neurological examinations revealed that one patient had left facial nerve paresis, one patient had convergent strabismus and discrete left pyramidal deficit, while other patients were deficit-free. Odontogenic focus was detected in one patient and antibiotic therapy was prescribed. All patients underwent oral mucosa biopsy and histopa-

Table 1. Main characteristics of each case
Tabela 1. *Karakteristike pacijenata*

Case *Pacijent*	Age *Starost (godine)*	Sex *Pol*	Duration of disease (years) *Trajanje bolesti (godine)*	Clinical findings *Forma bolesti*
1	32	F	2	LE/*OU*, LP
2	55	M	21	LE/*OU*, LP, PF
3	52	F	3	LE/*OU*
4	62	M	4	LE/*OU*, LP
5	52	F	7	LE/*OU*, LP, PF
6	50	F	2	LE/*OU*, LP, PF

Legend: M – male; F – female; LE – lip edema; LP - lingua plicata; PF - paresis facialis
Legenda: M – muški; Ž – ženski; OU – otok usana; LP − lingua plicata; PF − pareza facijalisa

Figure 2. Lingua plicata s. geographica in our patient with oligosymptomatic form of MRS
Slika 2. *Lingua plicata s. geographica kod našeg pacijenta sa oligosimptomatskom formom Melkerson-Rozentalovog sindroma*

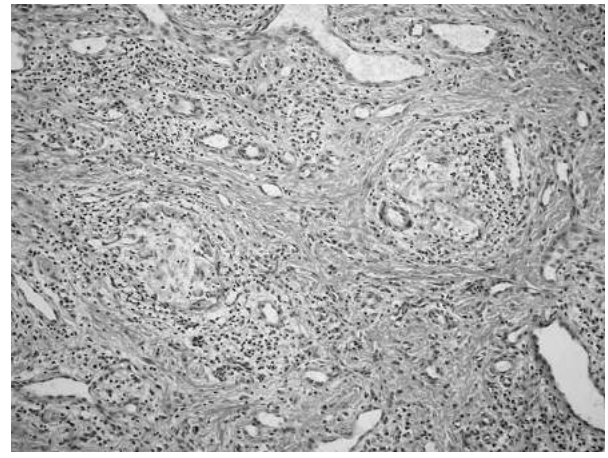

Figure 3. Histopathological finding of oral mucosa specimen shows chronic lymphocytic inflammation with noncaseating epitheloid granulomas (Staining with haematoxylin-eosin, magnitude x 200)
Slika 3. *Histološki nalaz biopsije oralne mukoze pokazuje hroničnu limfocitnu inflamaciju sa nekazifikujućim epiteloidnim granulomima (bojenje sa hematoksilin-eozinom, uvećanje 200 x)*

thological findings confirmed granulomatous cheilitis **(Figure 3)**.

Treatment included H1 and H2 antihistamines, corticosteroids (topical application in one patient), anabolics and antibiotics in a patient with verified odontogenic focus. No effect to applied oral corticosteroids and H1 and H2 antihistamines was recorded in 4 patients, while one patient had a partial and another a transient favorable response to this therapy. A partial improvement upon danazol treatment was observed in 3 patients, while a transitory favorable effect and long-lasting good effect were recorded in 1 patient each. A significant improvement was noted in one patient upon intralesional application of corticosteroids (triamcinolone). In one patient, antibiotic therapy for odontogenic focus resulted in resolution of the focus, but without any effect to the lip edema. The drug combination and treatment effects in our patients are illustrated in **Table 2**.

Discussion

When the complete triad of symptoms is present, it is not difficult to make the diagnosis of MRS. However, the classical triad is evident in only 8%-25% of patients [3]. The oligosymptomatic form is more common (lip edema, fissured tongue), and the most frequent is the monosymptomatic form (lip edema), which makes this syndrome harder to recognize [4]. It is questionable if the monosymtopmatic form of MRS (granulomatous cheilitis), which was found in one patient, is a part of MRS, or it is a part of heterogenous spectrum of orofacial granulomatosis diseases. Some authors believe that MRS is a part of the orofacial granulomatosis spectrum, along with sarcoidosis, tuberculosis and Chron's disease [5, 6].

Etiopathogenesis of MRS is still unknown. It has been assumed that it is the manifestation of microneurovascular lesion [7]. The association with infections (spirochetes, mycobacteria, herpes simplex virus, odontogenic foci) has been described, while the genetic predisposition has not been confirmed [8–10].

Differential diagnosis frequently implies allergic conditions such as angioneurotic type and hereditary angioedema.

Neurological manifestations, other than facial nerve paralysis/paresis, appearing in about 20% of MRS cases, may present as trigeminal neuralgia or migraine-type headache [7, 11, 12]. Three of our patients had the history of migraine headaches.

Table 2. Effects of various treatment combinations
Tabela 2. *Tretman i efekat terapije kod naših pacijenata*

Treatment *Terapija*	No effect *Bez efekta*	Partly effective *Delimičan efekat*	Temporary effect *Povremen efekat*	Long term good effect *Dugotrajni dobar efekat*
CS/*GK*; H1; H2	2, 4, 5, 6	3	1	
DA		4, 5, 6	2	1
iCS/*iGK*				2

Legend: CS – corticosteroids; iCS – intralesional corticosteroids, H1 - H1 antihistamines, H2 – H2 antihistamines, DA – Danasol
Legenda: GK − glikokortikosteroidi; IGK – intralezionalni glikokortikosteroidi, H1 - H1 antihistaminici, H2 - H2 antagonisti, DA – Danazol

No evidence of atopic constitution was found in our patients, such as sensibilization to some of inhalation and nutrition allergens. Moreover, history data on the duration of lip edema and a poor or no response to antihistamines and corticosteroid treatment failed to indicate angioneurotic edema caused by the known provoking factors (medicaments, preservations, additives).

Within the immunological evaluation, one female patient with oligosymptomatic MRS had a decreased function of C1s inhibitor (21.4%, normal value > 40%). Although hereditary angioedema was ruled out, it could have contributed to the clinical presentation of lip edema. Such associations have rarely been described in literature [13].

None of our patients had anamnestic, clinical and laboratory parameters of systemic connective tissue diseases or primary vasculitides. In addition, there were no anamnestic, clinical or laboratory indicators of systemic granulomatosis.

Melkersson-Rosenthal syndrome diagnosis is typically verified by histopathological analysis of oral mucosa specimen. During the early stages of the disease, it shows connective tissue edema and perivascular lymphocytic infiltration, while in cases of long disease duration, lymphocytic infiltration becomes denser and focal non-necrotizing granulomas, consisting of lymphocytes, epithelioid and giant cells, are formed. Histopathologically, these granulomas are indistinguishable from those found in sarcoidosis or Crohn's disease [3, 4, 14]. At the time of biopsy, two of our patients (No. 1 & 4) had a few granulomas, suggesting the early phase of disease, while other patients had findings corresponding to the chronic phase of granulomatous cheilitis.

Treatment of MRS is complex and various treatment modes have been described in literature: corticosteroids (systemic, intralesional), anabolics, antibiotics (metronidazole, tetracyclines, macrolides), clofazimine, dapsone, sulphasalazine, azathioprine, hydroxychloroquine, methotrexate, infliximab, as well as surgical intervention (cheiloplasty), but very rarely [4, 15–17].

According to our experience, treatment should be initiated with combined oral corticosteroids and H1 and H2 antihistamines, and in case of poor response to therapy, oral anabolics should be introduced. In addition, management of odontogenic foci as well as antibiotic treatment of orofacial region infection is mandatory. Intralesional corticosteroid application applied in one patient proved to yield good results.

Conclusion

In differential diagnosis, Melkersson-Rosenthal syndrome diagnosis primarily refers to conditions of angioneurotic and hereditary angioedema. Besides the complete trias, oligo- and monosymptomatic forms are commonly seen. Therefore, diagnosis should be verified by histopathological analysis of oral mucosa biopsy specimen. Evaluation and treatment of Melkersson-Rosenthal syndrome require multidisciplinary approach by an allergologist-immunologist, neurologist, dentist, maxillofacial surgeon and histopathologist. Regular follow-up of these patients is necessary, both for a possible development of complete trias in mono- and oligosymptomatic forms, and for the development of systemic granulomatous disease.

