Izdavačka delatnost Društva lekara Vojvodine Srpskog lekarskog društva, Novi Sad, Vase Stajića 9
Glavni i odgovorni urednik: prof. dr GORDANA DEVEČERSKI

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Publishing Sector of the Society of Physicians of Vojvodina of the Medical Society of Serbia, Novi Sad, Vase Stajica 9,
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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 700 copies. Advance payment for individuals from the territory of Serbia for the year 2013 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 the 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

M E D I C I N S K I P R E G L E D
ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA
Novi Sad Vase Stajića 9 Srbija

Med Pregl 2013; LXVI (3-4): 113-204. Novi Sad: mart-april.

SADRŽAJ

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 2013; LXVI (3-4): 113-204. Novi Sad: March-April.

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EDITORIAL

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Uvodnik
Editorial
UDK 616.853:159.942

EPILEPSY AND AGRRESSION: PREJUDICE AND FACTS

EPILEPSIJA I AGRESIJA: PREDRASUDE I ČINJENICE

Ksenija BOŽIĆ[1,2] i Gordana MIŠIĆ PAVKOV[1,3]

The association between epilepsy, aggression and violence has been a subject of debate for decades. Early epidemiological studies reporting an increased incidence of epileptic patients among prisoners and delinquents have promoted the opinion that epileptic patients show aggression and tend to express violent behavior more frequently than the general population [1,2]. This belief has further been strengthened by descriptions of bizarre and stereotypical behaviors during certain types of epileptic seizures, especially seizures originating in the frontal lobe, as well as by the not infrequent use of epilepsy as a defense strategy for crime perpetrators.

In the 1990s this widely held opinion gradually lost its popularity among experts after several large trials had demonstrated that aggressive phenomena, including completely destructive acts, might be induced by epileptic seizures. However, they are extremely rare [3].

The results of a recent large Swedish population study reported by Fazel and colleagues in 2011 show that epilepsy does not increase the risk of criminal offences [4]. The relationship between convictions for violent crime and previously established diagnoses of epilepsy and traumatic brain injury was studied on a sample that comprised the whole Swedish population followed from 1973 to 2009. The study included 22,947 people with epilepsy. The prevalence of convictions for violence was significantly higher in people with the diagnosis of epilepsy (4.2%) compared with the general population (2.5%) (OR = 1.5, 1.4-1.7). However, this significance was lost when individuals with epilepsy were compared with their healthy siblings, which suggests that the initial significance was influenced by genetic and/or early environmental factors and not epilepsy *per se*.

Yet, in spite of the evidence that violence during and between epileptic seizures is rare, negative stereotypes about epilepsy are still prevalent [5]. There is a common misbelief that aggression and violence are possible or likely during seizures and that individuals with epilepsy are dangerous and potentially violent, which increases stigmatization and discrimination of these patients.

Aggression and Epileptic Seizures

With regard to the time of occurrence, aggression in persons with epilepsy can occur during a seizure (ictal), before and after a seizure (periictal: pre-and postictal), and between seizures (interictal) [6].

Ictal Aggression

Ictal aggression is very rare. Literature data about ictal aggression are sparse and based mainly on reports of individual patients with frontal or temporal epileptic lesions [7-10].

In a large clinical series that included 5400 patients with epilepsy, aggressive behavior was recorded in 19 patients, and violent behavior during a seizure was observed in 13 [3]. In most cases aggression and violence during ictal electroencephalographic (EEG) discharges (ictal aggression) was non-motivated and unplanned, and in none of the cases was it associated with purposeful movements. In some cases, the patients demonstrated defensive aggression during another person's attempts to calm them down during or immediately after the seizure. Direct (directed) ictal aggression was extremely rare.

When aggressive behavior is a feature of an epileptic seizure, an aggressive act must be accompanied by typical characteristics of a seizure: a seizure starts suddenly without provocation, lasts a short time (1-3 minutes) and ends abruptly with a violent act which manifests in the context of impaired consciousness with consequent amne-

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Abbreviations
PIP – postictal psychosis
EEG – electroencephalographic

sia. Witnesses of the seizure may notice the person's confusion and fixed, glassy eyes. This aggressive behavior is completely void of rational elements. It usually occurs during complex focal seizures with stereotypical phenomena. Generalized seizures, either primary or secondary, may be associated with a violent act, but directed aggression cannot occur during convulsions. In order to confirm the epileptic nature of an aggressive act, aggression during epileptic automatism should be documented by video-EEG monitoring.

Sometimes, seemingly aggressive and violent behavior may be only physical manifestation of a seizure, such as stereotypical movements in frontal lobe epilepsy or violent muscle jerks in myoclonic seizures, and this behavior may be misinterpreted as directed aggression.

No case where a directed organized attack towards a concrete person or object is a dominant characteristic of a seizure has been documented so far [11].

Preictal Aggression

During the prodromal phase (several minutes, hours or days before the onset of seizure) some non-specific psychological changes may occur in the form of irritability, anxiety, depression, dysphoria, aggression, etc., which vary in intensity and cease with the seizure onset. Directed aggression is possible; however, behavior in this period is not a part of epileptic seizure.

Postictal Aggression

Postictal aggression is more frequent than ictal aggression. Episodes of postictal aggression last longer, the behavior is out of the person's character and there is usually amnesia for the event. Postictal aggression may occur during the postictal automatism or it may be a part of the postictal confusion state, and these two conditions may co-occur. The patients are confused, their behavior is inappropriate, sometimes aggressive, and more aggressive while others attempt to calm them down (defensive aggression). Significant violence in this period is rare.

Postictal aggression may occur during postictal psychosis (PIP). Definite incidence and prevalence of PIP is not known, it is estimated to occur in the range from 6% to 10% of patients with epilepsy [12,13] and in 18% of patients with pharmacoresistant focal epilepsy [14]. Generally accepted criteria for the diagnosis of PIP were established by Logsdail and Toone in 1988 [15]. PIP occurs characteristically after cluster seizures, after a lucid interval (period lasting several hours or days after the seizure cessation), with a sudden onset of psychotic symptoms of a combined affective picture, often associated with religious delusions and fear of impending death. Most postictal psychotic conditions are transitory, last less than a day to several weeks, and tend to recur in a stereotypical way. The patient is conscious and well oriented during the episode, and later has a memory of the episode. The fear associated with delusions and paranoid ideas during PIP may lead to violent behavior which may be hetero- or auto-destructive with frequent suicide attempts [16]. During these conditions there is a significantly higher possibility of directed aggression (23%) compared to acute interictal psychoses (5%) and postictal confusion (1%) [17].

Interictal Aggression

Aggression and violence are much more common outside (between) epileptic seizures, and even then the association with epilepsy is questionable.

Aggression which is not associated with a seizure is typically manifested as directed and socially understandable aggression – it is purposeful, coordinated and not stereotypical. Recovery is fast and there is no confusion. This aggression is often influenced by some events from the person's surroundings, although the trigger-factor is not always easily perceptible and may last longer (several minutes or longer). Adverse effects of drugs and combined intoxication may lower the threshold of frustration tolerance, and impaired memory is often a consequence of affect and not of epileptic seizure.

A significant risk factor for interictal aggression is the presence of a structural brain damage. Trauma and encephalitis are associated with a higher incidence of epilepsy; however, a causal relationship between epilepsy and interictal aggression has not been established [18]. Lesions of the frontal region, left hemisphere and limbic system are also in a positive correlation with interictal aggression [19]. Predisposing factors for aggressive behavior include cognitive disturbances which frequently accompany brain injuries [20]. Aggressive disposition is found particularly in young men of lower socioeconomic status and educational level and of lower level of intellectual functioning with long-term behavioral problems, whereas epilepsy has not been proved to be a risk factor for aggressive behavior [21].

In addition, aggression may be influenced by interictal psychopathology; and comorbidity, in the sense of more frequent affective and schizophrenic disorders in individuals with epilepsy, is significant. Interictal aggression may be viewed in the context of antisocial personality disorder resulting from a difficult psychosocial background of the epileptic patient.

Conclusion

Aggressive behavior may occur in different social circumstances and patients with epilepsy are

not immune to the possibility of being involved in an aggressive act. Although certain epidemiological studies report that epilepsy is twice or four times more frequent among prisoners than in the general population, its prevalence is the same as in the subpopulation with lower socioeconomic status. There is no evidence that aggression and violence are more frequent among epileptic patients compared to people without epilepsy, and there is no evidence that violence is more frequent in patients with temporal lobe epilepsy compared to patients with other types of epilepsy. Ictal aggression is extremely rare, stereotypical, defensive and non-directed. The association between violence, aggression, and epilepsy is multifactorial; they may co-occur in one person without affecting one another.

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Rad je primljen 3. XII 2012.
Prihvaćen za štampu 3. XII 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:117-119.

ORIGINALNI NAUČNI RADOVI
ORIGINAL STUDIES

General Hospital Subotica, Department of Orthopedics and Traumatology[1]
Clinical Centre of Vojvodina, Novi Sad
Department of Orthopedics and Traumatology[2]
Institute for Children's Health Care, Novi Sad
Department of Orthopedics and Traumatology[3]

Originalni naučni rad
Original study
UDK 616.748-001-02
DOI: 10.2298/MPNS1304121R

QUADRICEPS TENDON INJURIES

POVREDE TETIVE ČETVOROGLAVOG MIŠIĆA BUTA

Vladimir RISTIĆ[1], Mirsad MALJANOVIĆ[1], Iva POPOV[2], Vladimir HARHAJI[2] and Vukadin MILANKOV[3]

Summary

Introduction. The aim of study was to analyze risk factors, mechanisms of injury, symptoms and time that elapsed from injury until operation of complete quadriceps tendon ruptures. **Material and Methods.** This retrospective multicenter study included 30 patients operated for this injury, of whom 28 (93.3%) were men. The average age was 53.7 years (18-73). Twenty-six patients had reconstruction of unilateral rupture and four of bilateral one. **Results.** Eighty percent of them had some risk factors for rupture of the tendon with degenerative changes. Eight patients had diabetes, seven patients were on renal dialysis, two patients had secondary hyperparathyroidism, five patients were obese and two patients had former knee operations. These injuries occurred in 80% following minor trauma caused by falls on stairs, on flat surfaces and squatting. The most frequent symptoms were: pain, swelling, lack of extension of knee and defect above patella, and three cases were initially misdiagnosed. During the first 10 days after injury, acute and chronic ruptures were reconstructed in 22 (73.3%) and 8 patients, respectively. **Conclusion.** Quadriceps tendon injuries most often happen to male patients with predisposing conditions in their fifth and sixth decade of life due to trivial trauma. Patients on renal dialysis are the most vulnerable population group.

Key words: Tendon Injuries + etiology; Quadriceps Muscle; Risk Factors; Male; Diagnosis

Sažetak

Uvod. Cilj studije bila je analiza predisponirajućih faktora rizika, mehanizama povređivanja, simptoma i vremena proteklog od povrede do operacije, kompletnih prekida tetive četvoroglavog mišića buta. **Materijal i metode.** Retrospektivnom multicentričnom studijom, obuhvatili smo 30 operativno lečenih pacijenata sa navedenom povredom. Među njima 28 (93,3%) bilo je muškog pola, a prosečna starost iznosila je 53,7 godina (18−73). Kod 26 pacijenata izvršeno je operativno lečenje jednostrane rupture, kod četiri pacijenta − obostrane. **Rezultati.** Kod 80% ispitanika postojao je neki od faktora rizika za pucanje degenerativno izmenjenih tetiva. Osam pacijenata je imalo šećernu bolest, sedam su bili na dijalizi zbog hronične bubrežne insuficijencije, petoro su bili gojazni, dva su imali sekundarni hiperparatiroidizam, dva prethodne operacije zgloba kolena. Bezazlenim padovima na stepeništu, okliznućem i pri čučnju povređeno je 80% pacijenata. Najčešći simptomi bili su: bol, otok, nemogućnost opružanja potkolenice i defekt iznad čašice, ali je ipak došlo do tri (10%) početno previđena slučaja. Tokom prvih deset dana nakon povrede rekonstruisana je sveža povreda kod 22 pacijenta (73,3%), a zastarela kod 8. **Zaključak.** Povrede tetive četvoroglavog mišića buta češće se dešavaju kod muškaraca u petoj i šestoj deceniji života, bezazlenom traumom, sa predisponirajućim oboljenjima. Najrizičniji deo populacije za povredu ove tetive su dugogodišnji pacijenti na bubrežnoj dijalizi.

Ključne reči: Povrede tetiva + etiologija; Butni mišić; Faktori rizika; Muško; Dijagnoza

Introduction

Quadriceps femoris muscle is the largest muscle of anterior group of thigh muscles. It is a part of extensor mechanism of knee joint [1] and consists of four muscles (rectus femoris, vastus medialis, vastus lateralis and vastus intermedius). They begin from the pelvis, anterior surface of femur and intermuscular septa and end on the patella as conjoined quadriceps tendon. The distal end of extensor mechanism is the patellar tendon extending from the pole of patella to the tibial tubercle.

This muscle has an important function in the knee motion. Fibers rupture and tendon retraction can cause a limited range of motion, stiffness, arthrosis and disability in patients [2,3]. Partial ruptures are most common and they are usually treated non-operatively, with cylinder casts [2,3]. Com-

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plete ruptures of the quadriceps tendon usually occur in patients older than 40 years [2,3]. Bilateral ruptures are highly correlated with systemic diseases [2-4]. Since these injuries are rather rare and often misdiagnosed, surgical treatment is usually delayed and thus the repair is more difficult and post-operative results may be compromised [2-4].

The aim of study was to emphasize the importance of early diagnosis and to analyze risk factors, mechanisms of injury, symptoms and diagnostic methods for quadriceps tendon ruptures.

Material and Methods

This retrospective study was performed at general hospitals in Subotica and Zrenjanin and Clinical Centre of Vojvodina in Novi Sad from 2002 to 2011 and it included 30 patients operated for complete ruptures of the quadriceps tendons. The data were collected from patients' discharge lists and questionnaires.

Generally speaking, men are more commonly affected so the study sample consisted of 28 (93.3%) men and only two women. Their average age was 53.7 years. The youngest and the oldest patients were 18 and 73 years old, respectively. At the moment of injury, 26 patients (86.7%) were older than 40 years, with the peak incidence during the fifth and sixth decades of life (53.3%) **(Graph 1).**

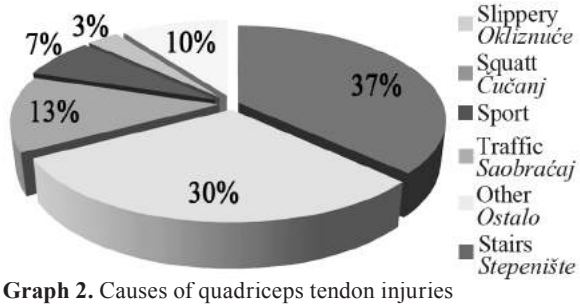
We performed 26 reconstructions of unilateral ruptures (86.7%). The left leg was injured in 16 cases, and the right one in 10. Four patients (13.3%) had simultaneous bilateral injuries.

The study excluded the patients with partial ruptures, and those who were treated non-operatively, or who had died in the meantime (two of them).

The results were analyzed, compared and presented in graphs.

Results

By analyzing causes of quadriceps tendon ruptures, we found that nine injuries had been caused by falls from the stairs and three by other types of falls, nine by sliding on flat surfaces, four by squatting, two occurred in recreational sports activities (volleyball, bicycling) and one in traffic accident (**Graph 2**).



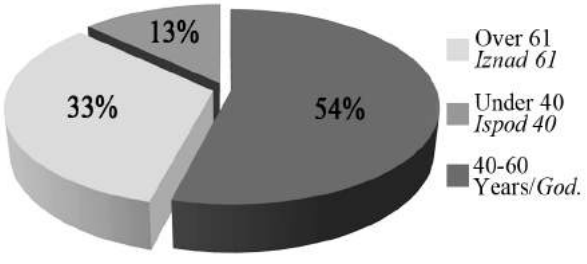
Graph 2. Causes of quadriceps tendon injuries
Grafikon 2*. Uzroci povređivanja tetive četvoroglavog mišića*

Eighty percent of them were injured by trivial trauma resulting from falls. The common mechanisms of trauma included a stumble, a simple fall, falling from the stairs or from a height.

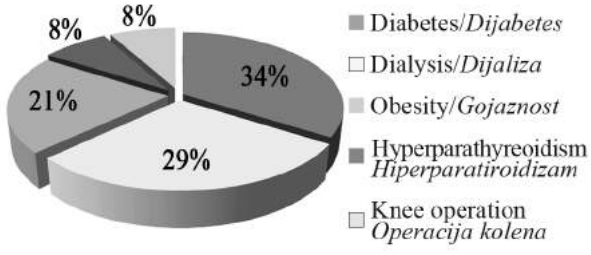
Twenty-four patients (80%) had some of the risk factors for rupture of tendons with degenerative changes. Eight patients had diabetes, seven patients suffered from severe renal diseases, five patients were obese, two patients had secondary hyperparathyroidism and two patients had former knee operations (patellar fracture and total knee replacement) (**Graph 3**).

Diabetes and chronic renal failure dominated among metabolic diseases. They were recorded in every other case. The patients who had been waiting for kidney transplantation between 4 and 8 years were at higher risk of getting injured which was proportional to the length of period they were on dialysis.

General Hospitals in Subotica and Zrenjanin and Clinical Centre of Vojvodina in Novi Sad cover the territory with a population of about one million people. Complete ruptures of quadriceps tendon are rare and only three patients are operated per year on average in this region. In these three regions of Vojvodina province there are 379 patients with chronic renal disease undergoing renal dialysis [5] and the incidence of getting injured among them is 0.7 patient a year, whereas the annual incidence in general population is 0.3/100.000. However, it is higher among the diabetics (8/100.000) and the highest incidence is in patients with chronic renal failure (185/100.000). It can be concluded that a patient on dialysis is at 555 times higher risk for tendon rupture than other people.



Graph 1. Age groups of injured patients
Grafikon 1. *Starosne grupe povređenih pacijenata*



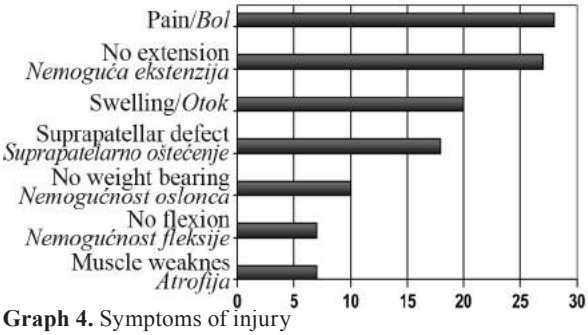
Graph 3. Risk factors for quadriceps tendon injuries
Grafikon 3. *Faktori rizika za pucanje tetive četvoroglavog mišića*

In our study sample, acute rupture was reconstructed in 22 patients (73.3%) within the first 10 days after injury, whereas 8 patients were operated for chronic rupture (1-9 months after rupture). Among delayed operated ruptures, three were initially misdiagnosed. Operations in other five patients were contraindicated at the beginning because of uremia, poor kidney conditions and complications of diabetes.

The most common observed symptoms after the injury were: pain, swelling, lack of extension of knee and defect above patella. The combination of all these clinical signs was found in 60% of patients. The inability of weight bearing and knee flexion, muscle weakness and other symptoms occurred much more rarely (**Graph 4**).

Ten patients (33%) said that they had felt pain in tendon even before the injury.

Standard initial X-ray examination was performed in all patients, whereas additional diagnostic methods were applied only in three patients (ultrasonography in one and magnetic resonance imaging in two patients).



Graph 4. Symptoms of injury
Grafikon 4. *Simptomi povrede*

Discussion

Quadriceps tendon ruptures are rare injuries, and they are presented most often as individual case reports [4-15] or reported as small series of 20-39 patients [3,16-18]. Less than a hundred cases of bilateral tendon ruptures have been published in international literature until now [2-4]. We operated 30 patients during the period of ten years, and four of them had simultaneous bilateral ruptures.

An epidemiologic study from the United Kingdom [19] reported an incidence of 1.37/100,000 (partial and complete ruptures) per year, with a mean age of 51 years. The average age in our sample was similar (53.7 years), and the incidence of complete ruptures was much lower due to the lack of data on partial ruptures.

Ruptures of patellar ligament occur in patients under the age of forty, while quadriceps tendon ruptures occur in older patients [1,2,20,21]. Although they can happen in young population [6,7], as it was the case in 13% of our sample, the greatest risk is in the fifth and the sixth decades of life [2,3,22,23]. As it has been shown in our study, men are more commonly affected [3,19,22] for reasons not well described in literature. We assume that reasons lie in increased load on knee joints in men and degenerative changes of tendon in former athletes, who are mostly men in the Republic of Serbia.

The quadriceps tendon is formed by the convergence of all 4 quadriceps muscles just proximal to the superior patella. The tendon has an average thickness of 8 mm and an average width of 35 mm [24]. The superficial layers are well vascularized. In the deep layer, there is an oval, avascular area that is 30 x 15 mm in size. It probably plays a significant role in tendon degeneration [24]. However, quadriceps tendon rupture is rare even among older people. A tendon thickness of >6.1 mm, a superior pole of patella erosion, the patellar enthesophytes and intratendinous calcification are all signs of chronic tendinopathy [24]. This tendon is an inherently very strong structure that is extremely resistant to heavy load. About 50-75% of its fibres need to be severed before it ruptures totally under a physiological load [2]. Rupture usually occurs distally 0-2 cm from the superior pole of the patella through pathologic tissue [25]. Various systemic conditions may cause damage to the tendon vascular supply or may disrupt its structure. Diabetes can cause arteriosclerotic changes in tendon vessels. Fibrinoid necrosis of tendons is seen with chronic synovitis. Hyperparathyroidism causes dystrophic calcifications and subperiosteal bone resorption at the tendon insertion. Obesity causes its fatty degenerative changes [25]. Fatty or fibrinoid degeneration and decreased collagen are seen with normal aging. Kannus and Jozsa [25] examined histopathological changes in 891 ruptured tendons; about 97% of the pathologic changes were degenerative. That is the reason why one third of our sample had previous pain above patella for months before injury.

According to different studies [2,4,22] 30-76% of quadriceps ruptures occur in patients with underlying medical predispositions, and this percentage was even higher in our study (80%). The associated diseased had been diagnosed before the injury in all our patients except in those having dysfunction of parathyroid glands. Their condition was diagnosed after surgery when accumulation of calcium was observed in reconstructed tendon. The high level of calcium in serum was decreased after partial removal of parathyroid glands, so heterotopic ossification did not develop further.

It is well documented that many conditions can contribute to degeneration of the quadriceps tendon, including the following: hyperparathyroidism [8], chronic renal failure [9], obesity [25], rheumatoid arthritis [25], diabetes mellitus [25], long term immobilization [23], jumper's knee [2]. Our patients also had these risk factors. Gout, systemic lupus erythematosus, infection, metabolic disease, steroid abuse, tumors and leukemia are also potential risk factors [15,23,25], which were not found

in our study sample. Our patients with chronic renal failure were the most vulnerable group for quadriceps tendon injury. This risk is higher in patients who are on dialysis for longer time, as it was the case in our study sample, when the patients had to wait for kidney transplantation for at least four years.

As other structures of extensor mechanism, quadriceps tendon can also get injured iatrogenically. Rare iatrogenic cases that have been reported are: rupture after total knee arthroplasty [10,26], lateral retinacular release [11], meniscectomy [12], anterior cruciate ligament reconstruction with central-third patellar tendon graft [13,20], local steroid injections [14], knee and patellar dislocations [23]. We had one case of tendon rupture after total knee arthroplasty. The prevalence of a quadriceps tendon tear after this procedure was only 0.1% (twenty-four out of 23,800) [26].

Most of these injuries have been reported to occur spontaneously and after seemingly trivial trauma as a result of an indirect mechanism [2-4,22,23,25]. The mechanisms of trauma include a stumble, a simple fall, falling from the stairs or from a height. Shah et al [22] have reported that 72% of ruptures are caused by falls, which is similar to our results (80%). Most of the injuries occur during an eccentric contraction of the quadriceps against the body weight, when the knee is flexed more than 60 degrees [23]. Other mechanisms of injury include direct blows, lacerations, and iatrogenic causes, which are considerably less frequent [23].

Chronic enthesopathy of the quadriceps can present as an anterior knee pain. The superior pole of the patella is the site of pathology in 25% of patients [2]. Every third patient had this symptom for months before injury. This was attributed to frequent jumping, squatting and kneeling at the beginning, and even at rest in the chronic phase [2]. Symptoms can be detected by X-rays with calcific shadows in tendon. However, the majority of injured do not have previous signs of chronic enthesopathy. Therefore, any underlying predisposing causes must be taken into account. The patients should be specifically asked about any history of systemic disease, steroid use, infection, tumors, or prior surgeries. There may be a history of an audible pop at the time of injury [23,27]. Obvious suprapatellar swelling, ecchymosis, and tenderness, palpable defect in the suprapatellar area and a low-lying patella are usually present. Testing for full, active extension against gravity is the most important aspect of the examination [2,4]. The degree of extension depends on the amount of retinaculum damage. The contralateral knee should be examined to rule out bilateral rupture. According to other authors [3], unilateral ruptures occurred 10-21 times more often than bilateral. This ratio was only 6.5:1 in our study sample. Some other studies [23], including ours [23], have shown that the non-dominant left leg is more often injured, but others disagree with this finding [3].