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Rad je primljen 21. I 2015.
Recenziran 14. VI 2015.
Prihvaćen za štampu 15. VI 2015.
BIBLID.0025-8105:(2015):LXVIII:11-12:401-404.

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Prikaz slučaja
UDK 616.728.3-089.2-036.2
DOI: 10.2298/MPNS1512405B

MANAGEMENT OF A DISTAL FEMORAL NON-UNION WITH COEXISTING FAILURE OF THE KNEE EXTENSOR MECHANISM USING OSTEOBRIDGE KNEE-ARTHRODESIS SYSTEM – A CASE REPORT

ZBRINJAVANJE NEZARASLOG DISTALNOG DELA FEMURA PRAĆENO NEUSPELOM UGRADNJOM MEHANIZMA ZA EKSTENZIJU KOLENA POMOĆU SISTEMA ARTRODEZE KOLENA OSTEOMOSTOM – PRIKAZ SLUČAJA

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Summary

Introduction. Reconstruction of bone defects is a long, challenging process both for the patient and for the treating surgeon. Bone defects frequently occur as a result of aggressive surgical debridement and bone resection in case of acute trauma, open fractures, chronic bone infections, tumors and non-unions. Early amputation is often superior to prolonged attempts at salvage because they can create serious problems in the patients' lives. There are numerous alternative methods of limb-salvage nowadays. **Case Report.** We report a case of a fifty-year-old man with a distal femoral non-union and a co-existing failure of the knee extensor mechanism, who was treated using an intramedullary segmental defect bridging knee arthrodesis system (Osteobridge). At the final check-up twenty four months later, he had excellent clinical, functional and radiological results. **Conclusion.** Osteobridge is an excellent knee arthrodesis system, which is preferable to other methods in case of resection of the distal femur along with the failure of the knee extensor mechanism.

Key words: Limb Salvage; Femoral Fractures; Knee Prosthesis; Arthrodesis; Arthroplasty, Replacement, Knee; Quality of Life; Treatment Outcome; Patient Outcome Assessment

Sažetak

Uvod. Rekonstrukcija defekta kosti je dug i izazovan proces i za pacijenta i za ordinirajućeg hirurga. Defekti kostiju se često dešavaju kao rezultat agresivnog hirurškog odstranjivanja i resekcije kosti u slučaju akutne traume, otvorenih fraktura, hroničnih infekcija kosti, tumora i nezarastanja. Rana amputacija je često bolja od dugotrajnih pokušaja spasavanja ekstremiteta zato što oni mogu stvoriti ozbiljne probleme u životu pacijenata. Danas postoje brojne alternativne metode spasavanja ekstremiteta. **Prikaz slučaja.** Prikazan je slučaj 50 godina starog muškarca sa lažnim zglobom donjeg okrajka butne kosti i koegzistirajućim oštećenjem ekstenzornog mehanizma kolena, koji je lečen korišćenjem unutarkoštanog sistema za premošćavanje defekta i ukočenje zgloba kolena (*Osteobridge*). Na poslednjem kontrolnom pregledu posle 24 meseca imao je odlične kliničke, funkcionalne i radiografske rezultate. **Zaključak.** Osteomost je odličan sistem artrodeze kolena koji je bolji od drugih metoda, u slučaju resekcije distalnog dela butne kosti, kad ne uspe ekstenzorni mehanizam kolena.

Ključne reči: Spasavanje ekstremiteta; Frakture femura; Proteza kolena; Artrodeza; Artroplastika, zamena kolena; Kvalitet života; Ishod lečenja; Procena pacijenta

Introduction

Bone defects may have negative consequences on the quality of life of the patient such as destitution, disability, divorce or depression and they present complex treatment challenges [1, 2]. They can result from an acute trauma with bone loss, tumor excision, chronic infections requiring bone resection or chronic non-unions with segmental bone defects [3]. In case of septic non-unions, most authors recommend aggressive resection of contaminated devitalized bone and surrounding scar tissue [3, 4]. Because of difficulty in managing bone defects and their poor outcomes, amputation used to be the preferred treatment [1]. Nowadays, the alternative methods of limb salvage and restoration of its functions include limb shortening, autologous nonvascularized cancellous bone grafts, free vascularized bone transfer, interpositional bone allografts, bone transport distraction osteogenesis or an intramedullary rod, segmental metallic prostheses and intercalary scaffolds augmented with growth factors [3–13]. We report the surgical treatment of a patient with distal femoral non-union and a co-existing failure of the knee extensor mechanism using a specific intramedullary segmental defect bridging knee arthrodesis system which is called Osteobridge (Osteobridge® Extended System PLUS Knee Arthrodesis, Merete, Berlin, Germany).

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Abbreviations
MRI – magnetic resonance imaging

Figure 1. Preoperative antero-posterior radiograph of both femurs and knees.
Slika 1. *Preoperativni antero-posteriorni rendgenski snimak obe butne kosti i kolena*

Figure 2. Preoperative antero-posterior and lateral radiographs of the distal third of the left femur and knee
Slika 2. *Preoperativni antero-posteriorni i lateralni rendgenski snimak distalne trećine leve butne kosti i kolena*

Case Report

A fifty-year-old man, who had had a car accident five years before resulting in an open complete articular, bicondylar fracture with supracondylar comminution of his left femur (AO Müller Classification: 33-C2), had eight separate surgical operations performed by three different surgeons in hospitals in Greek province. Initially, he was treated with an external fixator, which was replaced with a condylar buttress plate and screws three weeks later. A complete rupture of the quadriceps tendon was also diagnosed and repaired at the same time. Four months later, the plate was broken and replaced by a new larger buttress plate and autologous grafts from the iliac crest. However, the plate was removed after two months because of an infection and Staphylococcus Aureus was cultured. Intravenous antibiotics were administrated according to the antibiogram for six weeks. A splint extending from the hip and down to the ankle was placed to stay for the same time. After nine months, the patient had normal values of sedimentation rate and C-reactive protein and normal findings in the three-phase bone scintigraphy. Thus, a wide soft tissue debridement and dead bone resection along with a new open reduction and internal fixation with a buttress plate and bone autografts was attempted. A rupture of the patellar tendon occurred when the surgeon tried to mobilize the knee joint, which had been immobilized in the full knee extension for all these months. The tendon was repaired with suturing through bone tunnels within the tibial tubercle. Unfortunately, the plate was removed ten months later due to the hypertrophic non-union. The surgeon removed the devitalized bone and soft tissues and tried to cover the bone defect using the bone transport distraction osteogenesis method. Twelve months later the majority of the defect was successfully covered but non-union was confirmed at the fracture site. Moreover, after all these operations and the long-lasting immobilization of the knee, there was a complete failure of the extensor mechanism and the joint was ankylosed in the extended position. Finally, the surgeon suggested the transfemoral amputation of the left lower limb as the definite solution.

In January 2013, the patient came to the orthopedic department of our hospital asking if there was an alternative solution to prevent the amputation of his limb. He was screened preoperatively for the presence of infection by clinical signs and laboratory evaluation that consisted of complete blood cell count, erythrocyte sedimentation rate and C-reactive protein levels. Furthermore, he underwent the three-phase bone scintigraphy and magnetic resonance imaging (MRI). All these tests were found to be negative for the presence of infection. Moreover, MRI helped us to determine the amount of dead bone that was present, as well as the level where the dead bone had to be removed. Over the level of the non-union, the area of less than two centimeters of the proximal femoral fragment was found to be non-vital in contrast with the distal femoral fragment, which was found to be more than 80% dead. Additionally, new imaging tests (computed tomography and x-rays) of his left femur and knee were done **(Figures 1 and 2)**. Resection of the distal third of the left femur, distal to the level of the

Figure 3. Intra-operative application of intramedullary segmental defect bridging knee arthrodesis system
Slika 3*. Intraoperativna aplikacija unutarkoštanog sistema za premošćavanje defekta i ukočenje zgloba kolena*

non-union, was performed via the anteromedial approach. Two centimeters of the proximal femoral fragment, the patella and the proximal five millimeters of the upper tibia were also removed. This resulted in a twelve centimeter bone defect, which was reconstructed using an Osteobridge Extended System PLUS Knee Arthrodesis. All implant components of this system are made of titanium alloy (TiAl6V4), which ensures biological integration of the prosthesis into the bone structure [4]. Bridging of the defect and knee joint was achieved using two metallic spacers of five centimeters (angled at ten degrees of flexion and five degrees of valgus) and seven centimeters in length, which were connected with a spacer connector. Two intramedullary nails were used in order to anchor the implant to both the femur and tibia. These nails were statically locked into the bone using two interlocking screws at each of them. The spacers were assembled with their interconnectors in situ with the nails and each one of them was secured to the adjacent one with eight screws according to the manufacturer's instructions **(Figure 3)**. The surgical time was two hours and fifteen minutes and the patient lost about four hundred milliliters of blood. Neither limb length discrepancy nor intraoperative complications were recorded. The intensive rehabilitation program began three days after the operation. Passive and active exercises of both hip and ankle joints and muscular strengthening were performed for six weeks. Partial weight bearing was instructed after the fifth postoperative day, which was switched to full weight bearing in eight weeks. The follow-up protocol, which was based on clinical, functional (Knee Society Score) [14] and radiological findings, included interval assessments after one, three, six, 12 and 24 months postoperatively. The patient's Knee Society Score was 70 and the Knee Function Score was 90 24 months after the operation. He was able to walk for a long distance and get up from sitting position without pain or support, with no evidence of periprosthetic infection and without radiological findings of implant loosening or breakage **(Figures 4 and 5)**. Generally, he was completely satisfied with the results of the operation and returned to work and his daily activities.

Discussion

Osteobridge is a knee arthrodesis system which serves as an implant for bridging large bone defects, after resection of the distal femur and proximal tibia. It provides intra-operative modularity, limb length restoration, simple handling, short-time surgery, analgesia, low complication rate, stability, immediate mobilization, rapid rehabilitation and early weight-bearing [15, 16]. Extra stability is provided by the roughened titanium surface of the prosthesis stem, which stimulates osseointegration [4]. The position of the knee joint

Figure 4. Antero-posterior radiograph of both femurs and knees 24 months postoperatively
Slika 4. *Antero-posteriorni rendgenski snimak obe butne kosti i kolena 24 meseca posle operacije*

Figure 5. Lateral radiograph of the distal third of the left femur and knee 24 months postoperatively
Slika 5. *Lateralni rendgenski snimak distalne trećine leve butne kosti i kolena 24 meseca posle operacije*

(extension/flexion, varus/valgus) can be adjusted by rotation of the angled spacer [4]. Hollow spacer shells can be used as the carriers of antibiotics and bone grafts for the active stimulation of bone growth [4].

Compared with other techniques, such as the use of free vascularized fibular graft alone or in combination with allograft and with bone transport distraction osteogenesis, the application of Osteobridge seems to be an easier technique, which enables shorter treatment duration, better functional results, earlier weight-bearing and lower complication rate [10, 12, 17–19]. In the reported case, the Osteobridge Knee Arthrodesis System was preferred to a custom-made mega-prosthesis or an Ilizarov frame with the technique of bi/unipolar segment transport. A custom-made mega-prosthesis requires good functioning of the extensor mechanism of the knee [20]. Since there was a complete failure of the knee extensor mechanism in this patient, the use of a custom-made mega-prosthesis was excluded. On the other hand, the authors believed that the application of an Ilizarov frame and the bone transport distraction osteogenesis technique would not be reliable because the distal femoral bony fragment was found to be non-vital more than 80% according to the MRI findings. In this case, the modularity of the Osteobridge provided the straightforward and simple reconstruction system of a twelve centimeter bone defect and at the same time a stable knee arthrodesis system. The leg length was easily restored without the need for extensive pre-operative planning or the need of expensive custom-made mega-prostheses.

The advantages and the effectiveness of the Osteobridge system are mentioned in other studies in the literature as well. Mavrogenis AF et al. reported excellent oncological and functional results and no complications using Osteobridge in the treatment of a patient with adamantinoma of the tibia [4]. The results of two studies conducted by Sakellariou et al. supported the use of the Osteobridge technique [21, 22]. These studies suggest a promising future for the Osteobridge system. However, studies examining the long-term postoperative results of its use are scarce. Severe mechanical complications, such as loosening or breakage, have been reported in long-term follow-up studies with the use of other intercalary endoprosthesis [16]. In case of Osteobridge, we cannot be sure of possible disadvantages or future complications of this system without long-term follow-up and studies with larger patient populations.

Conclusion

No intra-operative or post-operative complications were recorded after the application of the Osteobridge Knee Arthrodesis System in this patient. No limb length discrepancy was observed. Full weight-bearing without pain or support were achieved eight weeks after the operation and the patient returned to his normal daily activities. He had good clinical (Knee Society Score 70), and extremely good functional (Knee Function Score 90) and radiological results 24 months after surgery at the last check-up.

Consequently, we believe that the Osteobridge Knee Arthrodesis System is an excellent lower limb salvage technique, which is preferable to other methods in case of the distal femur resection, along with the failure of the knee extensor mechanism.

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Rad je primljen 19. V 2015.
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Case report
Prikaz slučaja
UDK 618.33-091.8 i 618.25-007-091.5
DOI: 10.2298/MPNS1512410I

PENTALOGY OF CANTRELL IN TWINS: A CASE REPORT

KANTRELOVA PENTALOGIJA U BLIZANAČKOJ TRUDNOĆI: PRIKAZ SLUČAJA

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Summary

Introduction. Pentalogy of Cantrell is a very rare congenital multiple malformation with the poor outcome. Syndrome included the following pentad: abdominal wall defect, a defect of the lower sternum, anterior diaphragm defect, ectopia cordis, as well as a variety of intracardiac anomalies. **Case Report.** In the fifteenth week of the twin pregnancy, ultrasound examination showed multiple anomalies in one, as well as the absence of the nose apex in the other twin. The autopsy of the fetuses was performed after the abortion had been approved by the Ethics Committee. The external examination of the fetus number one showed ectopic heart and omphalocele. The internal examination revealed the existence of sternum cleft, ectopic heart and part of the left lung outside the thoracic cavity, the presence of diaphragmatic hernia with protrusion of abdominal organs, heart with only one large vessel and the horseshoe kidney. The full expression of the Pentalogy of Cantrell was confirmed. The external and internal examination of the other twin showed just agenesis of the nose apex. **Conclusion**. Recognition and diagnosis of the syndrome is of the exceptional importance. Proper and timely diagnosis should contribute to good outcome of the pregnancy and delivery.

Key words: Pentalogy of Cantrell; Prenatal Diagnosis; Ultrasonography, Prenatal; Twins; Pregnancy, Twin; Aborted Fetus; Abortion, Induced; Autopsy; Abnormalities, Multiple

Sažetak

Uvod. Kantrelova pentalogija je izuzetno retka kongenitalna multipla anomalija sa lošim ishodom. Sindrom se sastoji od sledeće pentade: defekt abdominalnog zida, defekt donjeg dela sternuma, defekt prednjeg dela dijafragme, ektopija srca, kao i različiti oblici srčanih anomalija. **Prikaz slučaja.** U petnaestoj nedelji blizanačke trudnoće, ultrazvučni pregled pokazao je multiple anomalije jednog i nedostatak vrha nosa drugog blizanca. Nakon abortusa, koji je odobrio Etički komitet, izvršena je autopsija oba fetusa. Spoljašnjim pregledom fetusa broj jedan nađeno je ektopično srce i omfalokela. Unutrašnji pregled pokazao je postojanje rascepa sternuma, ektopično srce, kao i deo levog plućnog krila, postojanje hernije dijafragme sa protruzijom abdominalnih organa, srce sa samo jednim velikim krvnim sudom i potkovičaste bubrege. Potpuna ekspresija Kantrelove pentalogije je potvrđena. Spoljašnjim i unutrašnjim pregledom drugog blizanca konstatovana je samo ageneza vrha nosa. **Zaključak.** Prepoznavanje i dijagnostikovanje sindroma je izuzetno važno. Pravovremeno postavljanje dijagnoze doprineće adekvatnom praćenju trudnoće i samog porođaja.