Profile X-rays show low-lying patella after tendon rupture (patella baja, inferior). X-rays should be made to exclude fractures. Ultrasonography and magnetic resonance imaging are helpful if the diagnosis is questionable and in determining whether the rupture is complete [4,28]. These additional diagnostic methods were not necessary in the majority of our cases. Laboratory analysis should be done prior to surgery, paying special attention to bone, lipid and renal profiles, blood glucose and serum uric acid. We did not have the opportunity to control the level of parathyroid hormones and thus we were unable to prevent heterotopic ossification.

If the patient is not seen in the acute phase, it becomes more difficult to diagnose the rupture. It can easily be missed especially in elderly patients. They were mistreated for strokes, radiculopathy, and myelopathy. Some studies, published forty years ago [27, 29], reported as many as 38-40% of initial misdiagnoses, when quadriceps tendon rupture was misdiagnosed as a neurological condition and less harmful knee injuries [27,29], as it was the case in 10% of our study sample. The incidence of misdiagnosed patients today is much lower because of available modern diagnostic procedures, but clinical examination is still basic for a valid diagnosis. If it is made too late, the intervention is delayed, the repair is more difficult and final results may be compromised [30].

The limitations of this study are connected with the lack of additional diagnostics in the majority of cases. Ruptures can be prevented if risk factors and mechanisms of quadriceps tendon injuries are well defined. Better operative results and early return to everyday activities are achieved if symptoms are recognized in due time and modern diagnostic methods are applied [28].

Conclusion

Quadriceps tendon injuries, although rare, happen to male patients with predisposing conditions (such as chronic renal failure, diabetes, hyperparathyroidism, former knee operations) most often in their fifth and sixth decade of life due to trivial trauma. Patients on renal dialysis are the most vulnerable population group.

Since reconstructions of acute injuries yield much better results than reconstructions of old ones, particularly those initially misdiagnosed, the importance of defining risk factors, mechanisms of injuring and recognition of symptoms is even greater.

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Rad je primljen 19 VI 2012.
Recenziran 9. XII 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:121-125.

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Originalni naučni rad
Original study
UDK 616.233-002-073.97
DOI: 10.2298/MPNS1304126L

ANALYSIS OF ELECTROCARDIOGRAM IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

ANALIZA ELEKTROKARDIOGRAMA KOD PACIJENATA SA HRONIČNOM OPSTRUKTIVNOM BOLESTI PLUĆA

Biljana LAZOVIĆ[1], Mirjana ZLATKOVIĆ ŠVENDA[2], Sanja MAZIĆ[3], Zoran STAJIĆ[1] and Marina ĐELIĆ[3]

Summary

Introduction. Chronic obstructive pulmonary disease is the fourth leading cause of mortality worldwide. It is defined as a persistent airflow limitation usually progressive and not fully reversible to treatment. The diagnosis of chronic obstructive pulmonary disease and severity of disease is confirmed by spirometry. Chronic obstructive pulmonary disease produces electrical changes in the heart which shows characteristic electrocardiogram pattern. The aim of this study was to observe and evaluate diagnostic values of electrocardiogram changes in chronic obstructive pulmonary disease patients with no other comorbidity. **Material and Methods.** We analyzed 110 electrocardiogram findings in clinically stable chronic obstructive pulmonary disease patients and evaluated the forced expiratory volume in the first second, ratio of forces expiratory volume in the first second to the fixed vital capacity, chest radiographs and electrocardiogram changes such as p wave height, QRS axis and voltage, right bundle branch block, left bundle branch block, right ventricular hypertrophy, T wave inversion in leads V1-V3, S1S2S3 syndrome, transition zone in praecordial lead and QT interval. **Results.** We found electrocardiogram changes in 64% patients, while 36% had normal electrocardiogram. The most frequent electrocardiogram changes observed were transition zone (76.36%) low QRS (50%) and p pulmonale (14.54%). Left axis deviation was observed in 27.27% patients. **Conclusion.** Diagnostic values of electrocardiogram in patients with chronic obstructive pulmonary disease suggest that chronic obstructive pulmonary disease patients should be screened electrocardiographically in addition to other clinical investigations.

Key words: Electrocardiography; Pulmonary Disease, Chronic Obstructive; Diagnosis; Predictive Value of Tests

Sažetak

Uvod. Hronični opstruktivni bronhitis četvrti je vodeći uzrok mortaliteta širom sveta. Definiše se kao perzistentno ograničenje protoka vazduha u plućima, obično je progresivno; nije u potpunosti reverzibilno na lečenje. Dijagnoza hroničnog opstruktivnog bronhitisa, kao i stadijum bolesti postavljaju se na osnovu spirometrijskog nalaza. Hronični opstruktivni bronhitis dovodi do promene u električnoj sprovodljivosti srca što se manifestuje karakterističnim elektrokardiografskim zapisom. Cilj ovog rada je uočavanje i procenjivanje dijagnostičke vrednosti elektrokardiografskih promena kod pacijenata sa hroničnom opstuktivnom bolešću pluća bez prisustva drugih komorbiditeta. **Materijal i metod.** Analiziran je elektrokardiografski zapis kod 110 klinički stabilnih bolesnika. Posmatrane su sledeće vrednosti: forsirani ekspiratorni volumen u prvoj sekundi, odnos forsiranog ekspiratornog volumena u prvoj sekundi i fiksnog vitalnog kapaciteta, radiogram grudnog koša, elektrokardiografska promena kao što su visina p-talasa, QRS osovina i voltaža, blok desne i leve grane, hipertrofija desne komore, inverzija T-talasa u odvodima V1-V3, sindrom S1S2S3, tranzitorna zona u prekordijalnim odvodima i QT interval. **Rezultati.** Karakteristične elektrokardiografske promene nađene su kod 64% bolesnika, dok je 36% imalo normalan elektrokardiografski zapis. Najčešća zabeležena elektrokardiografska promena bila je tranzitorna zona u prekordijalnim odvodima kod 76,36% bolesnika, niska voltaža QRS kod 50% i p-pulmonale kod 14,54%. Leva osovina srca zabeležena je kod 27,27% bolesnika. **Zaključak.** Na osnovu sprovedenog ispitivanja zaključeno je da elektrokardiogram ima značajnu dijagnostičku vrednost kod bolesnika sa opstruktivnim bronhitisom i da bi kod ovih bolesnika trebalo realizovati elektrokardiografski skrining, pored rutinskih kliničkih istraživanja.

Ključne reči: Elektrokardiografija; Hronična opstruktivna bolest pluća; Dijagnoza; Prediktivna vrednost testova

Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide. It is defined as a progressive disease characterized by the airflow limitation which can be either not reversible at all or only partially reversible. The term ”COPD” includes two main conditions-emphysema and chronic bronchitis [1,2]. Emphysema is defined as an abnormal permanent enlargement of air spaces distal to the terminal bronchioles, accompanied by the destruction of alveolar walls and without obvious fibrosis. COPD is associated with an abnormal inflammatory response of the lungs to the chronic inhalation exposure to smoke, dust and other air pollutants which involves a long-term cough with mucus. Emphysema frequently occurs in association with chronic bronchitis. The patients have been classified

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Abbreviations

COPD	– chronic obstructive pulmonary disease
ECG	– electrocardiogram
FEV1	– forced expiratory volume in the first second
FVC	– fixed vital capacity
LBBB	– left bundle branch block
RBBB	– right bundle branch block
RVH	– right ventricular hypertrophy
GOLD	– Global initiative for chronic Obstructive Lung Disease

as having COPD with either emphysema or chronic bronchitis predominance [3].

Comorbidities are common in patients with COPD and a number of these comorbidities are independently associated with an increased mortality risk. However, the major causes of morbidity and mortality in COPD lie in the impact of cardiac performances. It has been known for some time that COPD produces characteristic alternations in electrocardiogram (ECG). The first research was conducted in 1961. So far, there have been several studies on ECG characteristics in COPD and the criteria have been made accordingly [4]. COPD produces characteristic ECG changes as a result of pulmonary vasoconstriction due to hypoxemia, following pulmonary hypertension and enlargement of right ventricle as well as a dampening effect due to the presence of increased air between the heart and recording electrodes [5,6].

The aim of this study was to investigate characteristic changes in ECG produced by this disease and to evaluate the diagnostic values of ECG changes in COPD.

Material and Methods

The ECGs from 110 patients were studied. The diagnosis of COPD was made by spirometric tests according to GOLD criteria (Global initiative for chronic Obstructive Lung Disease), medical history, physical examination and chest radiograph. For the diagnosis of COPD the value of forced expiratory volume in the first second (FEV1) must be less than 80% of the predicted value and the ratio of forces expiratory volume in the first second to the fixed vital capacity (FEV1/FVC) must be less than 70% after bronchodilator inhalation.

All patients were classified into four stages: mild, moderate, severe and very severe based on the value of FEV1 (FEV1≥80%, 50-79%, 30-49% and <30%, respectively) and FEV1/FVC<0,7 [7]. The pulmonary function test (spirometry) was done in the stable state on discharge day. The best of three attempts was selected.

Chest radiograph was assessed on the first day of hospitalization and classified as normal or emphysematous. All projections were posterolateral (PA).

Electrocardiograms were done on the day of discharge and the following features were analyzed:

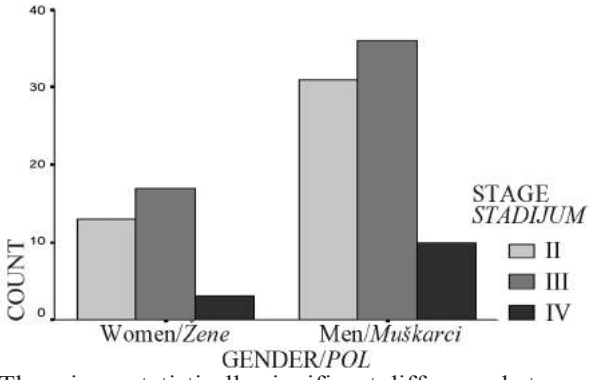
1. p pulmonale (peaked >2,5mm in any standard limb lead)
2. QRS axis (normal between -30 and 120 degrees; left deviation between -30 and -90 degrees; right deviation between +90 degrees and +180 degrees)
3. Right bundle branch block (RBBB): QRS duration more than 100 ms (incomplete block) or more than 120 ms (complete block), terminal R wave in lead V1 (e.g. R, rR', rsR', rSR' or qR), slurred S wave in leads I and V6.
4. Right ventricular hypertrophy (RVH) (right axis deviation, QRS < 0.12s, predominant R wave in lead V1, deep S in V6, inverted T waves in right praecordial leads - V2, V3, evidence of right atrial enlargement)
5. Left bundle branch block (LBBB): QRS duration must be ≥ 120 ms, rS with upright T wave in V1, V5 and V6 predominantly upright with inverted T, lead I predominantly upright with inverted T.
6. T-wave inversion (negative T waves) in leads V1-V3 as a signs of ischemia
7. S1S2S3 syndrome (QRS complex is not prolonged, terminal S wave in lead I, II, III, terminal QRS vector -90 and -150 degrees)
8. Transition zone in praecordial lead (QS, QRS, rSR, RS)
9. Low QRS (amplitude <5 mm in limb leads)
10. QT interval (normal <0,42s)

We included the patients who seldom suffered from COPD. The patients with suspicion of any other pulmonary disease or other comorbidities (arterial hypertension, angina pectoris, diabetes mellitus, heart or renal failure) were excluded from the study. Those having a chest or spine deformity were excluded from the study in order to eliminate other factors which could affect ECG patterns.

The following statistical analyses were used: descriptive, chi square test and correlations. The results were reported as mean ± SD.

Results

Out of 110 analyzed ECG, 33 belonged to women and 77 to men, whose age was from 32 to 84 years (mean 62.31±9.64). The average age was 60.9±1.64 and 63.26±1.64 years for women and men, respectively. As for the stage of disease, 13 women and 31



There is no statistically significant difference between gender and stage of disease (p=0.815)

Ne postoji statistički značajna razlika između pola i stadijuma bolesti (p=0.815)

Graph 1. Gender and GOLD stage

Grafikon 1. *Pol i GOLD stadijum*

Table 1. GOLD stage and axis
Tabela 1. *GOLD stadijum i osa*

	Axis/*Osa*		
Stage/*Stadijum*	Frontal/*Frontalna*	Left/*Leva*	Total/*Ukupno*
II*	39 (48.8%)	5 (16.7%)	44
III*	37 (46.3%)	16 (53.3%)	53
IV	4 (5%)	9 (30%)	13
Total/*Ukupno*	80	30	110

Table 2. Correlations between GOLD stage and emphysema with electrocardiogram findings
Tabela 2. *Neke korelacije između GOLD stadijuma i emfizem sa elektrokardiografskim nalazima*

	Axis/*Osa*	P pulmonale	RBBB	incRBBB	LBBB	Neg T V1-V3
Stage *Staadijum*	r=0.368 p=0.000**	r=0.121 p=0.207	r=-0.027 p=0.779	r=-0.202 p=0.034*	r=-0.004 p=0.968	r=0.090 p=0.349
Emphysema *Emfizem*	r=0.253 p=0.008**	r=0.184 p=0.054	r=-0.093 p=0.332	r=-0.048 p=0.617	r=0.047 p=0.628	r=-0.065 p=0.500

*p<0.05; **p<0.01, GOLD - Global initiative for chronic Obstructive Lung Disease

men were in GOLD stage II, 17 women and 36 men were in GOLD stage III and 3 women and 10 men were in GOLD stage IV (**Graph 1**). Smoking was a major risk factor and all patients were chronic smokers with average of 40 packs/year.

Emphysema was radiologically verified in 17 women and 41 men (**Graph 2**)

Graph 3 compares the axis with the stage of disease. The frontal axis is the most frequent in stage II (48.8% patients), while the left axis is the most frequent in stage III (53.3%). **Table 1** shows the distribution of axis according to the stage.

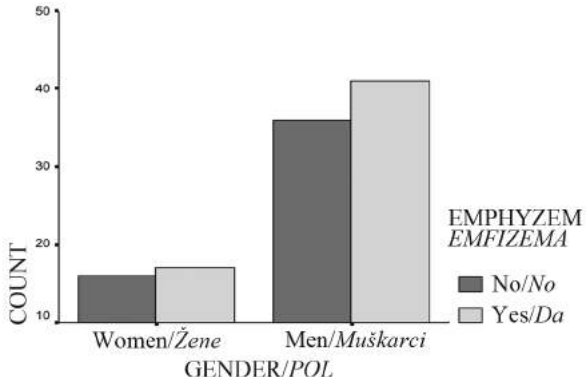
Graph 4 presence of emphysema in 45% patients with frontal axis and 73.3% with left axis.

Table 2 shows the correlation between the stage of disease and emphysema with characteristic ECG findings. It shows a high, statistically significant correlation between the axis and the stage (r=0.368 p=0.000) and between the axis and emphysema (r=0.253 p=0.008). There is an inverse correlation (r=-0.202, p=0.034) between incomplete right bundle branch block (RBBB) and the stage of disease which means that more severe disease produces less incomplete RBBB.

We found no RVH, and S1S2S3 syndrome. LBBB was recorded in one patient (3.33%). P pulmonale was found in 16 (14.54%) patients (1 patient was in GOLD stage IV, 12 patients were in GOLD stage III and three were in GOLD stage II). Low QRS was recorded in 55 patients; 15 (27.27%) were in GOLD stage IV, one (1.81%) was in GOLD stage II and the others were in GOLD stage III (70.92%). Transition zone was found in 25 (22.73%) patients, and all of them were in GOLD stage II. Negative T wave in V1-V3 was recorded in two patients.

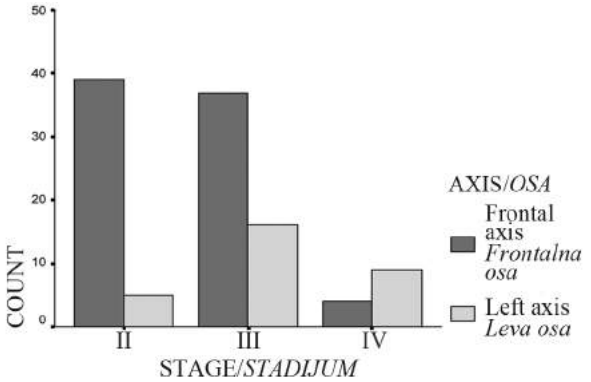
Discussion

Cardiovascular disease is common in patients with chronic obstructive pulmonary disease (COPD)



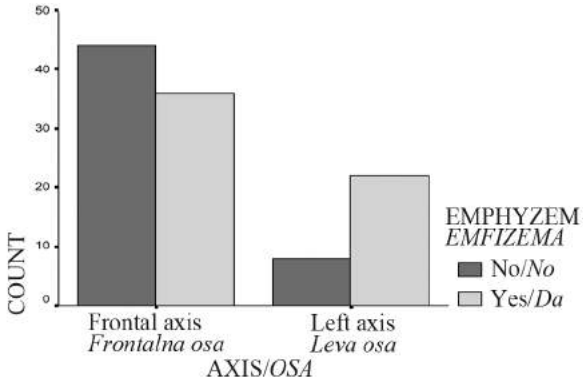
There is no statistically significant difference between gender and emphysema (p=0.868)
Ne postoji statistički značajna razlika između pola i emfizeme (p=0.868)

Graph 2. Gender and emphysema
Grafikon 2. *Pol i emfizem*



There is a statistically significant difference between the axis and GOLD stage (p=0.000)
Postoji statistički značajna razlika između ose i GOLD stadijuma (p=0.000)

Graph 3. GOLD stage and axis
Grafikon 3. *GOLD stadijum i osa*



There is a statistically significant difference between emphysema and axis (p=0.008)
Postoji statistički značajna razlika između prisustva emfizema i ose (p=0,008)

Graph 4. Emphysema and axis
Grafikon 4. *Emfizem i osa*

but it often remains unrecognized [8]. Ischemic ECG changes are associated with a higher risk of dying from coronary heart disease but have never been systematically evaluated in COPD [9]. Large population-based studies suggest that patients with COPD are two to three times more at risk for cardiovascular mortality, which accounts for about 50% of the total number of deaths [10].

We found ECG changes in 64% patients, while 36% of them had normal ECG. The most frequent ECG changes observed were transition zone (76.36%), low QRS (50%) and p pulmonale (14.54%). It is interesting that among 36% patients with no ECG abnormalities, one patient (7.69%) was in GOLD stage IV and 15 (28.30%) were in GOLD stage III.

Men are more affected by COPD than women, as it has previously been described (77 vs 33). Also, men have a severe form of disease and a larger number of them have emphysema. This could be explained by a higher prevalence of smoking in male population than in female [11]. The occurrence of left axis deviation in COPD was first recorded by Lenegre et al. in 1954 [12]. Many authors have noted that a small percentage of patients with pulmonary emphysema have left axis deviation in the absence of clinical coronary artery disease, heart failure, systemic hypertension or other heart disease. So, this finding indicates the necessity of further investigation for underlying cardiovascular disease [13]. Our study showed that left axis was present in 30 patients (27.27%), and 22 of them (73.33%) had emphysema. The greatest number of patients with left axis were in GOLD stage III (53.33%), 30% were in GOLD stage IV and 16.67% were in GOLD stage II.

RBBB was observed in 6 (5.45%), while incomplete RBBB was recorded in 15 (1363%) patients. According to this study, incomplete RBBB could be the first sign of COPD, as it has been proved that severe forms of disease do not produce such an ECG finding.

Conclusion

Since airflow obstruction in chronic obstructive pulmonary disease is not curable and amenable by treatment, the best solution in this disease is prevention. electrocardiogram screening for pulmonary disease (chronic obstructive pulmonary disease and emphysema) is not a routine tool, but could be a cheap and effective method of its prevention.

The present study suggests that an analysis of routine electrocardiogram could be useful for detection of heart disease.

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Rad je primljen 5. IX 2012.
Recenziran 18. X 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:126-129.

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Originalni naučni rad
Original study
UDK 616.61-008.6-78:616.155.194]-08
DOI: 10.2298/MPNS1304130P

RAZLIKE U ODGOVORU BOLESNIKA LEČENIH HEMODIJALIZAMA NA HUMANI REKOMBINOVANI ERITROPOETIN

DIFFERENT RESPONSE TO HUMAN RECOMBINANT ERYTHROPOIETIN IN PATIENTS UNDERGOING HEMODIALYSIS TREATMENT

Nenad PETKOVIĆ[1], Siniša RISTIĆ[2], Milan STOŠOVIĆ[3] i Ljubica ĐUKANOVIĆ[4]

Sažetak

Uvod. Primena humanog rekombinovanog eritropoetina omogućava oporavak bolesnika sa anemijom lečenih hroničnim hemodijalizama, ali su primećene velike individualne razlike u dozi humanog rekombinovanog eritropoetina koja je potrebna da se postigne željeni oporavak. U ovom radu je ispitan indeks rezistencije na eritropoetin kod bolesnika koji se leče hemodijalizama sa ciljem da se utvrde varijacije u odgovoru na eritropoetin i faktori koji na taj odgovor utiču. **Materijal i metode.** Ispitivanjem je obuhvaćeno 48 bolesnika, 25 muškog pola, prosečne starosti 67,5 godina, koji su lečeni hemodijalizama u Šamcu, prosečno 43,9 meseci. Svi su lečeni eritropoetinom od početka primene hemodijalize. Odgovor na terapiju eritropoetinom procenjen je pomoću indeksa rezistencije na eritropoetin. **Rezultati.** Primena eritropoetina omogućila je oporavak bolesnika od anemije i postizanje ciljne vrednosti hemoglobina kod svih bolesnika, ali je postizanje i održavanje ove vrednosti zahtevalo primenu različitih doza eritropoetina. Doza eritropoetina kretala se od 15 do 244 U/kg/nedeljno, a indeks rezistencije na eritropoetin od 0,13 do 2,46 U/kg/nedeljno/g/l. Zadovoljavajući odgovor uz indeks rezistencije na eritropoetin ispod 0,5 U/kg/nedeljno/g/l imalo je 14 (30%) bolesnika, dok je ovaj indeks kod 19 (40%) bolesnika bio iznad 0,7 U/kg/nedeljno/g/l, a čak kod 10 (21%) iznad 0,9 U/kg/nedeljno/g/l. Multivarijantna linearna regresiona analiza pokazala je da je C-reaktivni protein nezavisni prediktor povezan sa indeksom rezistencije na eritropoetin. **Zaključak.** Postizanje i održavanje ciljne vrednosti hemoglobina zahtevalo je primenu različitih doza eritropoetina kod pojedinih bolesnika, što je uslovilo i značajne individualne razlike u indeksu rezistencije na eritropoetin. Multivarijantna analiza izdvojila je C-reaktivni protein kao značajan nezavisni prediktor ovog indeksa.

Ključne reči: Hemodijaliza; Eritropoetin; Ishod lečenja; Rezistencija na lek; Anemija; C-reaktivni protein; Muško; Stari

Summary

Introduction. Treatment with recombinant human erythropoietin enabled the correction of anemia in the patients on regular hemodialysis but large individual differences in the dose required to achieve the target hemoglobin level were observed. In this study the erythropoietin resistance index was calculated in patients on hemodialysis in order to examine variations in the response to erythropoietin and factors that influence it. **Material and Methods.** The study included 48 patients (25 males) of mean age 67.5 years, who had been on regular hemodialysis in Šamac for 43.9 months on average. All were treated with erythropoietin from the beginning of hemodialysis treatment. Their response to erythropoietin therapy was estimated by the erythropoietin resistance index. **Results.** The use of erythropoietin enabled the correction of anemia but different doses were needed to achieve and maintain the target hemoglobin level. The individual weekly dose of erythropoietin ranged from 15 U/kg/week to 244 U/kg/week and the erythropoietin resistance index ranged from 0.13 U/kg/week/g/l to 2.46 U/kg/week/g/l. A satisfactory erythropoietin response with erythropoietin resistance index below 0.5 U/kg/week/g/l was found in 14 (30%) patients, while 19 (40%) patients had this index above 0.7 U/kg/week/g/l and 10 (21%) above 0.9 U/kg/week/g/l. Multivariate linear regression analysis detected C-reactive protein as a significant predictor of erythropoietin resistance index. **Conclusion.** Target hemoglobin levels were achieved and maintained by different doses of erythropoietin in individual patients, which resulted in great individual differences in response as estimated by the erythropoietin resistance index. Multivariate analysis indicated C-reactive protein as a variable significantly associated with this index.