Ključne reči: Petalogija Kantrel; Prenatalna dijagnostika; Prenatalna ultrasonografija; Blizanci; Blizanačka trudnoća; Abortirani fetus; Indukovani abortus; Autopsija; Multiple malformacije

Introduction

Cantrell et al. reported five cases of the syndrome named the Pentology of Cantrell (PC) in 1958 [1]. PC is a very rare congenital multiple malformation with the poor outcome. PC included the following pentad: abdominal wall defect, a defect of the lower sternum, anterior diaphragm defect, ectopia cordis, as well as a variety of intracardiac anomalies [1]. The exact cause of syndrome is not known. According to the description, it is associated with chromosomal disorders in some cases. Variants of PC without some of the five main anomalies listed above are more frequently described in literature [2, 3]. The full PC with all anomalies presented is extremely rare, and even less frequent in twins [2, 3]. It could be associated with some cranial and facial anomalies, clubfeet, malrotation of the colon, hydrocephalus and anencephaly [2, 3]. We report a case of the complete PC in the twin pregnancy. The malformation was diagnosed prenatally in the second trimester of the pregnancy in one of the twins, and the other one had agenesis of the nasal apex. PC in this case was combined with the kidney malformation.

Case Report

A pregnant woman underwent a routine ultrasound examination in the fifteenth week of the twin pregnancy, which showed multiple anomalies in one of the twins, as well as the absence of the nose apex

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in the other one. The induced abortion was approved by the Ethics Committee.

The Autopsy of the Fetus Number One

The external examination of the fetus number one demonstrated the ectopic heart and omphalocele **(Figure 1).** The internal examination showed the existence of sternum cleft, ectopic heart and part of the left lung outside the thoracic cavity, the presence of diaphragmatic hernia with protrusion of the spleen, a part of the stomach, small intestine and colon into the chest cavity. Further examination of the chest cavity showed the pericardium, and reduced size of the heart for that gestational age. The heart had only one large vessel. Both lungs were reduced in size. The abdominal cavity had inadequate organ position due to the presence of omphalocele at the base of the umbilical cord, with the content of the liver, part of the small intestine and colon. The liver, spleen and stomach were reduced in size. The horseshoe kidney was also found as an associated malformation.

The Autopsy of the Fetus Number Two

The external examination of the fetus number two showed the absence of the nose apex without any other malformations observed. The internal examination of the same twin proved the absence of any other anomaly.

Discussion

The etiology of PC is not precisely defined. It is believed that errors in the early embryonic development of the mesoderm occurring between the 14th and 18th days of gestation result in PC. Pentalogy of Cantrell can be caused by vascular dysplasia, as well as mechanical teratogens, genetic mutations or a viral infection in the first trimester of pregnancy [4]. Some PC cases have been reported in the consanguineous parents [5].

In 1972, Toyama classified 61 previously described cases of PC into three classes: Class 1- the presence of all five described defects; Class 2 - the presence of four defects with obligatory presence of intracardiac anomalies and defects of the anterior abdominal wall; Class 3-incomplete expression with a different combination of anomalies and the always present abnormality of the sternum [6]. Our case is the originally described syndrome of Class 1. Since the syndrome was diagnosed in a twin pregnancy, it is very rare, having been described only in few cases in the literature [7, 8].

Anomalies which are according to the literature associated with Pentalogy of Cantrell are: agenesis of the corpus callosum, hydrocephalus, anencephaly, lip and palate cleft, fusion of the adrenal gland with liver, colon malrotation, clinodactily [9, 10], the absence of tibia and radius, polysplenia, underdevelopment of the gallbladder [11]. An association with renal anomalies is described only in a few cases: the right kidney agenesis [12], dysplasia of the left kidney and the right kidney pyeloectasis [13], left kidney agenesis [14]. A horseshoe kidney, which is a part of the reported case, is the anomaly which has not been described so far as a part of PC.

Figure 1. External examination of the twin number one-ectopic heart and omphalocele
Slika 1. *Spoljašnji pregled blizanca broj 1 – ektopično srce i omfalokela*

Pentology of Cantrell can be diagnosed in the tenth gestational week at the earliest. The diagnosis can be made by 2D ultrasonography, as well as by 3D ultrasound, which is an additional method of assistance [15]. According to Toyama classes, there is a possibility of a little more difficulties in making the diagnosis if anomalies are not so extensive and easily recognized. In such cases, it is helpful to use magnetic resonance [15, 16]. The prognosis of PC depends on the presence of the anomalies, and the most difficult cases are lethal before the end of pregnancy, some newborns survive a few hours or days, but lethal outcome is certain without surgical intervention [16].

Conclusion

Recognition and diagnosis of the syndrome is of the exceptional importance. Proper and timely diagnosis could direct outcome of the pregnancy. If the anomalies are of such an extent that the life of a newborn is endangered, then the doctors should induce delivery and get ready to perform appropriate surgical interventions.

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Rad je primljen 23. VI 2015.
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Case report
Prikaz slučaja
UDK 616.34-006.3-091.8
DOI: 10.2298/MPNS1512413J

LEIOMYOSARCOMA OF THE COLON

LEJOMIOSARKOM DEBELOG CREVA

Vlado JANEVSKI[1], Redžep SELMANI[1], Vesna JANEVSKA[2], Liljana SPASEVSKA[2] and Julija ZHIVADINOVIK[3]

Summary

Introduction. Gastrointestinal stromal tumors are the most common mesenchymal tumors of the digestive tract. Leiomyosarcomas of the gastrointestinal tract are rare mesenchymal neoplasms which grossly and histologically resemble gastrointestinal stromal tumors. They may be differentiated from gastrointestinal stromal tumors by using immunohistochemistry and they are typically positive for α smooth muscle actin and desmin and negative for c-kit, CD34 and DOG1.1. They often express calponin and h-caldesmon. **Case Report.** We present a case of a 59-year-old male with anemia, weight loss, intermittent abdominal pain and right abdominal mass. Colonoscopy revealed an exophytic ulcerated neoplastic mass in the ascending colon and abdominal computed tomography scan showed an ill-defined heterogeneous tumor mass which surrounded almost the whole ascending colon. The patient underwent right hemicolectomy and partial resection of ileum. Histopathological examination revealed a leiomyosarcoma composed of atypical spindle cells positive for α smooth muscle actin, desmin and vimentin, and negative for c-kit, CD34, S100 and neuron specific enolase. The patient is alive 8 months after the operation, undergoing chemotherapy. **Conclusion.** We have concluded that the multimodal approach comprising chemotherapy and complete surgical resection controls the leiomyosarcomas.

Key words: Gastrointestinal Stromal Tumors; Leiomyosarcoma; Diagnosis, Differential; Diagnosis; Immunohistochemistry; Morphological and Microscopic Findings; Signs and Symptoms; Combined Modality Therapy; Tumor Markers, Biological; Actins; Desmin; Proto-Oncogene Proteins c-kit

Sažetak

Uvod. Gastrointestinalni stromalni tumori najčešći su mezenhimalni tumori digestivnog trakta. Lejomiosarkomi gastrointestinalnog trakta retke su mezenhimalne neoplazme koje makroskopski i histološki nalikuju gastrointestinalnim stromalnim tumorima. Lejomiosarkomi se mogu razlikovati od gastrointestinalnih stromalnih tumora upotrebom imunohistohemije i tipično su pozitivni za α-*smooth muscle actin* i desmin, a negativni za c-kit, CD34 i DOG1.1. Lejomiosarkomi obično pokazuju ekspresiju za kalponin i h-kaldezmon. **Prikaz slučaja.** Prikazujemo slučaj 59-godišnjeg pacijenata sa anemijom, gubitkom težine, povremenim bolom u stomaku i prisutnom abdominalnom masom. Kolonoskopija je pokazala egzofitičnu, ulcerisanu neoplastičnu masu u ascendentnom kolonu, a abdominalna kompjuterizovana tomografija je pokazala slabo ograničenu heterogenu tumorsku masu koja je okruživala skoro ceo ascendentni kolon. Pacijentu je urađena desna hemikolektomija i parcijalna resekcija ileuma. Histološkom analizom je dijagnostikovan lejomiosarkom, građen od atipičnih vretenoidnih ćelija, pozitivnih za α-*smooth muscle actin*, desmin i vimentin i negativnih za c-kit, CD34, S100 i *neuron specific enolase*. Pacijent je još uvek živ 8 meseci nakon operacije, sa hemoterapijom u toku. **Zaključak**. Zaključili smo da multimodalni pristup koji obuhvata hemoterapiju i kompletnu hiruršku resekciju kontroliše lejomiosarkome.