Key words: Renal Dialysis; Erythropoietin; Treatment Outcome; Drug Resistance; Anemia; C-Reactive Protein; Male; Aged

Uvod

Anemija predstavlja jedan od najčešćih poremećaja u hroničnoj bubrežnoj insuficijenciji (HBI) koji je pre više od 170 godina opisao Richard Bright [1]. Ona je posledica skraćenog životnog veka

Napomena: Istraživanja prikazana u ovom radu delom su finansirana sredstvima naučnoistraživačkog projekta broj 19/6-020/961-216/10 Ministarstva za nauku i tehnologiju Republike Srpske.

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Skraćenice

Epo – humani rekombinantni eritropoetin
ERI – indeks rezistencije na eritropoetin
CRP – C-reaktivni protein
HBI – hronična bubrežna insuficijencija
ACEI – inhibitori angitenzin-konvertujućeg enzima
Kt/V – indeks adekvatnosti dijalize
BMI – indeks telesne mase
HD – hemodijaliza
PTH – paratiroidni hormon
MAP – srednji arterijski pritisak

eritrocita, hroničnih gubitaka krvi, neadekvatne eritropoeze uzrokovane inhibitorima eritropoeze, ali u najvećoj meri neadekvatnog lučenja eritropoetina [2].

Eksperimentalne studije su pokazale da je bubreg primarno mesto sinteze eritropoetina kod odraslih, pri čemu je uloga jetre u njegovoj sintezi zanemarljiva [3]. Intersticijalne ćelije pozitivne za eritropoetin mRNA registrovane su duboko u korteksu i spoljašnjoj meduli bubrega, a sa produbljivanjem anemije ove ćelije se umnožavaju i šire u površni deo korteksa [4]. Kod bolesnika sa HBI stepen anemije je proporcionalan stepenu azotemije, a srednje bazalne vrednosti eritropoetina u krvi (19−30 mU/ml) znatno su niže nego kod zdravih osoba sa istim stepenom anemije [5]. Kod zdravih osoba koncentracija eritropoetina u plazmi može porasti od normalnih vrednosti 10−12 mU/ml na vrednost od oko 1 000 mU/ml ukoliko vrednost hemoglobina padne ispod 60 g/l. Kod bubrežnih bolesnika je ova negativna povratna sprega poremećena i koncentracija hemoglobina korelira direktno sa koncentracijom eritropoetina u plazmi. Istraživanja ukazuju da oboleli bubreg proizvodi izvesnu ali nedovoljnu količinu ovog hormona i nije u stanju da tu produkciju poveća u skladu sa povećanim zahtevima usled hipoksičnog stimulusa [2,5].

Otkriće humanog rekombinovanog eritropoetina (Epo) omogućilo je lečenje anemije svih bolesnika kod kojih je anemija prvenstveno uzrokovana nedostatkom eritropoetina. Prvo je Epo primenjen kod bolesnika sa terminalnom bubrežnom insuficijencijom lečenih redovnim hemodijalizama [6,7], a tokom protekle decenije njegova primena se proširila i na druge grupe bolesnika. Posle prvih pokušaja primene Epo kod bolesnika sa terminalnom insuficijencijom bubrega lečenih hemodijalizama, više je multicentričnih studija potvrdilo da taj preparat omogućava potpunu korekciju anemije ovih bolesnika [8−10]. Ove prve studije su, takođe, omogućile da se utvrde indikacije i kontraindikacije, optimalan način primene Epo, kao i njegova korisna i neželjena dejstva.

Prema Evropskom vodiču za lečenje anemije bolesnika sa hroničnom bubrežnom insuficijencijom, Epo treba primeniti kod svih bolesnika sa insuficijencijom bubrega kod kojih je hemoglobin manji od 110 g/l i hematokrit manji od 33% ako su prethodno isključeni i/ili otklonjeni svi ostali činioci koji bi mogli uzrokovati ili pogoršati anemiju bubrežnih bolesnika [11].

Brzina kojom se oporavljaju bolesnici od anemije tokom lečenja eritropoetinom, kao i doze neophodne da se postigne ciljna koncentracija hemoglobina, pokazuju velike individualne varijacije. Najčešće se oporavak postiže posle 7-8 nedelja sa prosečnom dozom oko 200 U/kg nedeljno, a prosečna doza održavanja najčešće je oko 70 U/kg nedeljno [8,9,12]. Varijacije u odgovoru primećene su u svim fazama lečenja, ali su uzroci ovih individualnih varijacija još uvek nedovoljno poznati [13−15]. U ovom radu je odgovor na terapiju eritropoetinom, procenjen pomoću indeksa rezistencije na Epo, ispitan kod bolesnika u terminalnoj insuficijenciji bubrega lečenih hemodijalizama. Cilj istraživanja bio je da se ispita prevalencija nedovoljnog odgovora na lečenje eritropoetinom kod ovih bolesnika i utvrde činioci koji utiču na pojavu nedovoljnog odgovora na Epo.

Materijal i metode

Ispitivanjem je obuhvaćeno 48 od 74 bolesnika koji su se lečili ponavljanim hemodijalizama u Centru za dijalizu Šamac. U studiju nisu uključeni bolesnici koji su dobijali *Mirceru*, njih 20, kao ni bolesnici koji su mesec dana pre početka ili tokom jednogodišnjeg perioda studije imali veći hiruški zahvat, krvarenje ili akutnu infekciju, ukupno njih 6. Svi bolesnici su bili na dijalizi 3 puta nedeljno, prosečno 4 časa; kod svih su primenjivani bikarbonatni puferi kao i biokompatibilne membrane (polisulfon, *high flux*). U ispitivanoj grupi bolesnika, 25 je bilo muškog pola; bolesnici su bili starosti 20−88 godina. Osnovna bubrežna bolest kod 29 bolesnika bila je balkanska endemska nefropatija (BEN), kod 4 bolesnika hronični glomerulonefritis, dijabetesna nefropatija, takođe, kod 4 bolesnika, kod tri hronični pijelonefritis, kod dva nefroangioskleroza, dok je kod po jednog bolesnika osnovna bubrežna bolest bila hipoplazija bubrega, uratna nefropatija, policistična bolest bubrega i kalkuloza bubrega. Kod dva bolesnika osnovna bubrežna bolest bila je nepoznata.

Svi bolesnici su lečeni eritropoetinom (*Recormon MD, Roche*) od momenta početka lečenja hroničnim hemodijalizama. Doza je određivana na osnovu ciljne koncentracije hemoglobina koja je iznosila 100−120 g/l a bolesnici su Epo dobijali 2 puta nedeljno supkutano na kraju hemodijalize. Bolesnici su praćeni godinu dana od 1. januara 2010. godine do 31. decembra 2010. i u tom periodu je redovno praćeno njihovo kliničko stanje, laboratorijski parametri, a posebno krvna slika, status gvožđa u organizmu, doza Epo i indeks rezitencije na eritropoetin (ERI).

Neposredno pre početka druge dijalize u nedelji, bolesnicima su uzimani uzorci krvi za laboratorijske analize. Kompletna krvna slika određivana je metodom protočne citometrije, a hemoglobin spek-

Tabela 1. Demografske i kliničke karakteristike ispitane grupe bolesnika
Table 1. *Demographic and clinical characteristics of the tested groups of patients*

Ukupan broj bolesnika/*Total number of patients*	48
Pol, muški/ženski/*Gender, male/female*	25/23
Starost, godine/*Age, years*	67,5 (13,1)
BMI, kg/m^2/*Body mass index, kg/m^2*	25,4 (5,5)
Trajanje lečenja HD, meseci/*Duration of HD, months*	43,9 (31,7)
Srednji arterijski pritisak, mmHg/*Mean arterial pressure, mmHg*	89,5 (15,7)
Terapija ACEI, da/ne/*Therapy with ACEI, yes/no*	16/32
Kt/V	1,40 (0,2)

BMI - indeks telesne mase/*body mass index*, HD - hemodijaliza/*hemodialysis*, ACEI - inhibitori angitenzin-konvertujućeg enzima/*angiotenzin-converting enzyme inhibitors*, Kt/V - indeks adekvatnosti dijalize/*index of adequacy of dialysis*

trofotometrijskom metodom (jedanput mesečno). Urea, kalcijum, neorganski fosfat određivani su spektrofotometrijskom metodom takođe jedanput mesečno, kao i kreatinin koji je određivan kinetičkom *Jaffe* reakcijom bez proteinizacije. Transferin i feritin određivani su imunohemiluminiscentnom metodom tromesečno kao i holesterol i gvožđe koje je određivano kolorimetrijskom metodom. Albumini i parathormon određivani su šestomesečno kao i C-reaktivni protein (CRP) koji je određivan imunoturbidimetrijskom metodom (referentne vrednosti 0−5 mg/l).

Indeks adekvatnosi dijalize *(*Kt/V) izračunat je po formuli Daugirdasa[16]:

$Kt/V = -\ln(R-0{,}008 \times t) + (4-3{,}5 \times R) \times UF/W$

gde je: R = koncentracija uree posle hemodijalize/ koncentracija uree pre hemodijaize, t = vreme trajanja hemodijalize, UF = ultrafiltracija, W = telesna težina na kraju hemodijalize

Indeks rezistencije na eritropoetin predstavlja količnik nedeljne Epo doze preračunate na kilogram telesne težine bolesnika i koncentracije hemoglobina:

$$ERI = \frac{\text{Epo doza U/kg/nedeljno}}{\text{Hb g/l}}$$

Na početku istraživanja dobijeni su podaci za sledeće varijable: starost bolesnika, trajanje hemodijalize, osnovna bolest, upotreba inhibitora angiotenzin-konvertujućeg enzima (ACEI). Hemoglobin, ERI i Epo doze su određivani svakog meseca, a ostale laboratorijiske analize u januaru, aprilu, julu i oktobru tokom perioda praćenja bolesnika. Izuzetak su paratiroidni hormon (iPTH), CRP i albumin koji su mereni samo u aprilu i oktobru. Od pojedinčanih varijabli koje su izmerene više puta tokom godine formirane su godišnje aritmetičke sredine za svakog bolesnika koje su korišćene dalje u statističkoj analizi. Muški pol je označen sa 1 a ženski sa 2. Bolesnici koji su upotrebljavali ACEI su označeni 1 a ostali sa 0.

Vrednosti u tekstu i tabelama prikazane su kao aritmetička sredina (standardna devijacija) ili kao frekvencije za obeležja kategorija. Odabir testova i analiza zasnivao se na osnovnim principima statistike. Prvo je urađena deskriptivna statistika. Statistička značajnost, razlika srednjih vrednosti procenjena je primenom dvosmernog Studentovog t-testa, a razlika između frekvencija primenom χ^2 testa. Statistička značajnost procenjivana je na osnovu nivoa značajnosti $p < 0{,}05$. Korelaciona analiza je urađena upotrebom Pirsonovih koeficijenta između parametrijskih varijabli a u ostalim slučajevima Spirmanovim testom. Pokazala je povezanost ERI i drugih varijabli kao i potencionalnu kolinearnost između pojedinih varijabli ($r > 0{,}5$ ili $\rho > 0{,}5$).

Za utvrđivanje činilaca povezanih sa ERI korišćena je linearna regresiona analiza. Pri tome je ERI bila zavisna varijabla, a sve ostale varijable su testirane kao nezavisne varijable. Univarijantnom regresinonom analizom odabrani su potencijalni prediktori povezani sa ERI ($p < 0{,}10$). Multivarijantna analiza je urađena metodom „korak po korak" (*stepwise*) i omogućila je selekciju nezavisnih prediktora povezanih sa ERI. Dijagnostika kolinearnosti rađena je na osnovu korelacione analize i na osnovu posebnih testova (VIF, *tolerance*, *eigenvaule*, *condition index*). Celokupna statistička obrada podataka izvedena je primenom programskog paketa SPSS.

Rezultati

U **Tabeli 1** prikazane su karakteristike ispitane grupe bolesnika. Bolesnici su bili starijeg životnog doba, prosečne starosti 67,5 godina. Svi su lečeni najmanje 12 meseci ponavljanim hemodijalizama a prosečno vreme provedeno na hemodijalizi bilo je 43,9 meseci. Od 48 bolesnika, dva su imala antitela na hepatitis C virus (HCV), dok kod ostalih nisu otkriveni markeri virusa hepatitisa. Prosečan srednji arterijski pritisak bio je u granicama normalnog, a samo 16 bolesnika koristilo je inhibitore angiotenzin-konvertaze u terapiji hipertenzije. Prosečan indeks adekvatnosti hemodijalize, Kt/V, bio je u preporučenom opsegu.

U **Tabeli 2** prikazano je kretanje laboratorijskih parametara tokom godine dana ispitivanja. Aritmetička sredina koncentracije uree i kreatinina bila je u granicama prihvatljivim za ovu metodu lečenja. Vidljivo je da su koncentracije kalcijuma, fosfora i alkalne fosfataze bile u granicama normalnih vrednosti, dok su vrednosti parathormona bile povišene. Tokom godine ispitivanja nije

Tabela 2. Laboratorijski parametri izmereni tokom jednogodišnjeg ispitivanja
Table 2. *Laboratory parameters measured during one-year follow up*

	Januar *January*	April *April*	Jul *July*	Oktobar *October*
Hemoglobin, g/l/*Hemoglobin, g/l*	110,2(12,1)	116,7 (15,2)	118,9 (12,8)	117,4 (11,8)
Hematokrit, %/*Hematocrit, %*	34,3 (4,1)	36 (4,8)	36,8 (4,2)	34,5 (3,9)
Urea, mmol/l/*Urea, mmol/l*	21,8 (7,1)	21,4 (4,6)	19,9 (2,5)	18,6 (3,4)
Kreatinin, µmol/l/*Creatinine, µmol/l*	695,9 (145)	717,2 (121,6)	705,7 (158)	626,6 (111,5)*
Kalcijum, mmol/l/*Calcium, mmol/l*	2,5 (0,3)	2,5 (0,2)	2,4 (0,2)	2,4 (0,2)
Fosfor, mmol/l/*Phosphorus, mmol/l*	1,3 (0,4)	1,3 (0,4)	1,3 (0,4)	1,4 (0,4)
Alkalna fosfataza, IU/L/*Alkaline phosphatase, IU/L*	81,9 (36,7)	87,2 (40,2)	85 (44,8)	87,5 (41,9)
PTH, pg/ml	–	189,7 (510,6)	235,1 (543,7)	–
CRP, mg/l		10,1 (19,4)	–	10,5 (18)
Albumini, g/l/*Albumins, g/l*		39,88 (2,5)	–	38,75 (2,9)
Gvožđe, µmol/l/*Iron, µmol/l*	15,1 (7,4)	15,8 (6,2)	17,4 (6,3)	20,1 (7,5)**
Transferin, g/l/*Transferrin, g/l*	1,4 (0,2)	1,5 (0,2)	1,4 (0,2)	1,4 (0,2)
Saturacija transferina, %/*Saturation of transferrin, %*	38,5 (19,7)	46,5 (18,6)	46,6 (25,68)	49,3 (12,3)**
Feritin, ng/ml/*Ferritin, ng/ml*	1346,7 (688,9)	1600,7 (601,8)	1634,1 (563,3)	1589,6 (550,3)

*p = 0,003 u odnosu na vrednost u aprilu/*compared to the value in April*, **p < 0,05 u odnosu na vrednost u januaru/*compared to the value in January,* PTH - paratiroidni hormon/*parathyroid hormone,* CRP - C-reaktivni protein/*C-reactive protein*

zabeležena značajna promena u koncentraciji ovih parametara. Koncentracije gvožđa i transferina, kao i saturacija transferina bile su u preporučenim intervalima, koncentracija feritina kretala se iznad preporučenih vrednosti.

U **Tabeli 3** je uporedo prikazana prosečna koncentracija i opseg izmerenih koncentracija hemoglobina, nedeljne Epo doze po kilogramu telesne težine, te ERI u četiri meseca ispitivanja i za celu godinu. Opseg individualnih vrednosti i hemoglobina i prosečne doze Epo pokazuju individualne razlike, ali su one bile mnogo veće za dozu Epo nego za koncentraciju hemoglobina. Upravo tim podešavanjima doze Epo postignuto je održavanje ciljne koncentracije hemoglobina. Zbog velikih individualnih razlika u dozi Epo i razlike između individualnih vrednosti ERI bile su velike, pa je najniža individualna vrednost ERI bila 0,13 U/kg/nedeljno/g/l, a najviša čak 2,46 U/kg/nedeljno/g/l.

Na **Grafikonu 1** prikazana je raspodela bolesnika prema prosečnoj koncentraciji hemoglobina i broj bolesnika kod kojih je koncentracija hemoglobina bar jedanput tokom godine dana bila ispod 100 g/l. Iako je prosečna koncentracija hemoglobina bila kod 46 od 48 bolesnika iznad 100 g/l, kod 19 bolesnika je tokom 2010. godine ova koncentracija jedan do 9 puta bila manja od 100 g/l. Kao što se i očekivalo, ovako niska vrednost hemoglobina češće se javljala kod bolesnika sa prosečnom koncentracijom hemoglobina manjom od

Tabela 3. Koncentracije hemoglobina, nedeljne doze Epo i ERI tokom jednogodišnjeg ispitivanja
Table 3. *Hemoglobin level, weekly doses of human recombinant erythropoietin (Epo) and erythropoietin resistance index (ERI) during one-year follow up*

Mesec/*Month*	Hemoglobin, g/l *Hemoglobin,g/l*	Doza rHuEPO, U/kg/nedeljno *Dose of rHuEPO,U/kg/week*	ERI, U/kg/nedeljno/g/l *ERI, U/kg/weekly/g/l*
Januar/*January*	110,2 (12,2) 86-139	87,9 (53,9) 22-244	0,83 (0,57) 0,19-2,46
April/*April*	116,7 (15,2)* 87-138	90,5 (51,5) 24-224	0,79 (0,47) 0,19-2,44
Jul/*July*	118,9 (12,8)* 94-140	70,4 (50,9)** 22-210	0,61 (0,51)* 0,17-2,14
Oktobar/*October*	117,4 (11,8)* 93-139	68,7 (43,6)** 15-220	0,59 (0,42)* 0,13-2,2
Za celu godinu/*For the whole year*	116,1 (7,4)	79,5 (45,8)	0,70 (0,52)

Vrednosti predstavljaju aritmetičku sredinu (standardna devijacija) i opseg/*The values present mean and range.*
rHuEpo − rekombinantni humani eritropoetin/*recombinant human erythropoietin;* *p < 0,05 u odnosu na vrednost u januaru/*compared to the value in January;* **p < 0,05 u odnosu na vrednost u aprilu/*compared to the value in April*

Tabela 4. Rezultati multivarijantne linearne regresione analize (korak po korak) kojom su izdvojene varijable statistički značajno povezane sa indeksom rezistencije na eritropoetin
Table 4. *Results of multivariate linear regression analysis (stepwise) which found out variables significantly associated with the erythropoietin resistance index*

Standardizovane vrednosti (z-score) *Standardized values*	Koeficijent *Coefficient*	Interval poverenja *Confidence interval*	p
zEPO doza/*dose*	0,33	0,31 do 0,34	< 0,01
zHb	-0,04	-0,95 do -0,03	< 0,01
zCRP	0,02	0,01 do 0,03	< 0,01

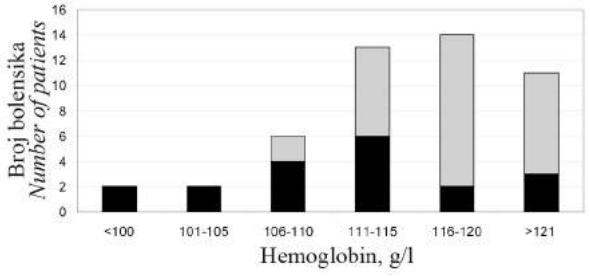
EPO - humani rekombinantni eritropoetin/*human recombinat erythropoietin*, CRP - C-reaktivni protein/*C-reactive protein*

110 g/l. Kod 7 bolesnika koncentracija hemoglobina ispod 100 g/l zabeležena je tri i više puta i to su bolesnici koji se mogu smatrati bolesnicima sa slabim odgovorom na Epo.

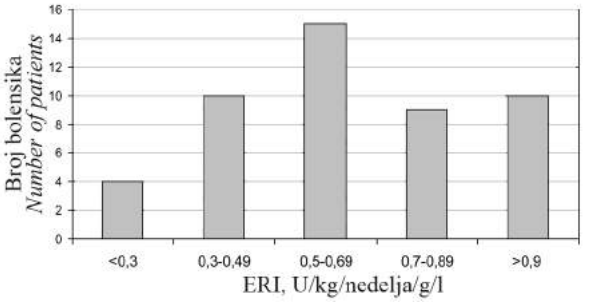
Analiza individualnih vrednosti ERI pokazala je velike razlike u vrednosti ovog indeksa između pojedinih bolesnika. Izračunata je prosečna vrednost ERI za svakog bolesnika na osnovu 12 vrednosti dobijenih tokom 12 posmatranih meseci. Pokazalo se da je najniža prosečna vrednost ERI bila 0,29 U/kg/nedeljno/g/l, a najviša vrednost, zabeležena kod jednog bolesnika, bila je 2,14 U/kg/nedeljno/g/l. **Grafikon 2** prikazuje distribuciju bolesnika prema veličini ERI. Vidi se da je 14 (30%) bolesnika imalo prosječan ERI ispod 0,5 U/kg/nedeljno/g/l, što ukazuje na dobar odgovor na Epo. Međutim, 19 (40%) bolesnika imalo je ERI iznad 0,7 U/kg/nedeljno/g/l, a čak 10 (21%) iznad 0,9 U/kg/nedeljno/g/l. To ukazuje da procenat bolesnika sa slabim odgovorom na Epo nije zanemarljiv.

Korelaciona analiza je, kao što se i očekivalo, pokazala da postoji jaka povezanost između ERI i doze Epo (Spearman, $\rho = 0,98$; $p < 0,01$), ERI i hemoglobina ($\rho = -0,60$; $p < 0,01$), ali i ERI i Kt/V ($\rho = -0.45$; $p < 0,01$) i ERI i indeks telesne mase (BMI) ($\rho = -0,38$; $p < 0,01$). Hemoglobin je statistički značajno korelirao sa Epo dozom ($\rho = 0,48$; $p < 0,011$). Epo doza je statistički značajno korelirala pored ERI i hemoglobina i sa Kt/V ($\rho = 0,50$; $p < 0,01$) i BMI ($\rho = -0,43$; $p < 0,01$). Statistički značajne korelacije postojale su između serumskog gvožđa i feritina (Pearson; $r = 0,99$; $p < 0,01$), saturacije transferina gvožđem i feritina ($r = 0,52$; $p < 0,01$), godina i kreatinina ($r = -0,55$; $p < 0,01$), godina i *mean arterial pressure* (MAP) ($r = -0.43$; $p < 0,01$), MAP i kreatinina ($r = 0,43$; $p < 0,01$), BMI i Kt/V ($r = -0,44$; $p < 0,01$) i MAP i albumina ($r = 0,38$; $p < 0,01$). Takođe, statistički značajne korelacije postojale su između meseci provedenih na dijalizi i BMI ($\rho = -0,51$; $p < 0,01$), meseci provedenih na dijalizi i nivoa kalcijuma u serumu ($\rho = 0,44$; $p < 0,01$), Kt/V i CRP ($\rho = -0.51$; $p < 0,01$), albumina i CRP ($\rho = -0,30$; $p < 0,05$), CRP i nivoa gvožđa u serumu ($\rho = -0,44$; $p < 0,01$), Ca i iPTH ($\rho = -0,54$; $p<0,01$).

Da bi se otkrili činioci koji utiču na terapijski odgovor tokom lečenja eritropoetinom urađena je linearna regresiona analiza. Zavisna varijabla je bio ERI a ostale (demografske, kliničke i laboratorijske) testirane su kao nezavisne varijable. Univarijantnom linearnom regresionom analizom izdvojene su starost, Epo doza, indeks adekvatnosti hemodijalize Kt/V, CRP, koncentracija hemoglobina, albumina, feritina, transferina i alkalne fosfataze, saturacija transferina i BMI kao potencijalni prediktori koji su povezani sa ERI. Korelaciona dijagnostika u regresionom modelu pokazala je moguće probleme u vezi sa kolinearnosti CRP pa je



Grafikon 1. Distribucija bolesnika prema prosečnoj koncentraciji hemoglobina i broj bolesnika kod kojih je tokom jednogodišnjeg ispitivanja bar jedanput koncentracija hemoglobina bila ispod 100 g/l (tamniji deo stubića)
Graph 1. *Distribution of patients according to the mean concentration of hemoglobin and number of patients with at least one hemoglobin concentration value below 100 g/l (the darker part of columns*)



Grafikon 2. Distribucija bolesnika prema prosečnoj vrednosti indeksa rezistencije na eritropoetin izračunatoj na osnovu 12 vrednosti zabeleženih u toku 12 meseci ispitivanja
Graph 2. *Distribution of patients according to the mean value of erythropoietin resistance index calculated from 12 values recorded in the 12 follow-up months*

urađena transformacija varijabli u standardizovane vrednosti (*z-score*) čime su problemi rešeni. Pri tome je koeficijent determinacije R^2 iznosio 0,99 što znači da je model objasnio gotovo celokupni varijabilitet te da se radi o vrlo jakom modelu. U **Tabeli 4** prikazani su rezultati multivarijantne linearne regresione analize koja je pokazala da su Epo doza, hemoglobin i CRP nezavisni prediktori povezani sa ERI. Kako je ERI količnik Epo doze i hemoglobina, jasna je njihova povezanost sa ERI, a u ovom modelu su upotrebljeni radi realnije analize (*adjusting*). Stoga je regresiona analiza otkrila jedino povezanost CRP sa ERI.

Diskusija

Istraživanja u ovom radu obuhvatila su 48 bolesnika koji su lečeni hroničnim hemodijalizama u *Fresenius Medical Care* centru za dijalizu u Šamcu. Svi bolesnici lečeni eritropoetinom praćeni su godinu dana i tokom tog perioda analiziran je njihov odgovor na lečenje, kao i činioci koji utiču na oporavak. Kod svih bolesnika je postignuta ciljna koncentracija hemoglobina 100-120 g/l ali je prosečna nedeljna doza Epo za pojedine bolesnike bila od 64,8 do 94,1 U/kg/nedeljno. ERI pojedinih bolesnika takođe je pokazao velike individualne varijacije i kretao se od 0,13 U/kg/nedeljno/g/l do 2,46 U/kg/nedeljno/g/l. Devetnaest (40%) bolesnika imalo je prosečan ERI iznad 0,7 U/kg/nedeljno/g/l, a čak 10 (21%) iznad 0,9 U/kg/nedeljno/g/l, što ukazuje da procenat bolesnika sa slabim odgovorom na Epo nije zanemarljiv. Multivarijantna regresiona analiza pokazala je da je CRP značajno povezan sa ERI.

Anemija je jedna od karakteristika i redovan pratilac HBI koji značajno utiče na kvalitet života, obolevanje i smrtnost bolesnika [17]. Iako je anemija u HBI multifaktorski poremećaj, uvođenje Epo omogućilo je njeno uspešno lečenje. Prema preporuci poznatih svetskih vodiča o lečenju anemije u HBI, ciljna vrednost koncentracije hemoglobina koju treba postići je 11-12,5 g/dl [11,18]. Međutim, klinička iskustva pokazala su da postizanje i održavanje tog ciljnog opsega hemoglobina nije jednostavno. S jedne strane, postoje velike varijacije u odgovoru na lečenje, a zbog toga i velike varijacije u dozi Epo potrebnoj da se postigne odgovarajući oporavak [19-21]. S druge strane, opisane su značajne varijacije u koncentraciji hemoglobina pojedinih bolesnika u funkciji vremena pa samo mali procenat bolesnika održava stabilnu ciljnu koncentraciju hemoglobina [14,15,22]. Posebna pažnja posvećena je istraživanjima nedovoljnog odgovora na lečenje Epo i činiocima koji uzrokuju taj neadekvatan odgovor [19,23].

Ispitivanjem parametara anemije kod naših bolesnika u toku 2010. godine pokazano je da su prosečne koncentracije hemoglobina i hematokrita bile u granicama normalnih vrednosti. Prosečna koncentracija hemoglobina kretala se između 110,2 i 118,9 g/l. Tokom cele godine prosečna koncentracija hemoglobina za celu grupu bila je iznad 110 g/l, što je u skladu sa preporukom Evropskog vodiča za lečenje anemije [11]. Povremeno se koncentracija hemoglobina kod pojedinih bolesnika smanjila ispod 100 g/l ali je neprekidnim podešavanjem Epo doze prosečna koncentracija hemoglobina bila u ciljnom opsegu. Upravo zbog tog neprekidnog podešavanja Epo doze prema koncentraciji hemoglobina, nedeljna Epo doza za pojedine bolesnike široko je varirala, a prosečna nedeljna doza Epo kretala se od 64,8 do 90,5 U/kg. Održavanje ciljne koncentracije hemoglobina postignuto je i redovnom kontrolom koncentracije gvožđa i feritina u serumu i podešavanjem doze gvožđa koje su bolesnici dobijali. To je omogućilo da se spreči sideropenija, kao glavni uzrok lošeg odgovora na Epo, ali i preopterećenje organizma gvožđem. Značaj održavanja koncentracije hemoglobina u ciljnom opsegu istakli su brojni autori. Održavanje hemoglobina ispod 100 g/l kao i česte varijacije sa padom koncentracije hemoglobina ispod 100g/l povezane su sa povećanim rizikom od smrtnosti [24–27]. S druge strane, pokušaji da se ciljni hemoglobin poveća pokazali su da je povećanje hemoglobina preko 130 g/l takođe povezano sa većim mortalitetom [26,28–31]. Zbog toga su razumljivi rezultati većeg broja autora koji su pokazali da je i varijacija hemoglobina u funkciji vremena povezana sa povećanom smrtnošću bolesnika, češćim komorbiditetima i češćim hospitalizacijama [14,15,31,32]. Da bi se koncentracija hemoglobina održavala u preporučenom, relativno uskom ciljnom opsegu, neophodne su redovne kontrole hemoglobina ovih bolesnika i podešavanje doze Epo.

Odgovor na terapiju eritropoetinom i varijacije u tom odgovoru procenjeni su u ovom radu pomoću ERI koji predstavlja odnos između Epo doze i odgovora izraženog koncentracijom hemoglobina. Pokazane su velike individualne varijacije u vrednosti ovog indeksa, što je u skladu sa brojnim studijama, koje su obuhvatile desetine hiljada bolesnika, i pokazale da su različiti bolesnici zahtevali različite Epo doze za održavanje ciljne vrednosti hemoglobina [14,15,24,31].

Da bi se otkrili činioci koji utiču na terapijski odgovor tokom lečenja eritropoetinom, urađena je linearna regresiona analiza. Multivarijantna linearna regresiona analiza izdvojila je CRP kao jedinu varijablu značajno povezanu sa ERI. Inflamacija i malnutricija su dobro poznati pratioci HBI, a veći broj radova je pokazao da je zapaljenje jedan od činilaca koji smanjuje odgovor na eritropoetin. U velikoj studiji koja je obuhvatila 1 754 bolesnika lečena hemodijalizama dokazana je visoko značajna korelacija između CRP i doze eritropoetina [33]. Slično je potvrdilo nekoliko manjih studija [34,35], kao i studija Locatellija i saradnika koja je obuhvatila 677 bolesnika [36]. Naši rezultati su u skladu sa svim ovim rezultatima, jer se CRP pokazao kao značajan nezavisan prediktor slabog odgovora na eritropoetin. S tim u skladu je i nalaz povezanosti između albumina i indeksa re-

zistencije, jer su albumini ne samo marker pothranjenosti nego i zapaljenja. Pored malnutricije i inflamacije kao prediktora slabog odgovora na Epo, opisani su i nedostatak gvožđa, hiperparatiroidizam, postojanje dijaliznog katetera, mnoga komorbidna stanja [23,34,36,37]. Zavisnost ERI od gvožđa nije pokazana u ovom radu najverovatnije zbog dobre kontrole feremije.

Vrednost ove studije je jednogodišnje praćenje odgovora bolesnika na Epo, što je duže nego u većini drugih studija [24,29,38]. Duže praćenje omogućava da se dobiju verodostojniji podaci o varijacijama hemoglobina, ali i o odgovoru na Epo. Nedostaci studije su što nisu bili uključeni bolesnici kod kojih su postojali dobro poznati uzroci anemija – krvarenja, operacije, hronične infekcije, maligne bolesti. Zbog toga se dobijeni rezultati ne mogu generalizovati. Međutim, ovakav izbor bolesnika omogućio je da se proveri da li i u populaciji bolesnika bez ovih dobro poznatih uzroka anemije postoje varijacije u hemoglobinu i razlike u odgovoru na Epo. Rezultati su potvrdili da ove varijacije postoje i da su uslovljene, pre svega, zapaljenjem, dobro poznatim pratiocem terminalne insuficijencije bubrega.

Zaključak

Istraživanja sprovedena u ovom radu potvrdila su da su za postizanje i održavanje ciljne vrednosti hemoglobina kod pojedinih bolesnika bile neophodne različite doze humanog rekombinantnog eritropoetina, kao i neprekidno podešavanje doze. To je pokazalo da postoje značajne individualne razlike u odgovoru na eritropoetin koji je procenjivan pomoću indeksa rezistencije na eritropoetin. C-reaktivni protein izdvojen je kao faktor značajno povezan sa indeksom rezistencije na eritropoetin. Zbog toga je neophodno da se neprekidno sprovodi prevencija i uporno lečenje svih komorbidnih stanja koja se javljaju kod bolesnika sa hroničnom insuficijencijom bubrega, posebno onih koja doprinose nastanku malnutricije i zapaljenja. Ove mere vodiće poboljšanju lečenja anemije koje ima značajan uticaj na kvalitet života, obolevanje, hospitalizaciju i preživljavanje bolesnika.

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Rad je primljen 12. VI 2012.
Recenziran 13. XII 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:130-137.

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

Printing of this journal ”Medical Review”
has been supported by
the Government of the AP of Vojvodina

STRUČNI ČLANCI
PROFESSIONAL ARTICLES

University of Novi Sad, Medical Faculty, Novi Sad[1]
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Stručni članak
Professional article
UDK 616.12-089.163/.168
DOI: 10.2298/MPNS1304139M

VOJVODINASCORE – LOCAL SYSTEM FOR CARDIAC OPERATIVE RISK EVALUATION

VOJVODINASKOR – LOKALNI SISTEM ZA EVALUACIJU KARDIOHIRURŠKOG OPERATIVNOG RIZIKA

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Summary

Introduction. The aim of the study was to investigate the prognostic value, sensitivity and specificity of both the logistic and additive European System for Cardiac Operative Risk Evaluation (as well as the European System for Cardiac Operative Risk Evaluation II and to assess the necessity for developing a local outcome prediction model in cardiac surgery. **Material and Methods.** The research included 406 consecutive patients who had undergone cardiac surgical procedures at Institute of Cardiovascular Diseases of Vojvodina from January 2012 to July 2012. The authors compared the predicted mortality according to the additive and logistic European Systems for Cardiac Operative Risk Evaluation, the new European System for Cardiac Operative Risk Evaluation II and the observed mortality (30 days after surgery). **Results.** The difference between the predicted and observed mortality regarding the whole group of 406 operated cardiac patients was not statistically significant for the additive European System for Cardiac Operative Risk Evaluation (p=0.081) and the European System for Cardiac Operative Risk Evaluation II (p=0.164), but it was statistically significant for the logistic European System for Cardiac Operative Risk Evaluation (p=0.031). The areas under the receiver operating characteristic curves are statistically different from 0.5 for both models (additive and logistic European System for Cardiac Operative Risk Evaluation), as well as for the European System for Cardiac Operative Risk Evaluation II. However, the proper classification of the patients has not been observed since their sensitivity and specificity are not satisfactory. **Conclusion.** The additive and logistic European Systems for Cardiac Operative Risk Evaluation overestimate while the European System for Cardiac Operative Risk Evaluation II underestimates the risk in cardiac surgery. We believe that a locally derived model would be of great use in the everyday clinical practice since it would faithfully illustrate the actual state of patient population of the region where it was developed. At the same time it would provide the accurate prediction of surgical outcome.

Key words: Risk Assessment; Cardiac Surgical Procedures + adverse effects; Cardiac Surgical Procedures + mortality; Predictive Value of Tests

Sažetak

Uvod. Cilj rada bio je da se ispitaju prognostička vrednost, senzitivnost i specifičnost tri sistema stratifikacije operativnog rizika u kardiohirurgiji (Evropski sistem za evaluaciju kardiohirurškog operativnog rizika - aditivni, logistički i najnoviji Evropski sistem za evaluaciju kardiohirurškog operativnog rizika II) i proceni da li je potrebno razviti lokalni sistem. **Materijal i metode.** Istraživanje je obuhvatilo 406 uzastopnih pacijenata kojima su, u prvih 6 meseci 2012. godine, u Institutu za kardiovaskularne bolesti Vojvodine, rađene kardiohirurške intervencije. Upoređivan je očekivani operativni rizik (mortalitet) sva tri navedena modela, sa stvarnim mortalitetom, koji je utvrđivan 30 dana posle kardiohirurške intervencije. **Rezultati.** Ustanovljeno je da nije bilo statistički značajnih razlika između očekivanog i stvarnog mortaliteta za aditivni model Evropskog sistema za evaluaciju kardiohirurškog operativnog rizika (p = 0,081) i novi Evropski sistem za evaluaciju kardiohirurškog operativnog rizika II (p = 0,164). Međutim, razlika je bila statistički značajna kada se uporedi stvarni operativni rizik sa očekivanim mortalitetom logističkog Evropskog sistema za evaluaciju kardiohirurškog operativnog rizika (P = 0,031). Sva tri modela pokazala su nedovoljnu senzitivnost i specifičnost. **Zaključak.** Aditivni i logistički Evropski modeli stratifikacije operativnog rizika precenjuju, a novi model Evropskog sistema za evaluaciju kardiohirurškog operativnog rizika potcenjuje operativni rizik u kardiohirurgiji. Verujemo da će lokalni model stratifikacije biti veoma koristan u svakodnevnoj kliničkoj praksi, jer će bolje ilustrovati stvarno stanje populacije kardiohirurških bolesnika i obezbediti tačnije predviđanje operativnog rizika.

Ključne reči: Procena rizika; Kardiohirurške procedure + neželjeni efekti; Kardiohirurške procedure + mortalitet; Prediktivna vrednost testova

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Abbreviations

EuroSCORE – European System for Cardiac Operative Risk Evaluation/*Evropski sistem za evaluaciju kardiohirurškog operativnog rizika*
STS – Society of Thoracic Surgeons
ROC – Receiver Operating Characteristic
AUC – Area under Curve

Introduction

The need to know the outcome of certain important medical intervention, such as cardiac surgery, has its roots in the human understanding and fear of death [1]. The outcome of a disease or surgery, in terms of survival, is obviously of great importance not only for the patient and his family but for his doctor as well. Mortality is only one of the determinants of the success of an intervention. Other indicators include: complications (morbidity), functional outcome (how fast and to what extent the patient has returned to his every-day activities), long-term survival, length of period before re-intervention, etc [2]. Since the patient population can significantly differ between institutions and geographical areas, neither the comparison of absolute numbers nor the results among institutions seem to suit its purpose [3]. Therefore, various risk stratification models have been developed trying to adjust the differences between the observed groups thus enabling the "real" comparison as well as the prediction of the surgical outcome. These models are means of determining the surgical outcome in relation to the preoperative patient condition [4]. Relatively speaking, a coefficient is assigned to the specific risk factor according to its influence on the outcome in order to provide a more accurate evaluation. Finally, the values of different risk factors are added to calculate the actual risk in terms of outcome (mortality, morbidity, price, etc.) for each patient. According to this value, the patients are classified into groups of low, mean and high risk level. In this way, a more objective comparison of surgical results is made possible and this approach is called risk stratification. Up to date, numerous risk stratification models have been developed – the most commonly used being the European System for Cardiac Operative Risk Evaluation (EuroSCORE), Society of Thoracic Surgeons (STS), Parsonnet, and Cleveland Clinic Score. Each of these models inspects closely a different number of factors, some of which overlap. The very fact that there are numerous models shows that none of them gives an absolutely precise prediction in terms of mortality.

The risk evaluation models in cardiac surgery are more developed than in any other medical field. The experience derived from their extensive use during the last two decades has led to their wide international acceptance and routine use in the outcome prediction. Everyone involved in the health system benefits from using the risk stratification models [5,6]. The new EuroSCORE II model was introduced last year [7].

Health authorities receive data about the number and severity of surgical procedures and they can plan their resources accordingly. The hospital management gains the tool enabling them to follow the success of an institution, the success of individuals and the possibility to evaluate each surgical procedure according to its risk. The doctors are given the opportunity to compare their results and to individualize their approach to each patient according to the severity of the disease. Finally and perhaps most importantly, the patients and their families are given objective information about the severity of disease and the risk which that specific surgical intervention carries.

The aim of the study was to investigate the prognostic value, sensitivity and specificity of both additive and logistic EuroSCORE as well as EuroSCORE II and to assess the necessity for developing a local outcome prediction model in cardiac surgery given all the specifics of the local population as well as customized healthcare system.

Material and Methods

Out of 406 consecutive patients from the study sample, 266 (65.5%), 78 (19.2%), and 62 (15.3%) patients had undergone coronary, valvular and combined surgery, respectively at the Institute of Cardiovascular Diseases of Vojvodina from January 2012 to July 2012. The authors analyzed the predicted mortality according to the EuroSCORE (additive and logistic), the EuroSCORE II and the observed mortality. Since the 30th postoperative day is of importance for the evaluation of results (operative risk evaluation) after cardiac surgery, all patients were contacted by phone in order to evaluate their status. Data were collected prospectively and analyzed retrospectively.

Statistical Analysis

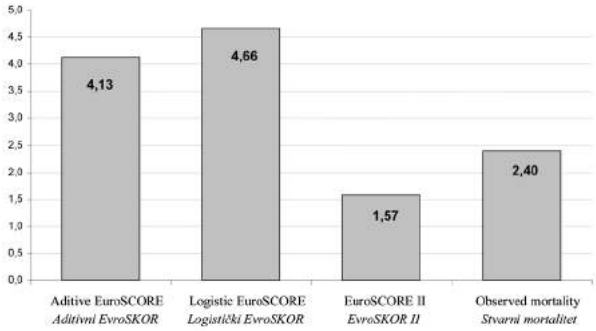
All results for continuous variables are expressed as median (the 25-th percentile–75-th per-

Table 1. All types of surgery
Tabela 1. *Svi tipovi hirurgije*

	Predicted mortality *Očekivani mortalitet*	Observed mortality *Stvarni mortalitet*	p value *p vrednost*
Additive EuroSCORE/*Aditivni EvroSKOR*	4.13%	2.4%	0.081
Logistic EvroSCORE/*Logistički EvroSKOR*	4.66%	2.4%	0.031
EuroSCORE II/*EvroSKOR II*	1.57%	2.4%	0.164

Table 2. Coronary surgery
Tabela 2. *Koronarna hirurgija*

	Predicted mortality *Očekivani mortalitet*	Observed mortality *Stvarni mortalitet*	p value *p vrednost*
Additive EuroSCORE/*Aditivni EvroSKOR*	3.73%	1.5%	0.055
Logistic EuroSCORE/*Logistički EvroSKOR*	4.66%	1.5%	0.029
EuroSCORE II/*EvroSKOR II*	1.57%	1.5%	0.828



Graph 1. Scores
Grafikon 1. *Skorovi*

centile). The comparisons between the groups were analysed by Mann-Whitney test. The percentages of 30-days mortality were compared by Chi-square test. The receiver operating characteristic (ROC) curve was generated and the area under the curve (AUC) was calculated. This method was used to investigate the prognostic value of additive, logistic EuroSCORE and EuroSCORE II. The sensitivity and specificity for optimal cut-off values were calculated. The differences were considered significant at $p<0.05$. The statistical analysis was performed using SPSS Version 18.

Results

The difference between the predicted and observed mortality regarding the whole group of 406 operated cardiac patients was not statistically significant for the additive EuroSCORE (p=0.081), and the EuroSCORE II (p=0.164), but it was statistically significant for the logistic EuroSCORE (**Table 1**).

The additive and logistic EuroSCORE overestimate, while the EuroSCORE II underestimates the risk in the whole group of 406 operated patients (**Graph 1**).

In coronary surgery, the difference between the predicted and observed mortality according to the additive and logistic EuroSCORE was significant, while it was not significant concerning the EuroSCORE II (**Table2**). The additive and logistic EuroSCORE overestimate the risk in coronary surgery.

In valvular surgery, the difference between the predicted and observed mortality according to the additive EuroSCORE, logistic EuroSCORE and the EuroSCORE II was not significant (p=0.979; p=0.927 and p=0.114, respectively – **Table 3**).

In combined, coronary and valvular surgery the difference between the predicted and observed mortality according to the additive EuroSCORE, logistic EuroSCORE and EuroSCORE II was not significant (p=0.661; p=0.466 and p=0.221, respectively – **Table 4**).

The areas under the receiver operating characteristics curves are statistically different from 0.5 for both models (the additive and logistic EuroSCORE), as well as for the EuroSCORE II. However, no reliable classification of the patients was

Table 3. Valvular surgery
Tabela 3. *Valvularna hirurgija*

	Predicted mortality *Očekivani mortalitet*	Observed mortality *Stvarni mortalitet*	p value *p vrednost*
Additive EuroSCORE/*Aditivni EvroSKOR*	3.79%	3.8%	0.979
Logistic EuroSCORE/*Logistički EvroSKOR*	4.05%	3.8%	0.927
EuroSCORE II/*EvroSKOR II*	1.6%	3.8%	0.114

Table 4. Combined surgery
Tabela 4. *Kombinovana hirurgija*

	Predicted mortality *Očekivani mortalitet*	Observed mortality *Stvarni mortalitet*	p value *p vrednost*
Additive EuroSCORE/*Aditivni EvroSKOR*	6.18%	4.8%	0.661
Logistic EuroSCORE/*Logistički EvroSKOR*	7.25%	4.8%	0.466
EuroSCORE II/*EvoSKOR II*	2.44%	4.8%	0.221

Table 5. Sensitivity and specificity
Tabela 5. *Senzitivnost i specifičnost*

	AUROC *AUROC*	p value *p vrednost*	Cut-off value *Granična vrednost*	Sensitivity *Senzitivnost*	Specificity *Specifičnost*
Additive EuroSCORE/*Aditivni EvroSKOR*	0.700	0.031	4.4	70%	60.5%
Logistic EuroSCORE/*Logistički EvroSKOR*	0.731	0.013	4.6	70%	71%
EuroSCORE II/*EvroSKOR II*	0.682	0.020	1.46	71.4%	63.7%

AUROC - Area Under the receiver operating characteristic curve

observed since the sensitivity and specificity are not satisfactory (**Table 5**).

Discussion

Choosing the most reliable model among many other models raises a question about how good the model really is in terms of effectiveness in relation to other models. Numerous factors can influence the model's predictive power: differences in risk factor definitions, the management of incomplete data, surgical procedure selection criteria, geographical differences etc. The prevalence of some risk factors can also change over time.

In our previous studies [8-11], we analyzed the predictive value of the EuroSCORE model in coronary surgery, as well as trends of risk factors included in the EuroSCORE model. It was observed that the profile of coronary patients undergoing surgery in one of the cardiac surgery centres is drastically changing primarily due to the significantly advanced percutaneous techniques for myocardial revascularization.

Nilsson et al. compared the characteristics of 19 different risk stratification models in cardiac surgery [12]. They followed both 30-day and 1-year outcome. This study involved 6222 patients who had undergone cardiac surgery in a single Swedish hospital from 1996 until 2001. The ROC curve analysis was used to test the performance and accuracy of different models. The EuroSCORE model was given the preference over other models because it was notably more accurate and reliable, included the acceptable number of involved variables and was widely spread all over the world.

The question of the optimal number of risk factors included in the outcome prediction model was raised. The model must be concise and able to give more accurate prediction with the least possible risk factors. The STS model, developed on more than 138,000 patients who had undergone surgery in 374 hospitals in the United States of America and Canada, shows excellent accuracy but uses 33 variables [13,14]. There are numerous reasons why it is important to restrict the number of variables. Beside the fact that big questionnaires demand more money, there is a danger of mistakes during data acquisition, coding and entering as well as of interdependence of risk factors. Contrary to the STS model, the original Cardiac Care Network (CCN) model had only 5 variables and, at the same time, showed the satisfying characteristics [15]. Similarly, Ranucci et al [16] suggested a model for elective cardiac surgery procedures consisting of only 3 variables: the patient's age, the increased level of creatinine and the percentage of the left ventricular ejection fraction (ACEF – *Age, Creatinine, and Ejection Fraction*).

The majority of the cardiac surgery centres perform less than 1500 cardiac surgical procedures annually. Surgeons in these institutions have three possibilities: 1) to apply and use some of the existing models („*ready-made*" model); 2) to recalibrate the existing model by defining new coefficients for specific factors (*recalibrate*); 3) to develop a completely new local model based on their experience calibrated in relation to their patient population (*remodel*). The later solution offers the best possibility to achieve adequate accuracy and good distinctive features of the model [15].