Ključne reči: Gastrointestinalni stromalni tumori; Lejomiosarkom; Diferencijalna dijagnoza; Dijagnoza; Imunohistohemija; Morfološki i mikroskopski nalazi; Znaci i simptomi; Kombinovana terapija; Tumor markeri; Aktin; Desmin; Proto-onkogen c-kit

Introduction

Primary mesenchymal tumors of the gastrointestinal tract (GIT) are rarely seen, representing only 0.1%-3% of all gastrointestinal cancers [1]. Leiomyosarcomas (LMS) of GIT are extremely rare mesenchymal neoplasms which account for 0.12% of colon cancers. Only a few reports have been published on GIT mesenchymal tumors [2–4].

Grossly and histologically, LMS resemble gastrointestinal stromal tumors (GIST). They may be differentiated from GIST by using immunohistochemistry and they are typically positive for α smooth muscle actin (SMA) and desmin and negative for c-kit, CD34 and DOG1. They often express calponin and h-caldesmon [5].

Leiomyosarcoma is an aggressive tumor with a high local recurrence rate as well as significant hematogenous spread. A treatment protocol has not been established due to limited patient population and a lack of prospective randomized clinical trials. After complete resection, the most common treatment approach is anthracycline-based adjuvant chemotherapy for patients with large tumor size and high-grade tu-

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Abbreviations

GIT	– gastrointestinal tract
LMS	– leiomyosarcomas
GIST	– gastrointestinal stromal tumors
HPFs	– high-power fields
SMA	– smooth muscle actin
HE	– hematoxylin and eosin
NSE	– neuron specific enolase
EMA	– epithelial membrane antigen
LMs	– leiomyomas
RT	– radiation therapy
CT	– computed tomography

mors [1]. Radiotherapy is a less effective treatment in leiomyosarcoma of the gastrointestinal tract. However, it has been reported that leiomyosarcoma can develop after radiotherapy [1].

The prognosis of LMS cannot be histologically predicted and, on the basis of the relatively small series, may be better than that in patients with GISTs with similarly high mitotic counts. The colonic GISTs included small (≤ 1 cm), incidentally detected tumors clinically indolent after enucleation. Tumors exceeding 1 cm that had low mitotic activity (five or fewer mitoses per 50 high-power fields - HPFs) usually showed the benign behavior. Tumor size of 5 cm or less and mitotic activity of five mitoses or fewer per 50 HPFs were prognostically favorable factors in univariate analysis. Colonic GISTs with mitotic activity higher than five mitoses per 50 HPFs appeared uniformly lethal. Although low mitotic rate does not guarantee the benign behavior, these findings support mitotic activity being the most reliable histologic criterion for dividing benign from malignant stromal tumors [4].

Case Report

A 59-year-old male presented with anemia, weight loss, intermittent abdominal pain and right abdominal mass. He decided to seek medical help when he felt weakness and found a lump in his abdomen.

Colonoscopy revealed an exophytic ulcerated neoplastic mass in the ascending colon and abdominal computed tomography (CT) scan showed an ill-defined heterogeneous tumor mass which surrounded almost the whole ascending colon **(Figure 1)**. The neoplasm infiltrated the lateral abdominal wall.

The patient underwent right hemicolectomy and partial resection of ileum.

After standard dissection protocol of the surgically resected specimen, histological examination was done. The obtained tissue specimens were formalin fixed, paraffin embedded and analyzed with routine hematoxylin and eosin (HE) stains. Additional immunohistochemical analysis was performed with SMA, desmin, vimentin, c-kit, CD34, S100 and neuron specific enolase (NSE).

A tumor located 2.5 cm proximal to the ileocecal valve measuring 10 x 9 cm incorporated in itself almost the whole ascending colon. There was a fragment of skeletal muscle adhered to the proximal right and anterior part of the ascending colon (5 cm long and 4 cm wide). A large ulceration of the mucosa measuring 2 cm in diameter was seen after opening the bowel. The serial sections of the tumor showed a tumor mass in the bowel wall, most of it being extraluminal along with a compact gray – pink to reddish tumor tissue with moderately by firm consistency and areas of hemorrhage and necrosis.

Figure 1. CT scan of the neoplasm. An ill- defined heterogeneous tumor mass surrounds almost the whole ascending colon

Slika 1. *Kompjuterizovana tomografija neoplazme. Slabo ograničena heterogena tumorska masa koja okružuje skoro ceo ascendentni kolon*

Twenty one lymph nodes with dimensions from 0.5 to 1.5 cm were isolated from the mesocolic and pericolic fat.

Histopathological examination revealed a highly cellular stromal cell neoplasm composed of atypical spindle cells with a low mitotic index; <5 mitotic figures/50 HPFs. The tumor cells had abundant eosinophilic cytoplasm and were arranged in parallel and whorl-like bundles **(Figures 2 and 3).**

Following immunohistochemistry, the neoplasm was diagnosed as leiomyosarcoma, positive for SMA, desmin and vimentin, and negative for c-kit, CD34, S100 and NSE **(Figures 4, 5 and 6).**

No lymph node metastases were found.

The patient is alive 8 months after the operation, undergoing chemotherapy.

Discussion

Gastrointestinal LMS originate in the smooth muscle cells of the intestinal wall and are most often located in stomach and small intestine [6, 7]. There are relatively few reports on leiomyosarcoma with the pri-

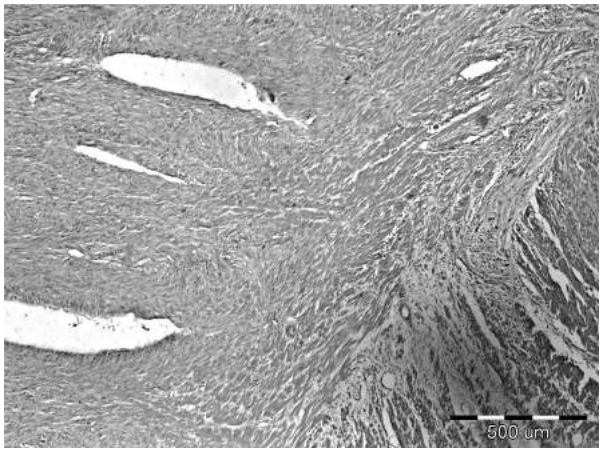

Figure 2. Leiomyosarcoma arising from tunica muscularis propria of the colon. A part of tunica muscularis propria can be seen in the bottom right corner and the neoplasm arising from it is shown in the rest of the photo (H.E 4 x10)
Slika 2. *Lejomiosarkom koji potiče iz tunike muskularis proprije kolona. Deo tunike muskularis proprije se može videti u donjem desnom uglu, a neoplazma koja potiče iz nje je prikazana u ostatku slike (H.E 4 x 10).*

mary occurrence in esophagus, colon and rectum [6]. They develop mainly in the fifth and sixth decade of life. Intestinal leiomyosarcoma spreads hematologically, mostly to the liver and peritoneum and less frequently to the lung. Lymph node metastasis is rare. The size and histological grade of the neoplasm are believed to affect the survival of patients with intestinal leiomyosarcoma. The prognosis ranges from fatal to poor [6].