If the affirmation of the EuroSCORE model is followed from its establishment till the current days, it can be observed that both its discriminative power and its accuracy have been decreasing [17-19]. AUC as a measure of the discriminative power had values from 0.74 to 0.87 on various samples while its highest value was on the Finnish population [20]. The results of this study showed that the AUC value for the additive EuroSCORE model was 0.813, while it was 0.815 for the logistic EuroSCORE model. These values put the EuroSCORE model among the models with a great discriminative power. However, the poor calibration was confirmed for both additive and logistic models in the last three independent series of patients [21-23]. This could be explained by the fact that in time some advances have been made in surgical techniques, anaesthesiology approach, perioperative medication therapy, adequate patient selection, and perioperative patient care. This technological advance raised the question of the prediction power of the EuroSCORE model [24]. However, proofs from several European national registers for operated patients show that, in the same cases, mortality was reduced to half in spite of the fact that the patient profile has significantly changed when risk factors are concerned [25]. Patients undergoing surgery today have more risk factors on average, which results in higher values of the EuroSCORE [26].

It is possible to correct the EuroSCORE model in relation to the success of the specific hospital using the following formula: expected mortality = (the value of the logistic EuroSCORE model x Average hospital mortality)/average value of the logistic EuroSCORE model [27].

We advocate the development of self-made model for a number of reasons. A self-made model can usually handle input data (specific patient profile, constraints and advantages of healthcare environment) more reliably yielding better risk estimation. A self-made model depicts the ”real” status of unique healthcare process.

This study is not intended to deny the validity of the existing EuroSCORE. Clinical benchmarking and comparison of the results with other hospitals around the world is extremely important and only possible through standardized models such as the EuroSCORE. However, certain risk factors, not included in the EuroSCORE, have significant impact on the postoperative outcome.

The results of our study show that the EuroSCORE models (additive and logistic) as well as the EuroSCORE II have good prognostic value, but low sensitivity and specificity. This was the reason why we decided to design our local model for cardiac operative risk evaluation „VOJVODINASKOR”, based on four-year Project, supported by the Provincial Secretariat for Science and Technological Development - Vojvodina.

Limitation of the study: The EuroSCORE II model was created last year and it has been in clinical use since the beginning of 2012 [7]. After six months of experience we compared the additive EuroSCORE, logistic EuroSCORE and the EuroSCORE II, although this group of 406 operated patients is relatively small for statistical computation.

Conclusion

The additive and logistic European System for Cardiac Operative Risk Evaluation overestimate, while the European System for Cardiac Operative Risk Evaluation II underestimates the risk in cardiac surgery. We believe that a locally derived model would be of great use in everyday clinical practice since it faithfully illustrates the actual state of patient population of the region where it was developed. At the same time it would provide an accurate prediction of surgical outcome.

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Rad je primljen 19. XI 2012.
Recenziran 22. XI 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:139-144.

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Stručni članak
Professional article
UDK 618.2-073.43:576.316
DOI: 10.2298/MPNS1304145K

MERENJA NUHALNE TRANSLUCENCIJE − DOPRINOS 3D/4D ULTRAZVUKA

NUCHAL TRANSLUCENCY MEASUREMENT – THE EFFECT OF 3D/4D ULTRASOUND

Gordana KOZAROV[1], Tanja MARJANOVIĆ MILOŠEVIĆ[2] i Boško VUKŠIĆ[2]

Sažetak

Uvod. Debljina nuhalne translucencije, potvrđen marker u skriningu fetalnih hromozomopatija, meri se ultrazvukom u prvom trimestru trudnoće. Cilj rada je odrediti uticaj korišćenja 3D/4D ultrazvuka na standardnu grešku merenja debljine nuhalne translucencije. **Materijal i metode.** Studija obuhvata 430 merenja kojima su zadovoljeni kriterijumi uključivanja (jednoplodna trudnoća, sonografija između 11^{+0} i 13^{+6} gestacijskih nedelja, dužina teme–trtica 45−84 mm, postnatalno potvrđeno odsustvo anomalija). Prikupljeni podaci raspoređeni su u dve grupe, prema korišćenoj ultrazvučnoj metodi (2D ultrazvuk starije generacije ili 3D/4D ultrazvuk). Izmerene vrednosti nuhalne translucencije konvertovane su u multiple medijane nuhalne translucencije i izračunat je 95% interval poverenja za dve grupe podataka. **Rezultati. S**tandardna greška srednje vrednosti smanjena je sa 0,027, kada je nuhalna translucencija merena 2D metodom, na 0,016 kada se koristi 3D/4D metod. **Diskusija**. Smanjenjem standardne greške srednje vrednosti merenja omogućeno je poboljšanje stepena detekcije i smanjenje stope lažno pozitivnih rezultata prenatalnih skrining testova. **Zaključak**. Usavršavanjem tehnologije i razvojem automatizovanog merenja nuhalne translucencije očekuje se poboljšanje u ranoj detekciji fetalnih hromozomopatija.

Ključne reči: Merenje nuhalne translucencije; Prenatalna ultrasonografija; Tridimenzionalno snimanje; Trudnoća, prvi trimestar; Prenatalna dijagnoza; Skrining; Kompjuterska analiza slike

Summary

Introduction. Nuchal translucency thickness has undoubtedly been proven as an important marker in screening for chromosomal abnormalities. It is measured in the first trimester by ultrasound. This study was aimed at determining the effect of 3D/4D ultrasound on standard error of mean nuchal translucency measurements. **Material and Methods**. Having satisfied the inclusion criteria, 430 nuchal translucency measurements were analyzed (singleton pregnancies, 11^{+0}-13^{+6} weeks of gestation, crown rump length 45-84mm, postnatally confirmed absence of anomalies). The data were divided into two groups, depending on the method used (older generation 2D ultrasound or 3D/4D ultrasound). The reported nuchal translucency measurements were converted into multiple of median values of nuchal translucency and 95% confidence interval was calculated for the two sets of data. **Results**. The standard error of mean values has decreased from 0.027, when nuchal translucency was mea-sured via 2D ultrasound, to 0.016 when 3D/4D ultrasound was used for the measurements. **Discussion.** The detection rates of prenatal screening tests can be increased and the false positive rates can be decreased by lowering the standard error of mean value. **Conclusion**. Advanced technology and developed automated measuring of nuchal translucency should result in further enhancements in early detection of fetal abnormalities.

Key words: Nuchal Translucency Measurement; Ultrasonography, Prenatal; Imaging, Three-Dimensional; Pregnancy Trimester, First; Prenatal Diagnosis; Mass Screening; Image Processing, Computer-Assisted

Uvod

Veza uvećane nuhalne translucencije (NT) i fetalnih hromozomalnih anomalija jasno je utvrđena i više puta potvrđena. Merenjem NT, kao zasebnog parametra, može se identifikovati čak više od 70% trudnoća sa trizomijom 21 u prvom trimestru trudnoće uz stopu lažno pozitivnih rezultata od 5% [1]. Integracijom skrining markera, određenih u različitim stadijumima trudnoće u jedan test, povećan je stepen detekcije hromozomopatija te postignuto sniženje stope lažno pozitivnih rezultata. Skrining kombinovanjem parametara NT i starost majke u našoj sredini ima senzitivnost od 66%, specifičnost od 96,8%, uz stopu lažno pozitivnih rezultata od 3,1% [2]. Izveštaj studije „Serum, urin i ultrazvučni skrinig8 (SURUSS) preporučio je Integrisani test (objedinjuje NT i biohemijske markere) kao test prvog izbora za prenatalni skrining fetalnih hromozomopatija, sa procenjenim nivoom detekcije 85% i stopom lažno pozitivnih rezultata od svega 0,9% [3].

Nuhalna translucencija, kao izolovani marker, ima značajno manju dijagnostičku vrednost, ali s obzirom da je sastavni deo prenatalnih skrining testova za detekciju fetalnih hromozomopatija, smanjenjem greške u merenju NT logično će dovesti i do porasta stepena detekcije, a smanjenja

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Skraćenice

NT	− nuhalna translucencija/*Nuchal translucency*
CRL	− dužina teme−trtica/*Crown-Rump Lenght*
SEM	− standardna greška srednje vrednosti
MoM	− umnožak medijane
GN	− gestacijska nedelja
US	– ultrazvuk

stope lažno pozitivnih rezultata u testovima čiji je NT sastavni deo.

Cilj ovog rada bio je da kvantifikuje koliko se upotrebom sofisticiranijih ultrazvučnih (US) aparata, koji omogućavaju 3D/4D prikaz, menja standardna greška srednje vrednosti (SEM) merenja NT.

Materijal i metode

U istraživanje su uključene trudnice sa jednoplodnom trudnoćom koje su se javile na UZ pregled između 11+0 i 13+6 gestacijske nedelje (dužina teme−trtica (CRL) 45−84 mm) u sklopu rutinske prenatalne nege u našoj ustanovi. U radu su analizirani samo podaci o trudnoćama sa potvrđenim ishodom, a tokom perioda istraživanja od osam godina (mart 2001–septembar 2009. godine). Kako bi se istraživanje ograničilo na određivanje uticaja metode merenja (2D ili 3D/4D) sva merenja vršio je jedan ginekolog-akušer. Korišćeni US aparati su *Toshiba SAL9900* (2D metoda merenja NT) i GE *Voluson730Expert* (3D/4D metoda merenja NT). U svim merenjima korišćena je transabdominalna sonda frekvencije 3,5 MHz. Merenja su vršena pri sagitalnom preseku fetusa i takvom uvećanju slike da glava i grudni koš fetusa zahvata najmanje 75% ekrana [4]. Nuhalna translucencija, translucencija između nuhalne kože fetusa i mekog tkiva, merena je na mestu najveće razlike. Višeplodne trudnoće, kao i trudnoće sa fetalnim cističnim higromom isključene su iz studije.

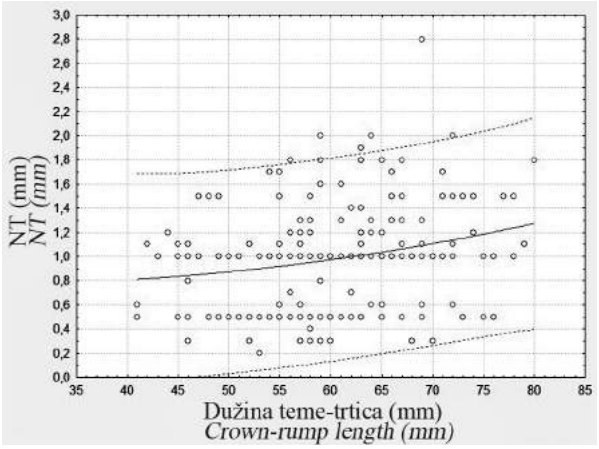
Prikupljeni podaci o izmerenoj debljini NT i dužini CRL upareni su i podeljeni u dve grupe − Grupa 1 merenja 2D metodom; Grupa 2 merenja 3D/4D metodom. U svakoj grupi podataka analiziran je odnos između NT i CRL primenom kvadratne linearne regresione jednačine. Kako bi se apsorbovale promene NT koje nastaju sa povećanjem CRL, sve vrednosti NT su relativizovane tj. konvertovane u multiple medijane (MoM) NT. Na kraju, izračunata je medijana MoM NT kao i standardna greška srednje vrednosti (SEM) MoM NT.

Tokom statističke analize korišćen je softverski program *Statistica 8.0* ($p < 0,05$ smatra se statistički značajnom).

Pregled populacije dat je u **Tabeli 1.**

Rezultati

Ukupno je analizirano 430 merenja koja su zadovoljila parametre studije. Krive odnosa NT/CRL za svaku od grupa podataka povučene su na osnovu dobijenih podataka. Korišćenjem regresione analize izračunata je jednačina za svaku od kriva, a potom i MoM NT, devijacija izmerene NT od očekivane NT za taj CRL izračunatog jednačinom linearne regresije.



Grafikon 1. 2D metoda; vrednost distribucije NT (nuhalna translucencija) prema CRL (dužina teme-trtica)
Graph 1. *2D method; Distribution of NT values (nuchal translucency) against CRL (Crown-rump length)*

Grafikoni 1 i **2** prikazuju distribuciju, 5. i 95. percentil, donji i gornji limit apsolutnih vrednosti NT.

Jednačina linearne regresije koja stavlja NT u odnos sa CRL za svaku od metoda merenja glasi:

2D metoda:

$NT\ (mm) = 0,8686 – 0,0082CRL + 0.0002CRL^2$

3D/4D metoda:

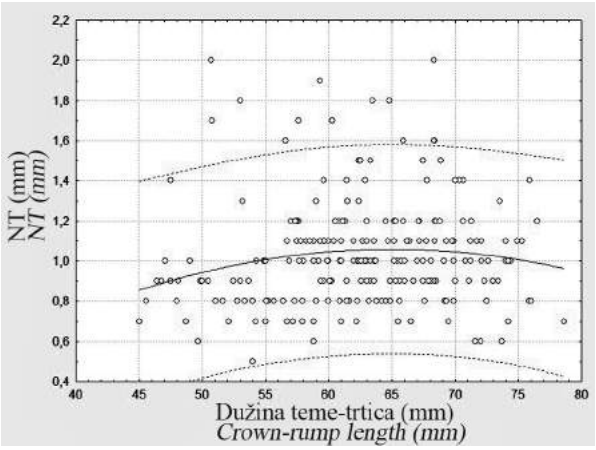
$NT\ (mm) = –1,1096 + 0,0668CRL – 0,0005CRL^2$

MoM NT, vrednost NT zavisna od CRL tj. gestacijske starosti, potom je upoređena između dve

Tabela 1. Opis populacije uključene u studiju
Table 1. *Description of study population*

	2D metoda/*2D method*	3D/4D metoda/*3D/4D method*
Populacija (N)/*(Population (N))*	200	230
Starost majke (godine)/*Maternal age (years)*	27,8 ± 8,9	30,7 ± 9,02
Nedelja gestacije/*Weeks of gestation*	12+1 ± 1+3	12+3 ± 1
Srednja vrednost CRL/*Mean CRL*	60,47 ± 17,25	62,7 ± 14,15
Srednja vrednost NT/*Mean NT*	0,99 ± 0,87	1 ± 0,5

CRL – dužina teme−trtica/*crown-rump lenght*, NT – nuhalna translucencija/*nuchal translucency*



Grafikon 2. 3D/4D metoda; vrednost distribucije NT (nuhalna translucencija) prema CRL (dužina teme−trtica)
Graph 2. *3D/4D method; Distribution of NT values (nuchal translucency) against CRL (Crown-rump length)*

(bez starosti majke) kao markera povećan stepen detekcije za 5% uz stepen lažno pozitivnih rezultata od 5% kada su korišćeni upravo ovi specifični referentni intervali [6].

Postavljenjem parametara istraživanja u smislu kriterijuma *odabira populacije* i kriterijuma *sva merenja* vrši jedan ginekolog-akušer, došli smo do zaključka da doprinos opreme kao faktora, a izraženo u promeni standardne greške merenja NT, čak 60%, nesumnjivo utiče i na krajnji rezultat antenatalnog skrining testa u koji je ovaj parametar integrisan. Vrednost smanjenja SEM od 60% u sebi sadrži dve komponente, korišćenu metodu merenja (2D/3D/4D) i rezoluciju aparata (*Toshiba SAL9900/GE Voluson730Expert*), koje bi u nekom od narednih istraživanja bilo zanimljivo raščlaniti i odvojeno analizirati.

Ono što smo praktično uočili tokom istraživanja jeste da se NT ne može adekvatno izmeriti na svakom pregledu zbog neodgovarajućeg položaja fetusa, te je tada neophodno zakazati dodatni pregled

Tabela 2. Rezultati
Table 2. *Results*

	2D metoda*/2D method*	3D/4D metoda*3D/4D method*
Srednja vrednost MoM NT/*Mean MoM NT*	0,89	0,90
SEM MoM NT/*SEM MoM NT*	0,027	0,016
95% interval poverenja NT/*95% Confidence interval*	0,94	0,93

SEM - standardna greška srednje vrednosti/*standard error of mean values*, MoM - umnožak medijane/*multiple of median*

grupe podataka. Cilj našeg istraživanja najbolje se iskazuje uočavanjem smanjenja SEM MoM NT za čak 60% (**Tabela 2**).

Diskusija

Korišćenjem 3D/4D metode za merenje NT postigli smo smanjenje SEM MoM NT-a od 60%.

Kao što je pokazano u radu Chunga i saradnika [1], jednačine krive izražene za celokupnu ljudsku populaciju veoma su aproksimativne i značajno smanjuju detekciju istovremeno povećavajući stepen lažno pozitivnih rezultata. U literaturi se dalje ukazuje na potrebu za primenom revidiranih, strožih referentih intervala (*cut-off margin*) pri ocenjivanju apsolutnih vrednosti izmerene NT, a kako bi se u obzir uzela i gestacijska starost ploda, edukacija i iskustvo lekara koji vrši merenje, kao i napredovanje tehnologije, sugerišući konstruisanje CRL/NT kriva specifičnih za lekara koji vrši merenje kao način da se navedeni faktori objedine pri interpretaciji rezultata [1,5].

Obimnije studije koje su uključivale više lekara koji vrši merenje u različitim ustanovama [6] ukazale su na postojanje sistemskih razlika između lekara koji vrši merenje (*inter observer*) te su apsolutne vrednosti NT konvertovane u MoM NT za svakog lekara koji vrši merenje ponaosob, a ne na nivou čitavog centra. Tako je korišćenjem samo NT radi bolje upotrebljivosti izmerenih rezultata. Najbolja uspešnost u merenju zabeležena je u 12. gestacijskoj nedelji, dok se stepen uspešnosti očekivano povećavao sa iskustvom lekara koji vrši merenje.

Kod lošeg merenja NT veća je verovatnoća da se previdi postojanje hromozomopatija a zbog malog raspona milimetaraskih veličina, što dovodi do postavljanja pitanja u osiguranje kvaliteta merenja. Predložena su dva rešenja [7,8]: podnošenje slika ekspertskom telu na analizu, a drugi način je kvantitativan, konstrukcija individualnih kriva NT/CRL koje se porede sa intenacionalno prihvaćenim referentim krivama [6,7]. Ipak, ostaje pitanje primenjivosti internacionalnih kriva na osnovu kojih će se vršiti ocena adekvatnosti merenja NT.

Fiksni refrentni interval za NT je neadekvatan [3]. Primenom ovakvog intervala predlaže se proglašavanjem apsolutne vrednosti NT izvan referentne granice kao visokoričnom za hromozomalne anomalije ali kada se ta ista vrednost analizira iz ugla CRL, tj. gestacijske starosti trudnoće, i u obzir se uzme činjenica da se sa povećanjem CRL povećava i NT ali i obrnuto [5], vrednost NT proglašena za povećan rizik u 11. gestacijskon nedelji (GN) može biti u granicama intervala referentnih vrednosti u 13. GN. Ali šta sa vrednošću NT u granicama fiksnog referentnog intervala proglašenom fiziološkom, ali patološki povišenom za tu GN?

Upotrebom MoM NT i 95. percentila kao praga za patološku vrednost NT mnogo je senzitivniji i specifičniji indikator, ali zahteva konstruisanje CRL/NT krive za svakog pojedinačnog lekara koji vrši merenje ali, kao što je u ovom radu i pokazano, i za metodu merenja koja se koristi.

U poslednje vreme sve više se saznaje o poluautomatizovanom merenju NT, kao jednoj od mogućnosti za smanjenje greške tokom merenja NT [9].

Zaključak

Savremeniji ultrazvučni 3D/4D aparati sa boljom rezolucijom značajno smanjuju standardnu grešku merenja nuhalne translucencije, uvećavajući upotrebnu vrednost u antenatalnom skriningu. Vrednosti nuhalne translucencije potrebno je posmatrati kroz prizmu gestacijske starosti trudnoće, tj. vrednosti dužine teme–trtica, a korišćenje fiksnog referentnog intervala apsolutnih vrednosti je neadekvatno. Radi daljeg poboljšanja preciznosti prenatalnog skrininga, kada god je to moguće, korisno je konstruisati referentne nuhalne translucencije/dužine teme–trtica krive za svakog lekara koji vrši merenje ponaosob, a u zavisnosti od korišćene metode merenja, te ovakve personalizovane krive koristiti u proceni verovatnoće postojanja fetalnih hromozomopatija.

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Rad je primljen 3. IV 2012.
Recenziran 11. VI 2012.
Prihvaćen za štampu 21. VI 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:145-148.

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Stručni članak
Professional article
UDK 616.314-001:616.314.18
DOI: 10.2298/MPNS1304149B

PULP VITALITY PRESERVATION AFTER TRAUMATIC DENTAL INJURIES TO PERMANENT TEETH

OČUVANJE VITALITETA PULPE NAKON TRAUME STALNIH ZUBA

Duška BLAGOJEVIĆ[1], Bojan PETROVIĆ[1], Dejan MARKOVIĆ[2], Sanja VUJKOV[1] and Ivana DEMKO RIHTER[1]

Summary

Introduction. The pulp vitality preservation after a trauma to permanent teeth is of great importance since dental injuries are common. The aim of our study was to investigate the pulp vitality preservation after tooth injuries. **Material and Methods.** A retrospective analysis of records of patients with a trauma was performed. The sample consisted of all patients who had been referred to the Department of Dentistry of Vojvodina for a trauma to permanent teeth during the period 2005-2010. We recorded the type of injury, treatment, state of vitality during the first visit and subsequent check-ups. **Results.** The study included 162 children and adolescents aged 6-18 years having a trauma to 314 permanent teeth. The most frequent type of injuries in permanent teeth was fractures (54.5%), whereas luxation was a less common trauma (45.5%). Though different kinds of traumas have different optimal time for treatment, a period of 24 hours was taken as optimal; hence, 189 teeth were treated in optimal time and 55 complications occurred in them; while 105 complications occurred in 114 teeth which were treated 24 hours after the trauma. A year after the trauma the pulp vitality was preserved in 88 teeth (32%), pulp necrosis and other complications developed in 160 teeth (68%). **Conclusion.** The therapy of pulp vitality preservation in injured teeth was found successful in 32% and unsuccessful in 68% of cases at check-ups over one year.

Key words: Dental Pulp; Tooth Fractures; Tooth Avulsion; Dental Pulp Necrosis; Dentition, Permanent; Tooth Injuries; Child; Adolescent; Treatment Outcome

Sažetak

Uvod. Očuvanje vitaliteta pulpe nakon traume stalnih zuba izuzetno je značajno, s obzirom da su povrede zuba česte. Gubitak vitaliteta pulpe povređenog zuba je osnov svih daljih komplikacija traumatskih povreda zuba. Cilj istraživanja bio je da se ispita stepen očuvanja vitaliteta pulpe nakon povrede stalnih zuba. **Materijal i metode.** Izvršena je retrospektivna analiza kartona traume pacijenata. Uzorak se sastojao iz svih slučajeva sa traumom stalnih zuba upućenih na Kliniku za stomatologiju Vojvodine, u vremenskom periodu 2005−2010. godine. Beležena je vrsta povrede, tretman, stanje vitaliteta na prvom i kontrolnim pregledima. **Rezultati.** U istraživanje je uključeno 162 dece i adolescenata uzrasta 6–18 godina, sa traumom na 314 stalnih zuba. Najzastupljeniji tip povreda kod stalnih zuba bile su frakture (54,5%). Ređe su bile zastupljene luksacije (45,5%). Iako je kod različitih vrsta trauma optimalno vreme za tretman različito, mi smo uzeli period od 24 h kao optimalan. U optimalnom vremenu tretirano je 189 zuba, od kojih se javilo 55 komplikacija, a 115 zuba tretirano je posle 24 h od traume, gde se javilo 105 komplikacija. Godinu dana nakon traume, vitalitet pulpe je očuvan kod 88 zuba (32%), nekroza pulpe i komplikacije razvile su se kod 160 zuba (68%). **Zaključak.** Terapija očuvanja vitaliteta pulpe kod povreda zuba u kontrolnom periodu od godinu dana uspešna je u 32%, a neuspešna u 68% slučajeva.

Ključne reči: Zubna pulpa; Prelom zuba; Luksacija zuba; Nekroza zubne pulpe; Stalni zubi; Povrede zuba; Dete; Adolescent; Ishod lečenja

Introduction

Dental injuries often occur in children and adolescents in modern living conditions.

Injuries to permanent teeth have a great clinical importance because damage to the dental and periodontal tissues impairs the aesthetic appearance of a child as well as the mastication function and speech.

According to current knowledge based on a lot of scientific research, it has been proved that an injury in a permanent dentition crown [1-3] and a fracture of the root [2-4] are more often than supporting tissue injuries (dislocation of the tooth and dental avulsion).

Dental injuries themselves represent a complication, and they also induce a number of additional complications. One of these is loss of the pulp vitality [5].

Loss of the pulp vitality may be caused by strong noxious agents acting through the dentinal tubules or directly to the pulp, or it may be due to damage to the nervous fibers in a tooth root apex or to blood vessels and occurrence of ischemia.

The basic aim of treatment of tooth crown and root fractures and dislocations is to preserve the pulp vitality. Since dental trauma occurs more frequently in young permanent teeth with incomplete root formation, the pulp vitality preservation is of

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a great importance. A diagnostic method which is usually used for evaluating the pulp condition immediately after dental trauma is the electric pulp test, whose results are unsafe and do not reflect the true condition of the pulp.

Successful treatment and prevention of complications can be achieved if the treatment is implemented correctly and the principles of modern concepts of therapy are respected.

The success of therapy depends on multiple factors: time elapsed between trauma and emergency care, degree of development of permanent teeth roots, type of injury, mechanism of injury, condition of the alveolar bone, and the previous condition of the tooth crown, pulp and periodontal tissues, as well as the existence of possible orthodontic irregularities [6,7].

The aim of our study was to investigate the pulp vitality preservation after tooth injuries, depending on the type of injury and therapeutic procedure.

Material and Methods

The research was conducted at the Department of Dentistry, Ward of Pediatric and Preventive Dentistry. The sample consisted of all patients who had been referred to the Department for a trauma of permanent teeth during the period 2005-2010. The study included 162 children and adolescents aged from 6 to 18 years (mean 8.2, SD 4.7) who had a trauma to 314 permanent teeth. Of the total number of patients, 47 (29.1%) were female and 115 (70.9%) were male.

Clinical data were obtained from the patients' records. These include all teeth with fractures and dislocations, with various degrees of root development. The study was performed as a retrospective clinical study, which analyzed patients' demographics, clinical examination, radiographs, types of treatments and check-ups.

Clinical examination

The data were collected on the number of injured permanent teeth, the type of injury and the pulp vitality immediately after dental injury and at the check-ups as well as on the success of therapy. The analysis was performed on the first examination and check-ups of traumatized teeth. Medical history was obtained and additional analyses of radiographs were performed. The detailed data on the results of vitality tests during the first examination were taken from the patients' dental records. Every positive result was considered as positive and the negative result of test vitality from the first examination was not recorded as negative until the therapeutic protocol or radiographic analysis confirmed the loss of vitality in the injured tooth.

Radiographic examination

All available radiographs were re-analyzed within this research in order to determine the existence of periapical lesion changes which would either confirm the clinical diagnosis or be the only sign of pulp vitality loss.

The choice of treatment

Depending on the type of injury and degree of root development, the administration of different endodontic therapy was differently classified with respect to the fact whether the pulp vitality was preserved or pulp necrosis had occurred. All teeth subjected to direct overlays, partial pulp amputation, high amputation were considered to be vital until this kind of endodontic treatment was found unsuccessful and identified as such in the therapeutic protocol.

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Check-up

The analysis of data obtained at the check-ups performed 7 days, 1 month, 3 months, 6 months and one year after the injury included the result of the electric pulp test (for the tooth with preserved pulp vitality) or information on the endodontic treatment (if an endodontic treatment was performed due to the pulp vitality loss between two check-ups).

Statistical Methods

Statistical analysis included standard methods of the descriptive statistical analysis (mean value, standard deviation). To determine the difference between the defined groups, λ^2 test was used with the significance level set at $p < 0.05$. The Kaplan-Meier survival analysis was used to determine the rate of pulp vitality preservation.

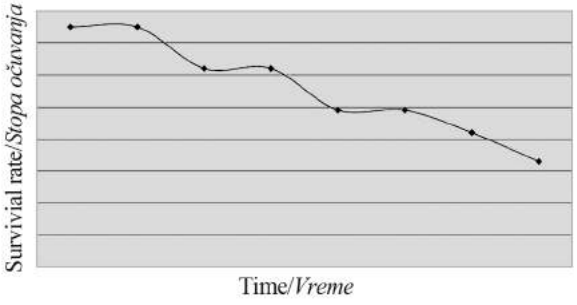
Results

The most frequent type of injuries in permanent teeth were isolated fracture injuries (84, i.e. 51.8%), followed by isolated dislocation injuries (44, i.e. 27.2%) and combination of dislocation-fracture injuries (34 i.e. 20%). In the sample of 314 teeth, the most frequent type of injuries in permanent teeth was fractures (54.5%). Dislocation was less common (45.5%).

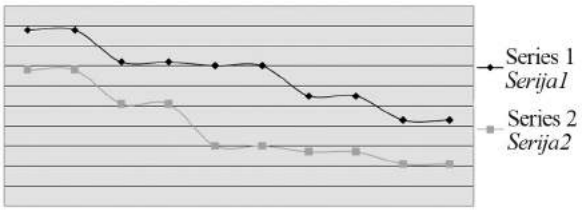
The initial examination and the check-up 7 days after the injury revealed 74 (out of 314) non vital teeth.

The pulp vitality loss was recorded in 115 out of 302 examined teeth, 137 out of 276 teeth, 152 of the 254 and 160 from 248 after one month, three months, six months and one year, respectively; whereas 66 teeth could not be included completely in testing because 53 patients were not available for all the check-ups. Having been analyzed, the rate of pulp vitality preservation was found to be 0.76 seven days after injury, 0.62 a month after injury, 0.50 three months after injury, 0.41 six months after injury and 0.32 one year after injury. The results of the Kaplan-Meier survival analysis of the rate of pulp vitality preservation after traumatic dental injuries are shown in **Graph 1**.

We analyzed the rate of pulp vitality preservation in relation to the type of dental injuries and noted the following results: of 74 teeth which were found to have lost pulp vitality during the first examination, 26 were with fracture, and 48 with dislocation trau-



Graph 1. Pulp vitality survival rate after traumatic dental injuries
Grafikon 1. *Stopa očuvanja vitalnosti pulpe nakon povređivanja*



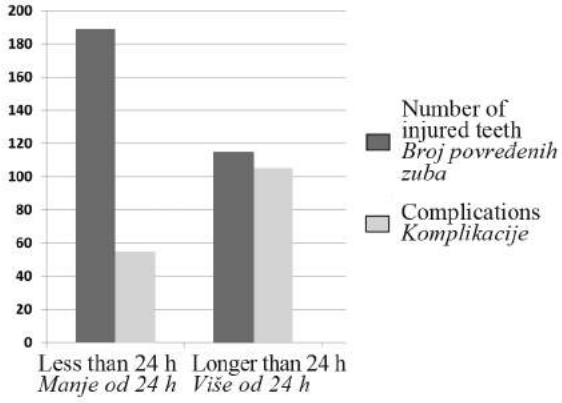
Graph 2. Pulp vitality survival rate in regard to injury type
Grafikon 2. *Stopa očuvanja vitalnosti pulpe u odnosu na vrstu povrede*

matic dental injuries. A considerably lower rate of pulp vitality preservation after dislocation injuries in relation to the tooth fracture was statistically significant ($p < 0.05$, λ^2 test).

The rates of pulp vitality preservation in fractures and dislocation injuries were compared over the entire period and the results are presented in **Graph 2**.

Kaplan-Meier survival analysis revealed a statistically significant difference between the two curves ($p < 0.05$).

Though different kinds of traumas have different optimal times for treatment, a period of 24 hours was considered as optimal. Consequently, 189 teeth were treated in optimal time, and complications occurred in 55 of them, whereas 105 complications occurred in 115 teeth which had been treated 24 hours after trauma. The results are presented in **Graph 3**.



Graph 3. Optimal treatment time
Grafikon 3. *Optimalno vreme tretmana*

Discussion

One of the basic drawbacks of this research lies in the study design. Longitudinal monitoring of patients is impossible in retrospective studies, so the percentage of respondents' dropout is high. Therefore, all the shortcomings of retrospective studies should be taken into account when the obtained results are being interpreted. The drawbacks of retrospective studies are presented in the majority of contemporary research which dealt with these issues [8-9]. On the other hand, retrospective analyses enable a complete analysis of a particular phenomenon on a sufficiently large sample of respondents.

This research included all cases of traumatic dental injuries referred to the Department of Dentistry of Vojvodina, Ward of Pediatric and Preventive Dentistry in the period from 2005 to 2010. The age of patients ranged from 6 to 18 years.

The results of this research are fully consistent with the majority of published epidemiological studies dealing with traumatic dental injuries, which reported a significantly higher incidence of injuries in boys than in girls and of fractures compared to dislocation dental injuries [9].

The analysis of treatment procedures in traumatic dental injuries leads to the conclusion that endodontic treatment is postponed even when the initial examination does not give a positive result with electric test. That is a reason why the survival analyses were performed taking into account the check-ups scheduled 7 days and a month after the initial examination. This approach is completely justified because there is evidence in literature that the pulp sensitivity returns after some time since the pulp is in a state of "local shock" immediately after the injury or several days afterwards and the negative response of the pulp does not mean the permanent loss of pulp vitality and indications for endodontic therapy [10,11].

In cases with persistent negative response, the endodontic treatment is almost always postponed until a definite sign of infection shows in the pulp, which is seen on radiograph as illumination in the periapical region [12].

The data analysis corroborates the fact that the pulp vitality loss is unavoidable in a relatively high percentage of injured teeth, regardless of the type and time of conducted treatment. The pulp vitality is preserved in only a half of the injured teeth three months after injury. Such a high rate of pulp necrosis is significantly higher in comparison with most of the published studies [8,13]. The reasons for such results should be sought in a big dissipation of the sample (66 injured teeth) and in the assumption that the majority of patients with complications complained

of them and asked for help, while those without symptoms often missed checkups.

We analyzed the pulp vitality preservation with regard to the type of dental injuries. There are no similar findings in literature; however, a significantly higher rate of pulp vitality preservation was recorded in our research after a dental fracture compared with dislocation injuries. The reasons for this finding are complex. The time elapsed between trauma and emergency care is a significant factor for the forecast of the pulp vitality preservation. Dental injuries are reasonably considered as emergency situations in dentistry, and treatment should be started as soon as possible. This is especially important in complex dislocation injuries and the fractures of the crowns with open pulp, where it is important to stop the bleeding as quickly as possible, to reposition the tooth, or to apply overlays directly on the open pulp. The explanation for a much higher incidence of pulp vitality preservation can be found in the nature of the injury.

In a dental fracture, the site of action of force is localized to a single isolated area of the tooth, and the clinician has no dilemma as to which treatment must be undertaken. In young permanent teeth with the exposed pulp after fracture and unfinished root development, surgical procedures of direct pulp capping methods and methods of vital amputation of the pulp tissue are most frequently used to preserve the tooth vitality and further development of root [14,15]. On the other hand, injuries in which the pulp vitality is rarely preserved (avulsion, high intrusion, extrusion of teeth) account for a great number of dislocation dental injuries. It is impossible to estimate the intensity of the ”shock” in which the pulp is, thus, the treatment of root canal is sometimes delayed even in situations when it is practically impossible to establish revascularization. Our results show that in the case of dislocation of permanent teeth, the decision was made to postpone the endodontic treatment two to three months after dental injury. Endodontic therapy was indicated in cases when the pulp vitality was negative six to nine weeks after dental injury.

Although the pulp of young permanent teeth has a significantly greater reparative potential both for revascularization and for dentin genesis, the time elapsed between trauma and emergency care is often too long, which leads to irreversible inflammatory changes in the pulp of young permanent teeth and cause pulp necrosis and other complications. Our results are in full compliance with quotes from other studies [5,15,16].

Conclusion

According to the obtained results we can conclude that loss OF the pulp vitality after traumatic dental injuries to permanent teeth is present in 68% of cases. The rate of loss of pulp vitality is greater after dislocation injury compared with fractures of dental hard tissues. The application of timely treatment is essential for the pulp vitality preservation.

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Rad je primljen 14. IX 2012.
Recenziran 29. X 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:149-152.

Primary Health Centre Banja Luka
Department of Family Medicine
Medical Faculty Banja Luka

Stručni članak
Professional article
UDK 614.23-057:159.944.072
DOI: 10.2298/MPNS1304153S

INFLUENCE OF AGE AND LENGTH OF SERVICE ON THE LEVEL OF STRESS AND BURNOUT SYNDROME

UTICAJ ŽIVOTNOG DOBA I DUŽINE RADNOG STAŽA NA NIVO STRESA I SINDROMA SAGOREVANJA NA POSLU

Kosana STANETIĆ and Gordana TEŠANOVIĆ

Summary

Introduction. The burnout syndrome is a response to chronic emotional and interpersonal stressors which are related to workplace. Medicine is one of the professions at the greatest risk of suffering from burnout syndrome. The aim of this study was to assess the presence of stress and burnout syndrome in relation with age and length of service in the family medicine physicians in the Republic of Srpska. **Material and Methods.** The study was carried out on the basis of a questionnaire survey among family medicine physicians in seven Primary Health Care Centres in the Republic of Srpska from February 1st to April 30th 2010. The participants fulfilled the questionnaire for self-assessment of stress level and the Maslach Burnout Inventory, which were amended with data regarding age, sex, length of service and educational and vocational level. **Results.** The study included 199 (83.3%) female and 40 (16.7%) male participants. The physicians aged over 46 years and with the length of service over 21 years had statistically significant higher level of stress and emotional exhaustion than younger participants and participants with shorter length of service. **Conclusion.** Age and length of service have important influence on the level of stress and burnout syndrome: the older the physicians and the higher the length of service the higher the level of stress and the higher the risk of burnout syndrome.

Key words: Age Factors; Stress, Psychological; Burnout, Professional; Employment; Questionnaires; Female; Male; Physicians

Sažetak

Uvod. Sindrom sagorevanja na poslu je odgovor na hronične emocionalne i međuljudske stresore koji su povezani sa radnim mestom. Zdravstveni radnici se bave jednom od profesija s najvećim rizikom za obolevanje od ovog sindroma. Cilj istraživanja bio je ispitivanje uticaja životnog doba i dužine radnog staža na nivo stresa i sindroma sagorevanja na poslu kod lekara porodične medicine u Republici Srpskoj. **Material i metode.** Istraživanje je sprovedeno metodom anketiranja lekara porodične medicine u sedam domova zdravlja u Republici Srpskoj i lekara na specijalizaciji iz porodične medicine u periodu od 1. februara do 30. aprila 2010. godine. Ispitanici su popunjavali anketni upitnik za samoprocenu nivoa stresa i *Maslach Burnout Invetory* koji su dopunjeni podacima o godinama, polu, dužini radnog staža i stepenu obrazovanja. **Rezultati.** Istraživanjem je obuhvaćeno 199 (83,3%) lekara ženskog i 40 lekara (16,7%) muškog pola. Lekari životnog doba preko 46 godina i sa dužinom radnog staža preko 21 godinu imali su statistički značajno veći nivo stresa i emocionalne iscrpljenosti u odnosu na ispitanike mlađeg životnog doba i sa manjom dužinom radnog staža. **Zaključak.** Životno doba i dužina radnog staža imaju značajan uticaj na nivo stresa i sindroma sagorevanja na poslu tako da se pokazalo da su lekari starijeg životnog doba i sa većom dužinom radnog staža imali veći nivo stresa i veći rizik od sindroma sagorevanja na poslu.

Ključne reči: Faktori godina; Psihološki stres; Izgaranje na poslu; Radno mesto; Upitnici; Žensko; Muško; Lekari

Introduction

The burnout syndrome is a response to chronic emotional and interpersonal stressors which are related to workplace. It results from the lack of harmonized relations between employees on the one hand and working environment on the other hand. It is characterized by emotional exhaustion, alienation and diminished self-confidence/self-esteem. The burnout syndrome at workplace is characterized by mental or emotional exhaustion, fatigue and depression, with a greater emphasis on psychological rather than physical symptoms. People suffering from burnout feel fatigue, malaise, had vague and undefined physical pains for longer period of time (headaches, back pain, insomnia, upset stomach/stomach problems, etc.). They are excitable and overexcited, constantly tense, impulsive, reserved; they often resort to alcohol or drugs and may express sadness, pessimism, emotional rigidity, hypersensitivity, helplessness, and despair [1-4].

Etiopathogenesis of burnout syndrome is complex, but prolonged ”negative stress” is generally thought to be the key factor in its development. Individual characteristics of people and their inability to overcome stress successfully are also very important.

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Abbreviations

MBI	− Maslach Burnout Inventory
MBI-HSS	− Maslach Burnout Inventory Human Services Survey

Negative feelings of persons with a high degree of burnout syndrome are related to the loss of commitment for professional obligations, loss of ability for self-realization and loss of personal perspective [5,6]. The feeling of meaningless existence and the loss of interest in everything that happens affect all the aspects of life of the person with the burnout syndrome. If such a situation persists for a longer period of time, the person loses the ability to enjoy life, and their quality of life is significantly decreased [7-10]. The burnout syndrome has similarities with stress and depression. It differs from stress because it is a chronic disorder and from depression because this disorder refers only to the work aspect and not to other aspects of person's life. The burnout syndrome could be compared with the highest level of stress and third stage of the General Adaptation Syndrome [11-14].

The burnout syndrome is defined as the chronic work-related stress which includes three dimensions: feeling of emotional exhaustion, negative approach to the service provided (depersonalization) and reduced sense of satisfaction and the lack of professionalism (sense of reduced personal accomplishment). This definition has been recommended on the grounds of basic studies, which were carried out in order to find the best instrument Maslach Burnout Inventory (MBI) in the study of this phenomenon [15-17].

Health workers are at a high risk of suffering from burnout syndrome because they put a high emotional stake in resolving the most subtle physical, psychological and social problems of their patients. The social contact of health care workers is not only directed towards their patients but also to the colleagues at work, superior structures, parents and relatives of patients and others [18,19].

Health care workers are at an increased risk of developing burnout syndrome also due to the impacts of other harmful factors related to workplace. Ionizing and non-ionizing radiation, vibration, different chemical vapours, unfavourable microclimatic conditions, work in non-physiological body positions, shift work and particularly night work are important risk factors for suffering from the burnout syndrome.

Stress at workplace and the so called "mental pollution" could influence the development of burnout syndrome.

Interpersonal relations at workplace (relations with patients, colleagues, managers), satisfaction or dissatisfaction with the work, possible conflict situations at workplace, insufficient education to perform work-related tasks, work overload, no promotion at work, etc, are considered to be the most common causes of workplace stress [20,21].

The aim of our study was to assess the impact of age and length of service on the level of stress and burnout syndrome at workplace in the family medicine physicians in the Republic of Srpska.

Material and Methods

This cross-sectional study was performed in 239 family medicine physicians employed in seven Primary Health Care Centres in the Republic of Srpska: Primary Health Care Centre Banja Luka, Primary Health Care Centre Doboj, Primary Health Care Centre Prijedor, Primary Health Care Centre Gradiška, Primary Health Care Centre Foča, Primary Health Care Centre Bijeljina and Primary Health Care Centre Trebinje and family medicine residents in Educational Centres of Family Medicine in Banja Luka and Doboj. The study sample represents (in percentage) the physicians employed in all regions of the Republic of Srpska equally.

In this study the following questionnaires were used: the questionnaire for self-assessment of stress level [22] and the Maslach Burnout Inventory Human Services Survey (MBI-HSS) [10], which were amended with the respondents' personal data (gender, age, length of service, place of employment and level of education).

The questionnaire was offered to all the physicians employed at the institutions where the study was conducted and the response was at least 50%. The survey was conducted in the period from February 1st to April 30th 2010. The questionnaire for self-assessment of stress level consisted of ten questions and it included four basic factors of overwork (chronic lack of time, excessive responsibility, lack of support, and exaggerated expectation of themselves and their environment). The options to answer the questions were: almost always (4 points), often (3 points), seldom (2 points) and almost never (1 point). The total sum of points was obtained by adding the points, while the maximum score was 40. The respondents who scored between 25 and 40 points were under high level of stress, while the respondents with the total sum of points less than 25 were under normal level of stress.

The original version of the MBI-HSS consists of 22 questions to which respondents could give the following answers: never (0 points), several times a year (1 point), once a month (2 points), se-veral times a month (3 points), once a week (4 points), several times a week (5 points) and daily (6 points). All questions are divided into three subscales serving as indicators which assess the degree of emotional exhaustion, depersonalization and personal satisfaction/accomplishment. The first subscale, which measures the degree of emotional exhaustion, emphasizes excessive demands expected to be fulfilled by service providers. The second subscale measures the presence of depersonalization characterized by negative relations between providers

and recipients of services. The third subscale measures the level of personal satisfaction/accomplishment. Emotional exhaustion is assessed by the answers to 9 questions, and the maximum score is 54 (low, moderate and high levels of emotional exhaustion are rated as < 17, 18-29 and > 30, respectively). Depersonalization is tested by using five questions, and the maximum score is 30 (low, moderate and high levels of depersonalization are rated as < 5, 6-11 and > 12, respectively), and personal satisfaction/accomplishment is assessed on the basis of answers to 8 questions; the maximum score is 48 (high, moderate and low levels of personal satisfaction/accomplishment are rated as < 33, 34-39 and > 40, respectively).

The obtained research data were statistically processed with advanced SPSS program. The descriptive analysis in the form of frequencies and percentages was used to examine the sample and the answer for every question separately. The reliability of the scales used was measured by Cronbach's alpha coefficient. The χ^2 (chi-square test) was used to evaluate the relationships between categorical variables. T-test was applied to compare the average values of the two groups of respondents, whereas the arithmetic means of three or more groups of data were compared by the analysis of variance ANOVA and LSD test. The level of significance was $p < 0.05$ in the applied analytical methods.

Results

The majority of respondents were women (199, i.e. 83.3%) and there were 40 (16.7%) men. The respondents were divided into three age groups. The largest number of physicians (92 or 38.5%) was older than 46, the number of physicians younger than 35 was 78 (32.6%), and the smallest number of respondents (69.i.e 28.9%) was between 36 and 45 years old. Regarding the length of service the respondents were divided into four groups: 66 (27.6%) physicians had more than 21 years of service; 64 physicians (26.8%) had less than five years of service; 61 physicians (25.5%) had from 11 to 20 years of service and 48 (20.1%) of them had 6 to 10 years of service. The majority of respondents were general practitioners (143 i.e. 59.8%) and 96 (40.2%) of them were specialists of some kind **(Table 1)**.

Table 2 shows the results from the questionnaire for self-assessment of stress level given for individual questions in the group of all respondents. The results obtained by processing the data from the questionnaire for self-assessment of stress level indicate that the majority of respondents (180, i.e. 75.3%) had a high level of stress, while 59 (24.7%) respondents were under normal stress level.

The level of stress was high mostly in the group of physicians older than 46, it was somewhat lower in the group of physicians between 36 to 45 years of age, while the lowest level of stress was in physicians younger than 35. The results of research showed that there was a statistically significant difference ($p = 0.000$) between the level of stress in the respondents of all three age groups, while the largest number of physicians with high levels of stress was older than 46 years, and the stress was expressed the least among the physicians younger than 35. A statistically significant difference ($p = 0.000$) in the stress level between the groups was found in relation to the length of service. The highest stress level was observed in the physicians with the highest length of service (over 21 years), and the lowest level of stress in the physicians with the length of service up to 5 years **(Table 3).**

Table 1. Demografic data of participants
Tabela 1*. Demografski podaci ispitanika*

	N (number/*broj*)	% (percent/*procenat*)
Gender/*Pol*		
Male/*Muški*	40	16.7
Female/*Ženski*	199	83.3
Age(years)/*Životno doba (godine)*		
< 35	78	32.6
from 36 to 45/*od 36 do 45*	69	28.9
46 and more/*preko 46*	92	38.5
Length of service (years)/*Dužina radnog staža (godine)*		
< 5	64	26.8
from 6 to 10/*od 6 do 10*	48	20.1
from 11 to 20/*od 11 do 20*	61	25.5
21 and more/*preko 21*	66	27.6
Education level/*Stepen obrazovanja*		
Specialists/*Lekari specijalisti*	96	40.2
General practitioners/*Lekari opšte prakse*	143	59.8

Table 2. Results from the Questionnaire (Girdin, Everly, Dusek, 1996) for self-assessment of stress
Tabela 2. *Rezultati iz anketnog upitnika za samoprocenu nivoa stresa (Girdin, Everly, Dusek, 1996) u grupi svih ispitanika po pojedinačnim pitanjima*

	Almost never *Skoro nikad*		Seldom *Retko*		Often *Često*		Almost always *Skoro uvek*	
	N	%	N	%	N	%	N	%
1. Find yourself with insufficient time for entertainment? *Događa li Vam se da imate premalo vremena za zabavu?*	8	3.3	55	23.0	118	49.4	58	24.3
2. Wish you had more support/assistance? *Osećate li da imate premalo podrške i pomoći?*	18	7.5	76	31.8	120	50.2	25	10.5
3. Lack sufficient time to complete your work most effectively? *Imate li premalo vremena da bi efikasno završili svoj rad?*	17	7.1	51	21.3	127	53.1	44	18.4
4. Have difficulty falling asleep because you have too much on your mind?/*Imate li poteškoće sa spavanjem zbog previše problema?*	47	19.7	102	42.7	72	30.1	18	7.5
5. Feel people simply expect too much of you? *Smatrate li da mnogo ljudi previše očekuje od Vas?*	5	2.1	61	25.5	123	51.5	50	20.9
6. Feel overwhelmed?/*Imate li osećaj shrvanosti?*	23	9.6	89	37.2	89	37.2	38	15.9
7. Find yourself becoming forgetful or indecisive because you have too much on your mind?/*Primećujete li da ste zaboravni i neodlučni zbog toga što ste preopterećeni?*	26	10.9	91	38.1	97	40.6	25	10.5
8. Consider yourself under high pressure? *Smatrate li da ste pod velikim pritiskom?*	10	4.2	45	18.8	123	51.5	61	25.5
9. Feel you have too much responsibility for one person? *Osećate li da imate previše odgovornosti?*	8	3.3	34	14.2	131	54.8	66	27.6
10. Feel exhausted at the end of the day? *Osećate li se premorenim na kraju radnog dana?*	5	2.1	28	11.7	112	46.9	94	39.3

Table 3. Results on the stress level in relation to age and the years of service
Tabela 3. *Rezultati nivoa stresa u odnosu na životno doba i dužinu radnog staža*

Age (years) *Životna dob (godine)*	Number of participants *Broj ispitanika*	Mean *M (srednja vrednost)*	Standard deviation *SD (Standardna devijacija)*	p
< 35	78	25.46	5.41	
36 to 45/*od 36 do 45*	69	27.91	5.13	
> 46	92	30.12	5.24	
Years of service/*Dužina radnog staža (godine)*	Number of participants *Broj ispitanika*	Mean *M (srednja vrednost)*	Standard deviation *SD (standarna devijacija)*	0.000
<5	64	24.47	5.07	
6 to 10/*od 6 do 10*	48	28.50	5.22	
11 to 20/*od 11 do 20*	61	28.84	4.71	
>21	66	30.15	5.65	

During this study the respondents filled in the MBI-HSS and answered 22 questions from the questionnaire. The results from the questionnaire MBI for each question are shown in **Table 4**.