The presenting symptoms and endoscopic findings may be nonspecific [8]. The most common symptom is abdominal pain, but an abdominal palpable mass, intestinal rhythm alteration or complications as hemorrhage, perforation or obstruction may also be present [9–12]. On imaging studies, the tumor margin can be

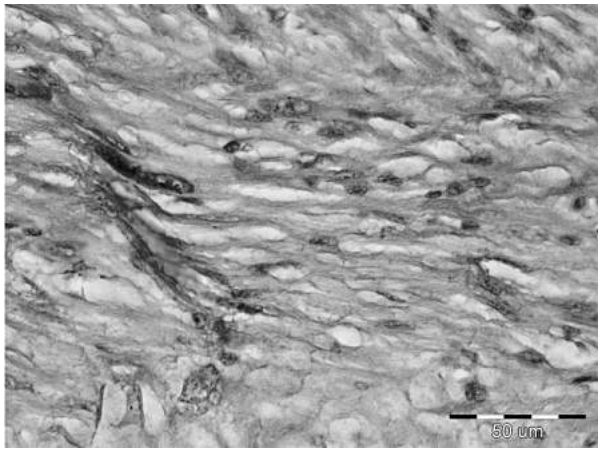

Figure 3. The same tumor at high magnification showing cellular atypia
Slika 3. *Isti tumor na većem povećanju pokazuje celularnu atipiju*

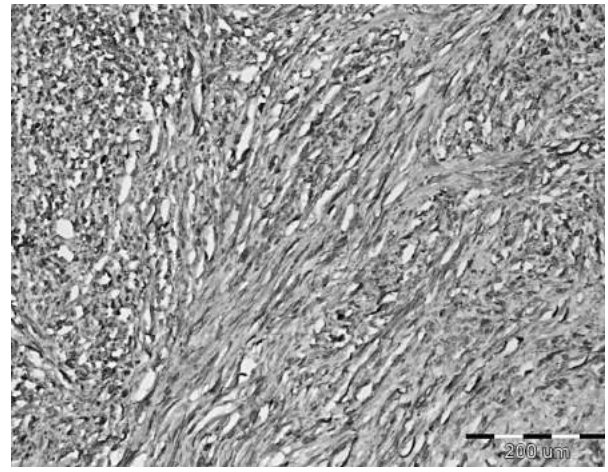

Figure 4. Leiomiosarcoma showing positive α smooth muscle actin immunohistochemical staining (αSMA 10x20)
Slika 4. *Lejomiosarkom pokazuje pozitivno imunohistohemijsko bojenje za α-smooth muscle actin (αSMA 10 x 20).*

smooth or lobulated, with endocolic, exocolic or combined growth. Internal necrosis and dystrophic calcification can be noted. Diagnosis is based on the histological and immunohistochemical study of the surgical specimen [13].

Histological diagnosis of leiomyosarcoma is made when the neoplasm consists of spindle-shaped cells grouped in bundles and exhibiting a storiform and pallisading appearance. The nuclei display pleomorphic characteristics as well as atypia. Additionally, immunohistochemical staining can elucidate the tumor type.

Smooth muscle actin, desmin and h-caldesmon are positive in great majority of leiomyosrcomas. Vimentin, which is a mesenchimal cell marker and nonspecific marker of smooth muscle, is also positive.

Desmin can be used to make distinction between well and poorly differentiated tumors; desmin is present in well-differentiated tumors and negative in

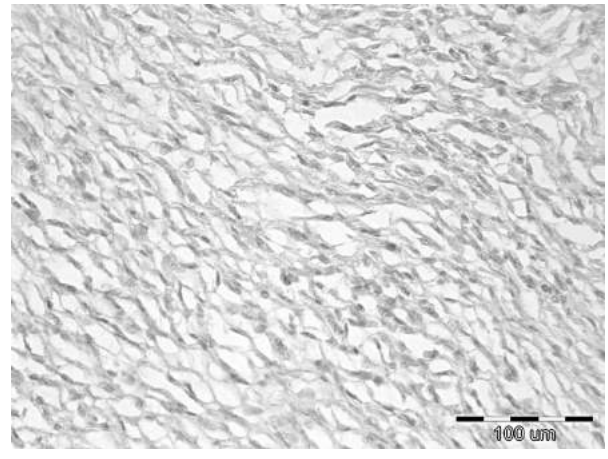

Figure 5. Leiomiosarcoma showing negative CD117 immunohistochemical staining (CD117 10x20)
Slika 5. *Lejomiosarkom pokazuje negativno imunohistohemijsko bojenje za CD117 (CD117 10 x 20).*

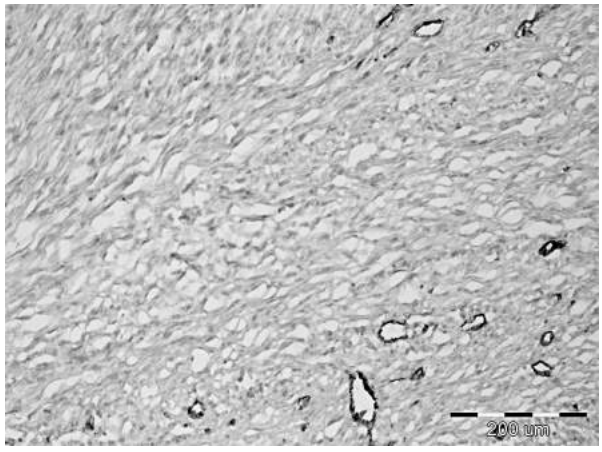

Figure 6. Leiomiosarcoma showing negative CD34 immunohistochemical staining (CD34 10x10)
Slika 6. *Lejomiosarkom pokazuje negativno imunohistohemijsko bojenje za CD34 (CD34 10 x 10).*

poorly differentiated tumors or poorly differentiated areas. SMA can show similar distribution of positive stain. Epithelial membrane antigen (EMA), CD34 and S-100 may be focally positive in some tumors. Staining for S100 receptors can be used to exclude malignant melanoma and neural tumors [14].

The neoplasm is considered a high-grade malignancy when more than 5 mitotic figures per 10 HPFs are found [6].

Aggressive behavior is usually found in tumors with greater than 10 mitoses/10 HPFs [14].

Definitive methods to differentiate LMS from GIST were introduced in the late 1990s, exactly in 1998 when Hirota et al. described the presence of an activating mutation of KIT a tyrosine kinase receptor proto oncogene, resulting in expression of KIT protein almost in about 94% of GIST. Leiomyomas (LMs) and LMSs are nowadays differentiated from GIST and thought to be rare in the GIT, except in the esophagus and muscle mucosa of colon and rectum where leiomyomas are the most common mesenchymal tumors [15–18].

Gastrointestinal stromal tumors constitute the most common mesenchymal tumors of the stomach and small intestine, whereas typical LMs are more common in the esophagus [4, 17]. The GISTs are usually positive for CD117 (KIT), which is perhaps the best defining feature of this specific group of tumors. Many of them, especially the malignant tumors, have also mutations in the exon 11 of the c-kit gene. In comparison, true LMs and leiomyosarcomas (LMSs), comparable to retroperitoneal or vascular LMSs, are negative for CD117 and positive for smooth muscle actin, desmin, or both. Such tumors appear to be rare, at least in the upper gastrointestinal tract [4, 17].

In differential diagnosis, tumors that must be separated from LMSs and colonic GISTs include the uterine-type LMs attached to the colon but arising externally to it (uniformly positive for actin and desmin), inflammatory myofibroblastic tumors (negative for CD117) and inflammatory fibrosarcoma, liposarcoma adherent to the colon (negative for CD117), and schwannoma (diffusely positive for S-100 protein and negative for CD117 and CD34) [4].

The possibility of metastatic LMS from other sites must also be considered.

The prognosis of true LMS cannot be predicted histologically.

The predominant intraluminal growth of the LMSs and their possibly earlier presentation by bleeding than that of the GISTs may contribute to a more favorable prognosis in some cases.

For the definitive treatment of LMS a surgeon must be involved. A hematologist/oncologist may be able to provide insights into the prognosis, define the grade of the tumor and offer possible chemotherapy. A radiation oncologist may be able to provide insight into possible preoperative, intraoperative, and/or postoperative radiation therapy (RT) [6]. Surgery remains the primary treatment for leiomyosarcoma. Leiomyosarcoma is an aggressive tumor with a high local recurrence rate as well as significant hematogenous spread, the liver being the most affected place whereas the lung metastases are infrequent. Recurrence after radical surgery is around 40%.

Due to its rarity and the scarce published data, the treatment for LMS of the large intestine is controversial. Chemotherapy generally plays a limited role in the treatment of LMS. A specific molecular therapy is currently available for GIST, but not for LMS. Reports indicate that 30–60% of clinical response rates can be achieved in the treatment of LMS using combinations of docetaxel and gemcitabine [2], and in the treatment of advanced soft tissue sarcoma using ifosfamide with anthracycline and/or dacarbazine [2]. According to Hamai et al. only first line chemotherapy with docetaxel and S-1 was found to be effective against both the gastric cancer and LMS. The overall response rate of this regimen is reported to be 56.3% for gastric cancer [2]. It was considered that docetaxel, which is so frequently used and effective against both LMS and gastric cancer, could simultaneously reduce the size of these tumors [2]. According to some authors, the most common treatment approach after complete resection is anthracycline-based adjuvant chemotherapy for patients with large tumor size and high-grade tumors [1]. Imatinib mesylate (Gleevec), a 2-phenylaminopyridine that functions as a tyrosine kinase inhibitor, targets the c-kit domain expressed by some GIST. It has been shown to improve disease-free intervals in patients after resection of the tumor. A similar compound, sunitinib (Sutent), has been shown to be effective in the patients with mutant GIST cells that are resistant to imatinib mesylate. Clinical trials are currently investigating agents, such as AP13573 and ET743, in patients with advanced leiomyosarcomas, liposarcomas, or osteosarcomas.