The results from the MBI questionnaire showed that 110 (46%) respondents had a high level of emotional exhaustion, 69 (28.9%) had a moderate level of emotional exhaustion, while only 60 (25.1%) had a low level of emotional exhaustion. The majority of respondents, 112 (46.9%), had a low level of depersonalization, 76 (31.8%) respondents had a moderate level of depersonalization, while the lowest number of respondents, 51 (21.3%), had a high level of depersonalization. A low level of personal satisfaction/accomplishment was reported by the majority of respondents, i.e. 103 (43.1%); 93 respondents (34.7%) had a moderate level of personal satisfaction/accomplishment, and only 53 respondents (22.2%) had a high level of personal satisfaction/accomplishment **(Table 5)**.

The largest and the smallest number of respondents with a high level of emotional exhaustion were in the group older than 46 years and younger than 35 years, respectively. The high level of depersonalization was found mostly in the respondents older than 46, while the lowest level was reported by those aged from 36 to 45 years. The highest level of personal satisfaction/accom-

Table 4. Results on Questionnaire Maslach Burnout Inventory (Maslach et al., 1996)
Tabela 4. *Rezultati iz anketnog upitnika Maslach Burnout Inventory (Maslach et al., 1996) po pojedinačnim pitanjima*

	Question *Pitanje*	Never *Nikada*		A few times a year *Nekoliko puta godišnje*		Once a month *Jednom mesečno*		A few times a month *Nekoliko puta mesečno*		Once a week *Jednom sedmično*		A few times a week *Nekoliko puta sedmično*		Every day *Svako-dnevno*	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
1	I feel emotionally drained from my work *Osećam se emocionalno iscrpljen/a od posla*	14	5.9	18	7.5	22	9.2	37	15.5	43	18.0	59	24.7	46	19.2
2	I feel used up at the end of the workday *Osećam se potrošeno na kraju dana*	7	2.9	11	4.6	15	6.3	36	15.1	36	15.1	65	27.2	69	28.9
3	I feel tired when I get up in the morning and have to face another day of job. *Osećam se umorno kada ujutro ustanem i moram se suočiti sa još jednim danom na poslu.*	34	14.2	36	15.1	19	7.9	33	13.8	29	12.1	50	20.9	38	15.9
4	I can easily understand how my patients feel about things *Mogu razumeti kako se moji pacijenti osećaju*	4	1.7	8	3.3	2	0.8	12	5.0	13	5.4	48	20.1	151	63.2
5	I feel I treat some patients as if they were impersonal ”objects”./*Osećam da se prema nekim pacijentima ponašam kao da su ”bezlični objekti”.*	119	49.8	43	18.0	19	7.9	23	9.6	15	6.3	14	5.9	6	2.5
6	Working with people all day is really a strain for me. *Rad sa ljudima ceo dan je veliki napor za mene.*	35	14.6	41	17.2	18	7.5	38	15.9	36	15.1	35	14.6	36	15.1
7	I deal very effectively with problems of my patients. *Vrlo efektivno rešavam probleme mojih pacijenata.*	1	0.4	2	0.8	1	0.4	10	4.2	11	4.6	75	31.4	139	58.2
8	I feel burned out from my job./*Osećam da sam sagorio/sagorila od posla.*	39	16.3	46	19.2	16	6.7	35	14.6	19	7.9	41	17.2	43	18.0
9	I feel I’m positively influencing other people lives through my work./*Osećam da pozitivno utičem na živote drugih ljudi kroz moj posao.*	2	0.8	4	1.7	4	1.7	19	7.9	18	7.5	52	21.8	140	58.6
10	I’ve become more callous toward people since I took this job./*Postao sam bezosećajniji/a prema ljudima od kada sam počeo raditi ovaj posao.*	142	59.4	36	15.1	10	4.2	25	10.5	13	5.4	9	3.8	4	1.7
11	I worry that this job is hardening me emotionally. *Zabrinut/a sam da me ovaj posao čini emocionalno neosetljivim.*	118	49.4	48	20.1	18	7.5	23	9.6	11	4.6	12	5.0	9	3.8

12	I feel very energetic/*Osećam se vrlo energično*	16	6.7	15	6.3	15	6.3	44	18.4	35	14.6	60	25.1	54	22.6
13	I feel frustrated by my job. *Moj posao me frustrira.*	69	28.9	48	20.1	26	10.9	31	13.0	26	10.9	22	9.2	17	7.1
14	I feel I'm working too hard on my job/*Osećam da previše radim na poslu*	14	5.9	27	11.3	17	7.1	33	13.8	21	8.8	49	20.5	78	32.6
15	I don't really care what happens to some patients. *Ne mogu dovoljno brinuti šta se događa sa mojim pacijentima.*	53	22.2	45	18.8	30	12.6	45	18.8	27	11.3	24	10.0	15	6.3
16	Working with people directly puts too much stress on me. *Rad sa ljudima je previše stresan za mene.*	46	19.2	48	20.1	18	7.5	58	24.3	19	7.9	24	10.0	26	10.9
17	I can easily create a relaxed atmosphere with my patients. *Lako mogu stvoriti opuštenu atmosferu sa pacijentima.*	7	2.9	2	0.8	2	0.8	12	5.0	16	6.7	66	27.6	134	56.1
18	I feel exhilarated after working closely with my patients. *Osećam se raspoložen/a nakon rada sa pacijentima.*	12	5.0	16	6.7	9	3.8	48	20.1	27	11.3	78	32.6	49	20.5
19	I have accomplished many worthwhile things in this job. *Osećam se ispunjen/a jer sam učinio mnogo stvari vrednih pažnje na mom poslu.*	1	0.4	14	5.9	12	5.0	43	18.0	19	7.9	76	31.8	74	31.0
20	I feel like I'm at the end of my rope./*Osećam da sam na kraju snage.*	49	20.5	58	24.3	18	7.5	40	16.7	20	8.4	33	13.8	21	8.8
21	In my work, I deal with emotional problems very calmly/*U svom poslu vrlo mirno rešavam emocionalne probleme*	10	4.2	10	4.2	9	3.8	31	13.0	17	7.1	71	29.7	91	38.1
22	I feel patients blame me for some of their problems. *Osećam da me pacijenti optužuju za neke od svojih problema.*	99	41.4	74	31.0	16	7.7	26	10.9	9	3.8	9	3.8	6	2.5

plishment was reported by the respondents younger than 35 years and approximately equally by the respondents from the other two groups.

A statistically significant difference was found in the respondents of all three age groups regarding the intensity of emotional exhaustion ($p = 0.000$). The largest number of respondents with high level of emotional exhaustion was older than 46 years, and the lowest number was among those younger than 35 years. No statistically significant difference was found among the respondents of different age groups regarding the level of depersonalization ($p = 0.229$) and the level of personal satisfaction/ accomplishment ($p = 0.538$).

In the groups of respondents formed on the basis of length of service the highest level of emotional exhaustion was reported by those with the highest length of service (over 21 years), and the highest level of depersonalization was found in the respondents with the length of service from 6 to 10 years. The lowest level of personal satisfaction/ accomplishment was reported by those with the length of service from 11 to 20 years, and the highest level of personal satisfaction/accomplishment was reported by the youngest physicians with the length of service up to five years.

A statistically significant difference was found in the level of emotional exhaustion ($p = 0.000$). The highest level of emotional exhaustion was reported by the respondents with a length of service of over 21 years, and the lowest level of emotional exhaustion was reported by the respondents with the length of service up to 5 years. No statistically significant difference was found among the groups formed by

Table 5. Results on the level of emotional exhaustion, depersonalization and personal accomplishment
Tabela 5. *Rezultati nivoa emocionalne iscrpljenosti, depersonalizacije i ličnog zadovoljstva*

Degree of burnout/*Stepen sindroma sagorevanja na poslu*	High/*Visok*		Moderate/*Umeren*		Low/*Nizak*	
	N	%	N	%	N	%
Emotional exhaustion/*Emocionalna iscrpljenost*	110	46.0	69	28.9	60	25.1
Depersonalization/*Depersonalizacija*	51	21.3	76	31.8	112	46.9
Personal accomplishment/*Lično zadovoljstvo*	53	22.2	93	34.7	103	43.1

Table 6. Results on the level of emotional exhaustion, depersonalization and personal accomplishment in relation to the length of service
Tabela 6. *Rezultati nivoa emocionalne iscrpljenosti, depersonalizacije i ličnog zadovoljstva u odnosu na dužinu radnog staža*

	Length of service (years)/*Dužina radnog staža (godine)*	Number of respondents *Broj ispitanika*	Mean *M (srednja vrednost)*	Standard deviation *SD (standarna devijacija)*	p
Emotional exhaustion *Emocionalna iscrpljenost*	< 5	64	22.51	12.07	0.000
	6 to 10/*od 6 do 10*	48	28.54	15.21	
	11 to 20/*od 11 do 20*	61	29.82	12.42	
	>21	66	33.24	13.41	
Depersonalization *Depersonalizacija*	< 5	64	6.19	5.37	0.336
	6 to 10/*od 6 do 10*	48	8.02	6.26	
	11 to 20/*od 11 do 20*	61	7.23	5.94	
	>21	66	7.82	6.37	
Personal accomplishment *Lično zadovoljstvo*	< 5	64	39.44	6.36	0.105
	6 to 10/*od 6 do 10*	48	38.42	5.78	
	11 to 20/*od 11 do 20*	61	36.64	6.94	
	>21	65	37.55	6.86	

the length of service with regard to the level of depersonalization (p= 0.336) and personal satisfaction/accomplishment (p = 0.105) **(Table 6).**

Discussion

The results of our study have shown that the level of stress and emotional exhaustion increases with the length of service and age, and therefore the highest level of stress and emotional exhaustion was found in the group of respondents with the highest length of service (over 21 years) and the oldest physicians while the lowest level was found among the youngest physicians with the shortest length of service. In the group of physicians formed in relation to their age and length of service, no statistically significant difference was found in the levels of depersonalization and personal satisfaction.

One of the major research projects on the presence of burnout syndrome among the physicians in the primary health care was conducted by the European research network (European General Practice Research Network Burnout Study Group) in 12 European countries: Bulgaria, Croatia, France, Greece, Hungary, Greece, Italy, Poland, Portugal, Spain, Sweden, and the United Kingdom [2]. The research results were published in 2008 showing that 43% of the respondents had a high level of emotional exhaustion, 35% had a high level of depersonalization, and 32% had a low level of personal satisfaction/accomplishment. The burnout syndrome is seen as a common problem among family medicine physicians throughout Europe and it is associated with personal and work overloads, tendency to change jobs, and use/abuse of alcohol, tobacco and drugs. The results of our research in the subscale of emotional exhaustion are very similar to the results of this research showing that 46.0% of respondents had a high level of emotional exhaustion. The physicians who were included in our study had, in a smaller percentage, a high level of depersonalization (21.3%), and a larger number of our respondents had a low level of personal satisfaction/accomplishment (43.1%) compared to the respondents from 12 European countries.

A large study conducted in Switzerland was aimed at investigating the prevalence of the burnout syndrome and exposure of physicians in the primary healthcare in Switzerland to the occupational and psychosocial factors [23]. The study included 1784 physicians. The results of this study showed that 19% of physicians had a high level of emotional exhaustion, 22% had a high level of depersonalization, and 16% had a low level of personal satisfaction/accomplishment. The most important

factors associated with a high level of burnout syndrome were: male gender, work in rural areas, excessive stress associated with high quota at work, exaggerated expectations of patients, difficulties in reconciling private and professional life, economic constraints in the management of practice, uncertainty of medical care and difficulties in relationships with non-medical staff. By comparing the results obtained by our research it is evident that the physicians who participated in our study showed a higher level of emotional exhaustion (46%) compared to the physicians in Switzerland. The level of depersonalization of physicians included in our study is not significantly different from physicians in Switzerland, while a higher percentage of physicians from our study (43.1%) had a low level of personal satisfaction/accomplishment compared to those from the Swiss study (16%).

Studies conducted among the physicians of different specialties in the neighbouring countries have shown a high level of burnout syndrome in all respondents. Research results of the Study Duricic et al. conducted among 150 physicians showed that 70% of physicians were in the first and second stage of burnout syndrome, and 10% of physicians had all the symptoms of disease [24]. Cankovic et al. conducted a study among 150 health care workers (physicians, nurses and physiotherapists), and the results of that study showed that 46.71% of respondents had a high level of emotional exhaustion [25]. A study conducted in Zagreb, which included 41 healthcare professionals working in Internal Medicine Intensive Care Unit and 30 healthcare professionals from the Surgical Intensive Care Unit showed that most respondents had a moderate degree of emotional exhaustion [26]. A study conducted in Belgrade among 30 orthopaedics and 40 general practitioners showed a high prevalence of emotional exhaustion in the physicians from both groups [27]. Vicentic et al. conducted a study among psychiatrists and general practitioners and showed that there was a high risk of burnout syndrome in both groups [28]. Generally speaking, the results of our research do not differ significantly from the results of these studies.

Regarding the influence of age and length of service as risk factors for a high level of stress and burnout syndrome, studies conducted until today did not provide a unified answer. In his research Peterson stated the most important risk factors for the development of this syndrome, including younger age as one of risk factors [12]. He explained this by the fact that the young physicians started to work with a lot of enthusiasm, goals set too high, pursuing quick success and career advancement. He believes that the stress level and hence the level of burnout syndrome in physicians is decreasing as they acquire experience and age. Also, older physicians with higher length of service usually progress in career and personal life, and are thus at a lower risk of developing this syndrome. Other authors believe that persons who are overloaded with work and are exposed to frequent interpersonal conflicts over a longer period of time mostly have symptoms of emotional exhaustion [5,10]. The long-time constant contact with patients and exposure to other risk factors in the working environment can increase the stress level and the risk of developing the syndrome [16].

The results of our study regarding the presence of stress and burnout syndrome are similar to the results of research conducted by the health workers at the Special Psychiatric Hospital "*Dr. Laza Lazarevic*". The respondents of all occupations in this hospital showed a high level of stress and burnout syndrome among workers of all professions. In relation to age the syndrome was mostly pronounced in the respondents from the age groups of 31 to 40 and from 41 to 50 years [29]. The results of one study in Lithuania showed a higher level of stress and burnout syndrome among elderly physicians – specialists than among younger physicians – general practitioners [30].

As for the influence of the length of service on the risk and morbidity of burnout syndrome the results of conducted studies showed different findings. A study conducted among Belgrade orthopaedics and general practitioners did not prove a correlation between the levels of burnout syndrome on either subscale related to the length of service [31]. The results of the study conducted among physicians- specialist in the primary healthcare showed that the symptoms of burnout were mostly present among female physicians, aged over 44 years and among the physicians with the length of service over 19 years [31]. A research on the presence of the burnout syndrome among gynaecologists was conducted in one hospital in Mexico and its results showed a high percentage of physicians with symptoms of burnout. The average age of physicians with symptoms of burnout syndrome was 44.81 years and the average length of service was 15.56 years [32].

The results of our study as well as other studies conducted worldwide, including the neighbouring countries, have shown a high prevalence of stress and the burnout syndrome among physicians. Physician's job means being in constant contact with human suffering, limitations of life and health as the highest values of the human existence. Intense exchange of emotions and compassion with patients, empathetic relationship with the sick and vulnerable may result in "wearing out" of feelings over time, which can lead to "professional insensitivity" [33]. Many forms of mental stress expressed through accountability (subjective and more and more legal), time limitation in work, too high or too intense engagement, organizational and technical constraints, threatened self-confidence and self-esteem, low material and moral acknowledgment of the profession by the society as an entity contribute to an increase in burnout among physicians [34].

The high prevalence of physicians at risk or with severe symptoms of burnout syndrome proven by numerous studies has prompted the authors to make recommendations to reduce the level of stress and burnout among the medical staff. Therefore, in her doctoral dissertation, Peterson gave recommendations for the prevention of burnout syndrome at work: improving skills and knowledge, improving conditions for work and rest, improvement of facilities and working conditions, increase in work motivation, changes in reward system, implementation of social programs for self-protection, introduction of the system for psychosocial draining and stress relief after working day, improving psychosocial atmosphere in organisation and recommendations to stop the development of burnout syndrome: cultivation of other interests, introducing changes in the work, introduction and implementation of new projects without waiting for the manager's consent, maintenance of good health habits including adequate habits regarding sleeping and nutrition, acquiring skills of meditation, satisfying social life, establishing contacts with some friends possibly from other professions, desire to achieve results without expecting to be always the best, ability to lose without the feeling of self-underestimation and aggressiveness, ability of self-assessment without thinking about the opinion of others, openness to new experiences, ability to provide sufficient time to achieve positive results in business and personal life, ability to take responsibility, to read literature not related to the profession, participation in seminars and conferences where there is a chance to meet new people and share experience with colleagues, occasionally working together with colleagues with whom you disagree in professional and/or private life, participation in the work of professional groups and thus have the opportunity to discuss their personal problems connected with recommendations on the work, nurturing hobbies which bring joy and satisfaction [12].

In order to overcome the burnout syndrome the American Association of Internist proposed five basic measures which should be applied by every physician to prevent the development of burnout syndrome. The recommendations of this Association, given in 2001, are:

1. Care of yourself, first consider your own safety program. Include fun or some other distraction in your work. When you are under stress, it is important to be with your family more than usually, and find time for your hobbies.

2. Define the boundaries/limits of your work, consider your practice and see where it is necessary to draw the line. Maybe you need to change your working hours, your patient load, number of examinations, or reduce the number of problematic patients. Saying "no" to the patient and thus risk him leaving you and going to another doctor is healthier than constantly appease and satisfy unreasonable patient's demands.

3. Determine methods for coping with stress. Select the person who you can confide to. If you do not want to discuss your problems with your colleagues, contact old classmates, former professor or mentor.

4. Analyze yourself, figure out what your values and desires are, what your skills are and what you like doing and what you do not like or hate doing. Burning often results from the imbalance between desires, assessments and interest on the one hand and the job requirements on the other.

5. Overcome the complex that others are always better than you and that this happens only to you. Physician's job is very demanding and subject to constant changes. However, this happens in other professions as well. In order to be protected from the development of burnout syndrome the physicians must develop skills which will help them to cope with constant change and to create the necessary defence mechanisms [35].

Conclusion

Age and length of service have important influence on the level of stress and burnout syndrome:the older the physicians and the higher length of their service were the higher the level of stress and the higher the risk of burnout syndrome they had. During the last ten years the reform in primary healthcare has extensively been implemented in the Republic of Srpska, which is certainly an extremely important cause of high level of stress and burnout syndrome among family medicine physicians. Additional requests for education, working system change, increased daily administration, responsibility for the registration of citizens, financial responsibility, and other changes within the reform are, according to our opinion, the most important reasons for the high prevalence of burnout syndrome among family medicine physicians in the Republic of Srpska. We believe that the long term, permanent contact of physicians in primary healthcare with patients and their families is one of the important causes of accumulated stress, which has led to an increased risk and suffering from the burnout syndrome. These results suggest the need to educate physicians and to undertake measures in order to reduce stress and risk of burnout syndrome.

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Rad je primljen 17. VII 2012.
Recenziran 30. X 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:153-162.

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Stručni članak
Professional article
UDK 613.29-057.875(497.11 Niš)
DOI: 10.2298/MPNS1304163M

INFORMISANOST, STAVOVI I UPOTREBA DIJETETSKIH SUPLEMENATA KOD STUDENATA UNIVERZITETA U NIŠU (SRBIJA)

KNOWLEDGE, ATTITUDES AND USE OF DIETARY SUPPLEMENT AMONG STUDENTS OF THE UNIVERSITY OF NIS (SERBIA)

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Sažetak

Uvod. Dijetetski suplementi su preparati koji dopunjuju normalnu ishranu i predstavljaju koncentrovane izvore vitamina, minerala i drugih supstancija sa hranljivim i fiziološkim efektima. Osnovni cilj rada je da se utvrdi upotreba, informisanost i stavovi o dijetetskim suplementima među studentima Univerziteta u Nišu. Poseban cilj rada bio je da se utvrde razlike u korišćenju, informisanosti i stavovima o dijetetskim suplementima među studentima muškog i ženskog pola. **Materijal i metode.** U istraživanju je korišćen originalni upitnik kojim je anketirano 330 studenata Univerziteta u Nišu. Uzorak je stratifikovan prema fakultetu, godini studija i polu. Od svih upitnika izdvojen je 301 upitnik koji je ispravno popunjen i oni su dalje analizirani. **Rezultati.** Od ukupnog broja anketiranih 68,1% je koristilo dijetetske suplemente. Devojke su koristile dijetetske suplemente više od momaka. U suplementaciji su najčešće korišćena dva ili više preparata. Najčešće korišćeni preparati bili su multivitamini. Najveći broj ispitanika se pridržavao deklaracije (77,07%). Mali broj studenata je imao oštećenje zdravlja (2,93%). Više od polovine je smatralo da nema dovoljno informacija o dijetetskim suplementima. Najčešći izvor informacija bili su mediji i prijatelji. **Zaključak.** Zbog nekontrolisane upotrebe dijetetskih suplemenata trebalo bi izvršiti edukaciju zdravstvenih radnika i korisnika dijetetskih suplemenata kako bi upotreba dijetetskih suplemenata postala bezbedna, kontrolisana i racionalna.

Ključne reči: Dijetetski suplementi; Studenti; Stavovi; Muško; Žensko; Upitnici

Summary

Introduction. Dietary supplements, being concentrated sources of vitamins, minerals and other substances with nutritional and physiological effects, are products that supplement the normal diet. The aim of this study was to determine the use, attitudes and knowledge on dietary supplements among students of the University of Nis, paying special attention to differences in responses between male and female students. **Material and Methods.** The study used the original questionnaire which was distributed to 330 students from the University of Nis. The sample was stratified by school, year of study and sex. Out of 330 questionnaires, 301 were classified as correct and they were further analyzed. **Results.** Dietary supplements were used by 68.10% of the respondents. Females used dietary supplements more than males. Two or more products were most commonly used. Multivitamins were the most widely used products. The majority of respondents adhered to the declaration (77.07%). A small number had health damage (2.93%). More than half of the students stated that they were not properly informed about dietary supplements. The most common source of information was the media and friends. **Conclusion.** Health professionals and users of dietary supplements should be educated better on the use of these products in order to make the supplement use safe, controlled and rational.

Key words: Dietary Supplements; Students; Attitude; Male; Female; Questionnaires

Uvod

Dijetetski suplementi su preparati koji dopunjuju normalnu ishranu i predstavljaju koncentrovane izvore vitamina, minerala i drugih supstancija sa hranljivim i fiziološkim efektima. Dijetetski suplementi u svom sastavu mogu sadržati različite vitamine, minerale, proteine, masne kiseline, probiotike, koenzim Q-10, aktivne principe izolovane iz biljaka i druge metabolički aktivne supstancije [1].

Fizička neaktivnost, emocionalni stres, nepravilna i neizbalansirana ishrana, pušenje, kao i konzumacija alkohola faktori su rizika za nastanak hroničnih nezaraznih oboljenja među kojima se najčešće javljaju: hipertenzija, šećerna bolest, koronarna bolest srca, cerebrovaskularne bolesti [2,3]. Veliki troškovi lečenja i svesnost ljudi da su svakodnevno izloženi velikom broju faktora rizika za hronična oboljenja navode ih da se okrenu preventivnim aktivnostima u koje se ubraja i automedikacija dijetetskim suplementima. Odluku o korišćenju dijetetskih suplemenata korisnici najčešće donose samostalno, pod uticajem informacija iz medija i od prijatelja, bez konsultacija sa lekarom ili farmaceutom, smatrajući ove preparate potpuno bezbednim i bezopasnim po svoje zdravlje [4−6].