Radiotherapy is a less effective treatment in leiomyosarcoma of the gastrointestinal tract [1]. According to other authors, neither radiotherapy nor

chemotherapy has any proven efficacy as adjuvant therapies for this tumor [13].

With curative resection, the 5-year survival rate for patients with leiomyosarcoma of the small intestine is 40-50% according to Hill's review [19]. In cases in which the grade of the tumor was documented, the median survival for patients with high-grade tumors was 25 months in one study, whereas the median survival for patients with low-grade tumors was approximately 98 months [6]. A benign initial report on a resected tumor does not spare the patient from consequences because these tumors sometimes recur as malignancies-about 6% in one study [20]. In a report on the characteristics of duodenal GISTs, Miki et al. compared the clinicopathologic findings and recurrence-free survival of 7 patients with these lesions with the same data for 34 patients with GISTs of the stomach or elsewhere. The investigators determined that the rates for symptomatic lesions were 86% in the duodenum, 32% in the stomach, and 56% elsewhere, with melena and anemia being the most common symptoms associated with duodenal GISTs. The rates of 2-year recurrence-free survival among patients were 51.4% for duodenal GISTs, 78.4% for stomach GISTs, and 100% for other GISTs. Using multivariate Cox analysis, the authors concluded that in terms of GIST recurrence, significant prognostic factors included symptoms, mitotic index, and tumor location [21].

Conclusion

Leiomyosarcomas of the colon are rare but aggressive neoplasms with poor prognosis. They may be differentiated from gastrointestinal stromal tumors by using immunohistochemistry and they are typically positive for α smooth muscle actin and desmin and negative for c-kit, CD34 and DOG1.1. Treatment protocols of primary mesenchymal tumors have not been established yet. We have concluded that the multimodal approach comprising chemotherapy and complete surgical resection control the leiomyosarcomas.

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Rad je primljen 3. IV 2015.
Recenziran 30. V 2015.
Prihvaćen za štampu 15. VI 2015.
BIBLID.0025-8105:(2015):LXVIII:11-12:413-417.

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Case report
Prikaz slučaja
UDK 616.34-008.314.4-02:615.276 i
UDK 616.34-008.314.4:616.61-008.6-78
DOI: 10.2298/MPNS1512418D

COLITIS AND "DIAPHRAGM DISEASE" OF THE COLON IN HEMODIALYSIS PATIENT DUE TO PROLONGED USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUG

KOLITIS I BOLEST DIJAGRAFME KOLONA KOD PACIJENTA NA HEMODIJALIZI ZBOG DUGOTRAJNE UPOTREBE NESTROIDNOG ANTIINFLAMATORNOG LEKA

Nada DIMKOVIĆ[1,2], Danijela BOJIĆ[1,3], Petar SVORCAN[1,3], Aleksandar JANKOVIĆ[2], Petar ĐURIĆ[2] and Jelena TOŠIĆ[2]

Summary

Introduction. The use of non-steroidal anti-inflammatory drugs may lead to stricture of the small intestine and less frequently of the colon. Colonic strictures have not been described in patients on dialysis and the aim of this report is to show the case of dialysis patient who was followed for recurrent and prolonged diarrhea. **Case Report.** We present the patient on chronic dialysis for 15 years who used non-steroidal anti-inflammatory drugs due to chronic pain and who developed recurrent diarrhea. Diagnosis was made by endoscopy and confirmed by histology. Specific therapy was applied with a good response. **Conclusion.** Although not described in the literature, non-steroidal anti-inflammatory drug-induced colitis and/or diaphragm disease could be a potential reason for recurrent or prolonged diarrhea in dialysis patients.

Key words: Colitis; Colonic Diseases; Anti-Inflammatory Agents, Non-Steroidal; Renal Dialysis; Diarrhea; Chronic Disease; Diagnosis; Therapeutics; Fibrosis; Colonoscopy; Morphological and Microscopic Findings

Sažetak

Uvod. Upotreba nesteroidnih antiinflamatornih lekova može dovesti do strikture tankog creva, a ređe i kolona. Striktura kolona navedene etiologije do sada nije opisana u literaturi kod bolesnika na dijalizi te je cilj ovoga prikaza bolesnik na dijalizi koji je praćen zbog dugotrajnih proliva. **Prikaz slučaja.** Prikazan je bolesnik lečen hroničnim dijalizama 15 godina koji je koristio nesteroidne antiinflamatorne lekove usled hroničnog bola. Kod bolesnika su se razvili recidivantni i prolongirani prolivi; dijagnoza je postavljena endoskopski a potvrđena histološki. Primenjena je specifična terapija sa dobrim ishodom. **Zaključak**. Iako do sada nisu opisivani u literaturi, kolitis i/ili dijafragma kolona mogu biti uzrok recidivantnih i prolongiranih proliva zbog upotrebe nesteroidnih antiinflamatornih lekova kod bolesnika na dijalizi.

Ključne reči: Kolitis; Oboljenja kolona; Nesteroidni antiinflamatoni lekovi; Hemodijaliza; Dijareja; Hronično oboljenje; Dijagnoza; terapija; Fibroza; Kolonoskopija; Morfološki i mikroskopski nalazi

Introduction

The adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs) on the upper gastrointestinal tract and small intestine are well established. The effect of such therapy on the large intestine, the so called NSAID colopathy, is less well described. Debenham reported the first case of NSAID-induced colonic damage in 1966, highlighting a case of cecal ulceration in a patient taking oxyphenbutazone for rheumatoid arthritis [1]. Since then, the association between NSAIDs and colonic damage has become well established, albeit less well recognized than NSAID-induced gastropathy and enteropathy. Isolated case reports of NSAID colopathy range from the more acute complication of inflammation and ulceration to the more chronic picture of fibrosis and stricture formation. Since literature data are scarce, the aim of this case report is to present the patients on chronic hemodialysis with NSAID colopathy.

Case Report

A 55-year-old patient had been on regular hemodyalsis since 1996 (home hemodialysis since 2001) due to hypertensive nephrosclerosis. He was dialyzed for 5 hours, three times per week using high-flux polysilfone membranes. His co-morbid conditions included secondary hyperparathyroidism and peripheral vascular disease. Therefore, he underwent subtotal parathyroidectomy six years before and bilateral aorto-femoral bypass in January 2011. Two years letter, his peripheral vascular disease deteriorated and he developed very painful and pronounced ischemic lesions of the legs. Unbeknownst he used over the counter (OTC) drugs (Diclofenac) in high doses for several months.

Due to the secondary infection of the ischemic lesions and positive inflammatory syndrome, antibiotic treatment was prescribed to him. Soon the-

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Abbreviations
NSAID – non-steroid anti-inflamatory drugs

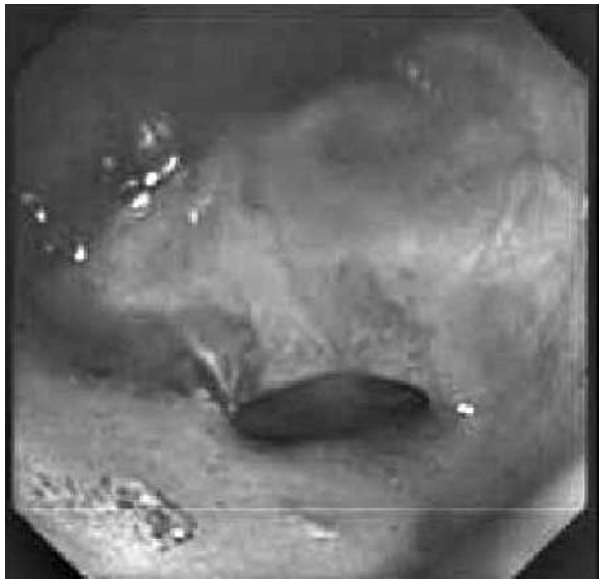

Figure 1. Stricture of the ascending colon with shallow ulcerations (Colonoscopy)
Slika 1. *Suženje ascedentnog debelog creva sa plitkim ulceracijama (kolonoskopija)*

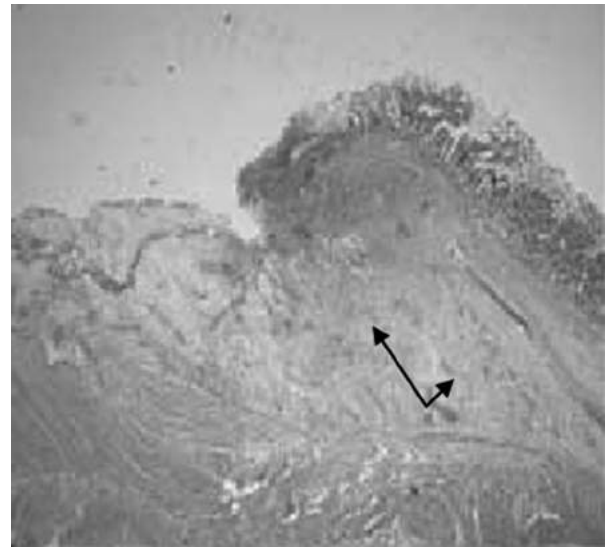

Figure 2. Histological finding of the colonic stricture: submucosal fibrosis (black arrows) and edema with moderate chronic inflammatory infiltrate in the centre of the lesion, without vasculitic changes.
Slika 2. *Histološki nalaz suženja debelog creva: submukozna fribroza (crne strelice) i edema sa umerenim hroničnim inflamatornim infiltratom u centru lezije, bez vaskulitičnih promena*

reafter he complained of diarrhea that was treated as antibiotic colitis but without clinical improvement. At that time he refused suggested colonoscopy. During 2013, the patient attended outpatient clinic repeatedly complaining of recurrent episodes of diarrhea. Laboratory analyses revealed low serum albumin (30 g/L) and iron (6.2 umol/L) levels in addition to positive inflammatory syndrome (CRP 180 mg/dl). Colonoscopy was performed in February 2014 and it confirmed a small (5 mm) polyp in the rectum, scarce inflammation of the colonic mucosa and circumferential stricture of the ascending colon (close to hepatic flexure), with a couple of small shallow ulcerations at the inner brim and surface of the stricture **(Figure 1).**

Histology confirmed colitis and "diaphragm disease" (i.e. diaphragm-like stricture) of the colon. The presence of edema with moderate chronic inflammatory infiltrate in the centre of the lesion, without vasculitis changes can be seen **(Figure 2).**

The patient was treated with oral mesalazine 3g/day for 3 months with a good clinical response. Diarrhea stopped within 10 days and hypoalbuminemia improved to 34 g/L two weeks later.

Discussion

A spectrum of symptoms within NSAID colopathy is a relevant differential diagnosis when encountering a patient presenting with classical symptoms of colon cancer or an inflammatory bowel disease. Although the effect of NSAIDs is not likely to be dose related, our patients were taking doses between 50 mg to 150mg daily for several months and it is possible that the duration of treatment was highly significant demonstrating a temporal relationship between drug administration and the spectrum of endoscopic findings. Colonic strictures are more frequent in the right colon [2], as was the case in our patient.

Pathophysiology and factors predisposing the location of such colonic strictures are not entirely elucidated. The use of NSAID affects the metabolism of arachidonic acid in favor of proinflammatory prostaglandin production, which then induces mucosal damage (usually in terminal ileum and colon). It triggers an inflammatory chain reaction by attracting the neutrophils in the mucosa and submucosa with the consequent erosions and/or ulcerations [3]. As submucosal inflammation matures into collagenous tissue, strictures develop at the sites of healed ulcers. Colonic ulceration is thought to be one of the early stages of stricture formation [4]. Ulceration and stricture formation predominate within the ascending colon, and are thought to be due to the increased use of slow-release formulations of NSAID [5, 6], designed for absorption in the distal parts of digestive tube, thus avoiding NSAID-related damage of the stomach and duodenum. The reports on rectal bleeding, ulceration and local stenosis due to the use of NSAID suppository preparations support the direct/topical mode of action [7].

Through systemic action, NSAIDS can increase the permeability of bowel mucosa [8, 9] (confirmed by scintigraphy with radioactive marker) as well, which induces increased protein losing into the bowel. This

often results in clinically overt diarrhea with a decreased serum albumin level, which was the case with our patient.

It is hypothesized that NSAIDs induce subtle intracellular events, such as increased fragility of lysosomes and decreased oxidative phosphorylation, resulting in accelerated apoptosis [10]. This contributes to increased local irritation of bowel mucosa and subsequent local and systemic NSAID adverse events.

NSAID related colitis is not a common finding in patients on hemodialysis. They are prone to digestive bleeding and these drugs are avoided. Perhaps this is the reason why NSAIDs colitis is rarely described in the nephrology literature. This case can remind doctors that NSAIDs may be the cause of chronic diarrhea in patients on hemodialysis thus shortening the precious time needed for making diagnosis.

Treatment recommendation is to stop NSAID use (if necessary switch to cyclooxygenase-2 (COX-2) inhibitors) and to start oral mesalazine 3 g/day for 3 months in patients with diarrhea (as we did in our patient) or steroids p.o. for 3 weeks [11, 12]. In case of bowel occlusion due to diaphragm, balloon dilatation or surgery is indicated [12]. Fortunately, our patients had a good response to mesalazine.

Conclusion

When a patient on chronic hemodyalisis program and on prolonged non-steroidal anti-inflammatory drug therapy presents with chronic or recurrent diarrhea, it is useful to think of non-steroidal anti-inflammatory drug colitis and/or diaphragm disease as a possible differential diagnosis. With the increasing use of enteric coated and sustained release non-steroidal anti-inflammatory drug preparations this condition is likely to become more frequent. Increasing awareness of its clinical presentation and of its spectrum of endoscopic findings facilitates a more prompt diagnosis and appropriate treatment to be established, thus avoiding potential toxic effects of other treatments.

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Rad je primljen 15. XI 2014.
Recenziran 19. VII 2015.
Prihvaćen za štampu 24. VII 2015.
BIBLID.0025-8105:(2015):LXVIII:11-12:418-420.

REGISTAR ZA 2015. GODINU

INDEKS AUTORA

INDEKS KLJUČNIH REČI

INDEX KEY WORDS

Štampu ovog časopisa ”Medicinski pregled”
pomogla je **Vlada AP Vojvodine**

Printing of this journal ”Medical Review”
has been supported by
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∗ *Organizacija kao autor*

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

∗ *Nisu navedena imena autora*

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

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

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

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

Knjige i druge monografije:

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

∗ *Poglavlje u knjizi*

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

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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.

∗ *Disertacije i teze*

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

Elektronski materijal

∗ *Članak u Časopisu u elektronskoj formi*

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

∗ *Monografije u elektronskoj formi*

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

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

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

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

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

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

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

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

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

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

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

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

– No names, initials or case history numbers should be given.

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

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

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

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

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

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

5. References. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by et 'al'.

Articles in journals

∗ *A standard article*

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

∗ *An organisation as the author*

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

∗ *No author given*

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

∗ *A volume with supplement*

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

∗ *An issue with supplement*

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

∗ *A summary in a journal*

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

Books and other monographs

∗ *One or more authors*

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

∗ *Editor(s) as author(s)*

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

∗ *A chapter in a book*

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

∗ *A conference paper*

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

∗ *A dissertation and theses*

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

Electronic material

∗ *A journal article in electronic format*

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

∗ *Monographs in electronic format*

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

∗ *Acomputer file*

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

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

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

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

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

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

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

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

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in colour, they will have to pay additional cost.

7. Manuscript submission

The manuscripts can be submited on the web-page: **aseestant.ceon.rs/index.php/medpreg/**. The authors have to register with the journal prior to submitting their manuscript, or, if already registered, they can simply log in and begin the 5 step process.

8. Additional requirements

If the author and all co-authors have failed to pay the subscription for Medical Review, their paper will not be published.

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