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Skraćenice
SAD – Sjedinjene Američke Države

Nepravilna i neracionalna upotreba dijetetskih suplemenata kao i moguće interakcije između dijetetskih suplemenata i lekova mogu dovesti do oštećenja zdravlja i brojnih neželjenih reakcija [7–16]. S obzirom da na tržištu raste broj dijetetskih suplemenata i njihovih korisnika, u budućnosti treba očekivati mogući porast broja neželjenih reakcija i oštećenja zdravlja prouzrokovanih ovim preparatima. Usled toga postoji potreba za edukacijom zdravstvenih radnika i korisnika dijetetskih suplemenata kako bi njihova upotreba postala racionalna i bezbedna [17].

Osnovni cilj rada bio je da se utvrdi upotreba, informisanost i stavovi o dijeteskim suplementima među studentima Univerziteta u Nišu.

Poseban cilj rada bio je da se utvrde razlike u korišćenju, informisanosti i stavovima o dijetetskim suplementima među studentima muškog i ženskog pola.

Materijal i metode

Studija je dizajnirana kao deskriptivna studija preseka. Uzorak je činilo 330 studenata sa medicinskih nauka (studenti medicine, stomatologije i farmacije) i nemedicinskih nauka (studenti Pravnog, Ekonomskog, Filozofskog, Prirodno-matematičkog, Fakulteta zaštite na radu, Fakulteta sporta i fizičke kulture, Građevinsko-arhitektonskog, Mašinskog, Elektronskog i Fakulteta umetnosti) Univerziteta u Nišu, što čini 1,5% celokupne studentske populacije ovog univerziteta. Uzorak je stratifikovan prema fakultetu, godini studija i polu.

Podaci o informisanosti, stavovima i upotrebi dijetetskih suplemenata među studentima prikupljeni su originalnim epidemiološkim upitnikom, koji je popunjavan u pauzama redovne teorijske nastave u prostorijama navedenih fakulteta Univerziteta u Nišu, u periodu februar–april 2009. godine. Ispitanici su ga popunjavali samostalno u prisustvu studenata istraživača, koji su bili na raspolaganju u slučaju poteškoća u razumevanju pojedinih pitanja. Anketa je bila anonimna, a ispitanici su odabrani metodom slučajnog uzroka. Kriterijumi za učešće u anketiranju bila je dobrovoljnost i redovnost studiranja. Od svih upitnika izdvojen je 301 upitnik koji je ispravno popunjen i oni su dalje analizirani. Upitnik se sastojao iz četiri dela. Prvi deo Upitnika sadržao je pitanja o demografskim podacima studenata (pol, godina studija, fakultet i imovinsko stanje studenata). Drugi deo činila su pitanja o informisanosti, treći o stavovima i četvrti o upotrebi dijetetskih suplemenata među studentima. Sva pitanja u upitniku imala su ponuđene odgovore koje su ispitanici zaokruživali, osim pitanja o vrstama dijetetskih suplemenata koje ispitanici koriste. Na ovo pitanje odgovarali su upisivanjem naziva preparata. Upitnik u prilogu **(Prilog 1)**.

Prilog 1. Upitnik
Annex 1. *Questionnaire*

MEDICINSKI FAKULTET U NIŠU, 2009.
ANKETA DIJETETSKI SUPLEMENTI

1. Pol Ž M
2. Godina studija I II III IV V VI
3. Fakultet (upisati) _____
4. Imovinsko stanje:
   1. dobro 2. srednje 3. slabo
5. Da li smatrate da imate dovoljno informacija o dijetetskim suplementima?
   1. Ne 2. Da
6. Od koga ste dobili informacije o dijetetskim suplementima?
   1. Od lekara.
   2. Od farmaceuta.
   3. Od prijatelja.
   4. Iz medija.
   5. Od članova porodice.
   6. Ostalo _____
7. Da li su Vam poznata neželjena dejstva dijetetskih suplemenata?
   1. Ne 2. Da
8. Dijetetske suplemente treba koristiti iz sledećih razloga:
   1. Da ojačate imunitet.
   2. Da sprečite nastanak bolesti.
   3. Da kompenzujete neadekvatnu ishranu.
   4. Da poboljšate koncentraciju.
   5. Ne treba ih koristiti.
   6. Ostalo.
9. Da li smatrate da dijetetski suplementi mogu imati štetne uticaje na zdravlje?
   1. Ne 2. Da
10. Prema Vašem mišljenju, dijetetski suplementi su:
   1. Skupi. 2. Pristupačni.
11. Da li koristite dijetetske suplemente?
   1. Da, stalno. 2. Da, povremeno. 3. Ne.
12. Ukoliko koristite, molimo Vas upišite koje dijetetske suplemente koristite?

_____

13. Da li se pridržavate deklaracije prilikom upotrebe dijetetskih suplemenata?
   1. Ne 2. Da
14. Da li je neki od dijetetskih suplemenata koji ste koristili izazvao oštećenje Vašeg zdravlja?
   1. Ne 2. Da
15. Da li neko iz Vaše porodice koristi dijetetske suplemente?
   1. Ne 2. Da
16. Gde kupujete dijetetske suplemente?
   1. U drogerijama i prodavnicana zdrave hrane.
   2. U supermarketima.
   3. Isključivo u apoteci.
   4. Od ovlašćenih distributera.
   5. Ostalo _____

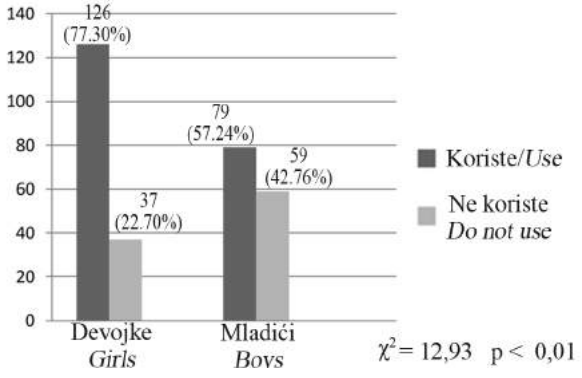
ANKETA JE ANONIMNA.
HVALA ŠTO STE UČESTVOVALI!

U radu je korišćen statistički metod kvantitativne analize. Rezultati istraživanja su sistematizovani, prikazani tabelarno i grafički (*Excel 2003 i Word 2003*). U deskripciji podataka korišćen je indeks strukture. Od statističkih testova korišćeni je χ^2 i Fišerov egzaktni test. Za obradu rezultata istraživanja korišćen je statistički program *SPSS 18*. Vrednosti $p < 0,01$ uzimane su kao statistički značajne.

Rezultati

Od ukupnog broja ispitanika, 163 (54,15%) bili su studenti ženskog pola i 138 (45,85%) bili su studenti muškog pola.

Od ukupnog broja anketiranih, 205 (68,1%) koristilo je dijetetske suplemente. Devojke su znatno češće 126 (77,3%) koristile dijetetske suplemente nego mladići 79 (57,24%). Postoji statistički značajna razlika u broju korisnika dijetetskih suplemenata između mladića i devojaka ($\chi^2 = 12,93$, $p < 0,01$) (**Grafikon 1**).



Grafikon 1. Upotreba dijetetskih suplemenata među studentima
Graph 1. *Use of dietary supplements among students*

Najveći broj anketiranih studenata je povremeno koristio dijetetske suplemente – njih 185 (90,24%), bez statistički značajne razlike između studenata muškog i ženskog pola ($\chi^2 = 0,75$, $p > 0,01$) (**Tabela 1**).

U suplementaciji najčešće je bilo korišćeno 2 ili više preparata 128 (62,44%). Veći je broj studenata ženskog pola 86 (68,25%) koji koriste 2 ili više preparata u odnosu na studente muškog pola 42 (53,16%). Ne postoji statistički značajna razlika među studentima različitih polova u broju preparata koji koriste u suplementaciji ($\chi^2 = 4,09$, $p > 0,01$) (**Tabela 1**).

Prilikom upotrebe dijetetskih suplemenata, veći broj ispitanika 158 (77,07%) pridžavao se deklaracije o upotrebi. Mladići su se u neznatno većem broju – njih 62 (78,48%) pridržavali deklaracije u odnosu na devojke 96 (76,19%), bez statistički značajne razlike ($\chi^2 = 0,04$, $p > 0,01$) (**Tabela 1**).

Mali broj ispitanika – 6 (2,93%) imali su oštećenje zdravlja uzrokovano upotrebom dijetetskih suplemenata, bez statistički značajne razlike između polova (Fišerov egzaktni test $p = 1$, $p > 0,01$) (**Tabela 1**).

Najčešće korišćeni preparati u suplementaciji bili su multivitamini 185 (61,46%) koji su najčešće sadržali kombinaciju vitamina C, nikotinamida, pantotenske kiseline, vitamina E, B6, B1, B2, B12 i folne kiseline. Najčešće suplementisani minerali bili su kalcijum (4,65%) i selen (3,32%). Devojke su u nešto većem broju koristile multivitamine, biljne preparate, propolis i minerale (Ca i Se) od mladića, dok su mladići u većem broju koristili omega 3 masne kiseline, proteine i kreatinin. Ne postoji statistički značajna razlika među studentima suprotnih polova u korišćenju pojedinih vrsta dijetetskih suplemenata ($\chi^2 = 1$ 4,09, $p > 0,01$) (**Tabela 2**).

Više od polovine ispitanika 188 (62,46%) smatralo je da nema dovoljno informacija o dijetetskim suplementima, bez statistički značajne razlike među studentima različitih polova ($\chi^2 = 3,05$, $p > 0,01$) (**Tabela 3**).

Najveći broj ispitanika izjasnilo se da su informacije o dijetetskim suplementima dobili iz više izvora 105 (34,88%). Ispitanici koji su kao izvor informacija naveli jedan izvor izjasnili su se da su informacije o dijetetskim suplementima najćešće

Tabela 1. Specifičnosti upotrebe dijetetskih suplemenata
Table 1. *Specificities of use of dietary supplement*

		Devojke/*Girls*	Mladići/*Boys*	Ukupno/*Total*	Test
Učestalost upotrebe *Frequency of use*	Stalno/*Constantly*	10 (7,94%)	10 (12,66%)	20 (9,76%)	$\chi^2 = 0,75$ $p > 0,01$
	Povremeno/*Periodically*	116 (92,06%)	69 (87,34%)	185 (90,24%)	
	Ukupno/*Total*	126 (100%)	79 (100%)	205 (100%)	
Broj preparata *Number of supplements*	Jedan/*One*	40 (31,75%)	37 (46,84%)	77 (37,56%)	$\chi^2 = 4,09$ $p > 0,01$
	Dva i više/*Two or more*	86 (68,25%)	42 (53,16%)	128 (62,44%)	
	Ukupno/*Total*	126 (100%)	79 (100%)	205 (100%)	
Pridržavanje deklaracije *Adhere to declaration*	Pridržava se/*Yes*	96 (76,19%)	62 (78,48%)	158 (77,07%)	$\chi^2 = 0,04$ $p > 0,01$
	Ne pridržava se/*No*	30 (23,81%)	17 (21,52%)	47 (22,93%)	
	Ukupno/*Total*	126 (100%)	79 (100%)	205 (100%)	
Oštećenje zdravlja *Health damage*	Nije imalo/*No*	122 (96,83%)	77 (97,47%)	199 (97,07%)	*Fisher exact* $p = 1$ $p > 0,01$
	Imalo/*Yes*	4 (3,17%)	2 (2,53%)	6 (2,93%)	
	Ukupno/*Total*	126 (100%)	79 (100%)	205 (100%)	

Tabela 2. Najčešće korišćene vrste dijetetskih suplemenata u populaciji studenata
Table 2. *The most frequently used types of dietary supplements among students*

Dijetetski suplementi/*Dietary supplements*	Devojke/*Girls*	Mladići/*Boys*	Ukupno/*Total*
Multivitamini/Multivitamins	117 (71,78%)	68 (49,27%)	185 (61,46%)
Multivitamini i multiminerali/*Multivitamins and multiminerals*	23 (14,11%)	18 (13,04%)	41 (13,62%)
Biljni preparati/*Herbal supplements*	8 (4,9%)	5 (3,62%)	13 (4,31%)
Omega 3 masne kiseline/*Omega 3 fatty acids*	4 (2,45%)	8 (5,79%)	12 (3,89%)
Kreatin, proteini, glutamin/*Creatine, protein, glutamine*	0 (0%)	3 (2,17%)	3 (0,99%)
Selen/*Selenium*	8 (4,9%)	2 (1,44%)	10 (3,32%)
Kalcijum/*Calcium*	10 (6,13%)	4 (2,89%)	14 (4,65%)

Tabela 3. Informisanost studenata o dijetetskim suplementima
Table 3. *Students' knowledge about dietary supplements*

		Devojke *Girls*	Mladići *Boys*	Ukupno *Total*	Test
Informisanost o dijetetskim suplementima *Knowledge about dietary supplements*	Nedovoljna/*Insufficient*	94 (57,66%)	94 (68,12%)	188 (62,46%)	$\chi^2 = 3,05$ $p > 0,01$
	Dovoljna/*Sufficient*	69 (42,33%)	44 (31,88%)	113 (37,54%)	
	Ukupno/*Total*	163 (100%)	138 (100%)	301 (100%)	
Izvor informacija o dijetetskim suplementima *Sources of information about dietary supplements*	Lekar i farmaceut *Doctor and pharmacist*	26 (15,95%)	13 (9,42%)	39 (12,95%)	$\chi^2 = 15,7$ $p < 0,01$
	Prijatelj/*Friend*	16 (9,82%)	23 (16,67%)	39 (12,96%)	
	Mediji/*Media*	35 (21,47%)	42 (30,43%)	77 (25,58%)	
	Članovi porodice/*Family members*	14 (8,59%)	6 (4,35%)	20 (6,64%)	
	Ostalo/*Other*	7 (4,29%)	14 (10,14%)	21 (6,98%)	
	Više izvora/*Multiple sources*	65 (39,87%)	40 (29,98%)	105 (34,88%)	
	Ukupno/*Total*	163 (100%)	138 (100%)	301 (100%)	
Poznavanje neželjenih dejstva *Knowledge about adverse effects*	Ne/*No*	110 (67,5%)	100 (72,46%)	210 (69,77%)	$\chi^2 = 0,66$ $p > 0,01$
	Da/*Yes*	53 (32,5%)	38 (27,54%)	91 (30,23%)	
	Ukupno/*Total*	163 (100%)	138 (100%)	301 (100%)	

Tabela 4. Stavovi o upotrebi dijetetskih suplemenata
Table 4. *Attitudes about the use of dietary supplements*

		Devojke *Girls*	Mladići *Boys*	Ukupno *Total*	Test
Oštećenje zdravlja *Health damage*	Nemoguće/*Impossible*	83 (50,92%)	62 (44,92%)	145 (48,17%)	$\chi^2 = 0,85$ $p > 0,01$
	Moguće/*Possible*	80 (49,08%)	76 (55,07%)	156 (51,83%)	
	Ukupno/*Total*	163 (100%)	138 (100%)	301 (100%)	
Razlozi za upotrebu dijetetskih suplemenata *Reasons to use dietary supplements*	Ojačati imunitet/*To strengthen immunity*	69 (42,33%)	45 (32,61%)	114 (37,87%)	$\chi^2 = 15,71$ $p < 0,01$
	Sprečiti bolest/*To prevent disease*	9 (5,52%)	5 (3,62%)	14 (4,65%)	
	Popraviti ishranu/*To improve nutrition*	17 (10,43%)	14 (10,14%)	31 (10,30%)	
	Poboljšati koncentraciju *To improve concentration*	2 (1,23%)	1 (0,72%)	3 (1%)	
	Ne treba ih koristiti *They should not be used*	10 (6,13%)	28 (20,29%)	38 (12,62%)	
	Iz više razloga/*For more reasons*	56 (34.35%)	37 (26.81%)	93 (30.89%)	
	Ukupno/*Total*	126 (100%)	79 (100%)	301 (100%)	

dobili iz medija 77 (25,58%) i od prijatelja 39 (12,96%). Od zdravstvenih radnika (lekara i farmaceuta) informacije je dobilo 39 (12,96%). Devojke su češće dobijale informacije od zdravstvenih radnika u odnosu na mladiće, dok su mladići češće u odnosu na devojke dobijali informacije o

dijetetskim suplementima iz medija i od prijatelja, tako da postoji statistički značajna razlika između njih ($\chi^2 = 15,74$, $p < 0,01$) (**Tabela 3**).

Veliki broj anketiranih mladića i devojaka – 210 (69,77%) izjasnilo se da ne poznaje neželjena dejstva dijetetskih suplemenata tako da među njima nema statistički značajne razlike ($\chi^2 = 0,66$, $p > 0,01$) (**Tabela 3**).

Oko polovine anketiranih 156 (51,83%) smatralo je da dijetetski suplementi mogu imati štetan uticaj na zdravlje. Ne postoji statistički značajna razlika po pitanju štetnosti dijetetskih suplemenata po zdravlje korisnika između momaka i devojaka ($\chi^2 = 0,85$, $p > 0,01$) (**Tabela 4**).

Najveći broj studenata smatrao je da dijetetske suplemente treba koristiti iz više razloga 93 (30,89%). Najčešći razlog za upotrebu dijetetskih suplemenata među studentima koji su naveli jedan razlog bio je jačanje imuniteta 114 (37,87%), zatim kompenzovanje neadekvatne ishrane 31 (10,30%) i sprečavanje nastanka bolesti 14 (4,65%). Devojke su češće navodile da dijetetske suplemente koriste kako bi ojačale imunitet 69 (42,33%) dok su mladići u većem broju smatrali da dijetetske suplemente ne treba koristiti 28 (20,29%). Razlika u stavovima o razlozima korišćenja dijetetskih suplemenata između studenata muškog i ženskog pola statistički je značajna ($\chi^2 = 15,71$, $p < 0,01$) (**Tabela 4**).

Diskusija

Od ukupnog broja anketiranih studenata u našoj studiji, njih 205 (68,1%) koristilo je dijetetske suplemente. Najveća upotreba dijetetskih suplemenata je na Tajlandu i Filipinima (66%), zatim u Litvaniji (59%) [18], dok ih u Americi koristi 56% stanovništva, u Evropi 30%, Latinskoj Americi 28% [19]. U Australiji je 93,7% studenata farmacije koristilo je dijetetske suplemente pre upisa na fakultet [20].

U našem istraživanju veći je broj studenata ženskog pola koji su koristili dijetetske suplemente u odnosu na studente muškog pola. U Sjedinjenim Američim Državama (SAD) oko 50% žena je koristilo alternativnu i komplementarnu medicinu za najčešća medicinska stanja i to znatno više od muškaraca [21]. Studenti farmacije muškog pola u Pakistanu imali su konzervativnije stavove prema alternativnoj medicini od studenata ženskog pola [22]. U našem istraživanju 9,76% ispitanika je stalno koristilo dijetetske suplemente dok ih u Americi redovno koristi 79%, u Norveškoj 80%, u Danskoj 81% [18].

Naši ispitanici su u suplementaciji češće upotrebljavali 2 ili više preparata (62,44%). Jedan preparat je koristilo 37,56% dok u Americi, 47% korisnika je koristilo takođe jedan preparat [23].

Najčešće upotrebljavani preparati bili su vitamini i to najčešće u vidu multivitaminskih kompleksa. Među anketiranim studentima, 61,46% je koristilo multivitaminske preparate. Najčešće korišćeni preparati su sadržali kombinaciju vitamina C, nikotinamida, pantotenske kiseline, vitamina E, B6, B1, B12 i folne kiseline. Samo 8% studenata je suplementisalo minerale i to najčešće kalcijum i selen. U ishrani stanovnika Srbije zabeleženi su nedostaci vitamina B12, E, D i C i minerala Ca, Mg i F [24] što ukazuje na potrebu za edukacijom o korišćenju adekvatnih preparata kako bi suplementacijom bile obuhvaćene one supstancije koje su deficitarne u ishrani. U Poljskoj, 99,5% studenata je koristilo vitamine i minerale u suplementaciji [4]. U Americi, 35% koristi multivitamine i multiminerale u redovnoj upotrebi [25].

Mali broj anketiranih se nije pridržavao deklaracije (22,93%) prilikom upotrebe dijetetskih suplemenata. Nepridržavanje deklaracije i unos većih doza od preporučenih može imati toksične efekte. Intoksikacija vitaminom D dovodi do hiperkalcijemije koja izaziva povraćanje, poliuriju, polidipsiju, encefalopatiju i bubrežnu disfunkciju [7]. Akutna intoksikacija vitaminom A izaziva stanje poznato kao *pseudotumor cerebri* koje se manifestuje glavoboljom, povraćanjem, bolovima u leđima, diplopijom, papiloedemom, dilatiranim zenicama [8]. Hronična intoksikacija vitaminom A izaziva benignu intrakranijalnu hipertenziju [9].

Mali broj ispitanika (2,93%) imao je oštećenje zdravlja, verovatno zbog toga što su najzastupljeniji u suplementaciji bili hidrosolubilni vitamini koji se brzo eliminišu iz organizma i što se radi o relativno zdravoj populaciji ispitanika koja nije na dugoročnoj terapiji lekovima usled nekih hroničnih oboljenja. Istraživanje koje je sprovedeno u Turskoj pokazalo je da je oštećenje zdravlja imalo 8,4% korisnika dijetetskih suplemenata u vidu mučnine, povraćanja, gastrointestinalnih poremećaja i insuficijencije jetre [6].

Oko polovine ispitanika u našem istraživanju smatralo je da dijetetski suplementi mogu imati štetan uticaj po zdravlje korisnika. Kao najčešće razloge za upotrebu dijetetskih suplemenata, u našem istraživanju, ispitanici su naveli: jačanje imuniteta (37,87%), popravljanje ishrane (10,3%), sprečavanje nastanka bolesti (4,65%), dok je 12,62% smatralo da ih ne treba koristiti. Studenti muškog pola su u većem broju smatrali da dijetetske suplemente ne treba koristiti u odnosu na studente ženskog pola. U Americi, 62% korisnika ih je koristilo kako bi izbalansirali ishranu dok 60% korisnika u Aziji koristilo ih je da ojača imunitet [19]. U SAD žene su najčešće koristile preparate alternativne i komplementarne medicine da bi ublažile simptome dismenoreje, premenstrualnog sindroma i menopauze [21]. U našem istraživanju ispitanice nisu navodile ove razloge za upotrebu dijetetskih suplemenata.

Veći broj ispitanika (62,46%) smatrao je da nema dovoljno informacija o dijetetskim suplementima, a najveći broj ispitanika je naveo da je informacije dobijao iz više izvora (34,88%). Studenti koji su podatke dobili iz jednog izvora u najvećem broju su naveli medije (25,58%) kao izvor podataka o dijetetskim suplementima. Glavni izvor informacija o dijetetskim suplementima studentima u Poljskoj bio je in-

ternet [4]. S obzirom da veliki broj dobija informacije iz medija i od prijatelja potrebno je posvetiti veću pažnju promociji pravilne upotrebe dijetetskih suplemenata koju realizuju lekari i farmaceuti. U SAD 72% lekara i 89% medicinskih sestara preporučuju upotrebu dijetetskih suplemenata [26].

Oko 70% anketiranih ne poznaje neželjena dejstva dijetetskih suplemenata. U svetu su zabeleženi mnogi slučajevi neželjenih reakcija i interakcija između dijetetskih suplemenata i medikamenata konvencionalne medicine. Biljni suplementi (fitohemikalije) mogu uzrokovati promene u ćelijama na transkripcionom i posttranskripcionom nivou, što uzrokuje indukciju enzima koji učestvuju u metabolisanju lekova (I i II faza), transportera i nuklearnih hormonskih i nehormonskih receptora i nekih transkripcionih faktora [27].

Kantarion je popularni biljni preparat koji se koristi za lečenje depresije. Kantarion indukuje citohrom P 450 (CYP) i izoenzime CYP 3A4, CYP 2C19, CYP 2C9 i p-glikoprotein [10]. Istraživanja su pokazala da kantarion smanjuje koncentracije nekih lekova u krvi kao što su: amitriptilin, ciklosporin, digoksin, fensofenadin, simvastatin, takrolimus, teofilin, varfarin [11]. Opisan je slučaj odbacivanja transplantata bubrega i pankreasa usled smanjenja doze ciklosporina u plazmi do supterapijskih doza zbog interakcije ciklosporina sa kantarionom [12]. Kantarion u kombinaciji sa antidepresivima dovodi do serotoninskog sindroma jer dodatno zadržava serotonin u sinapsama [11].

Ginkgo biloba je biljni preparat koji je dosta korišćen za poboljšanje pamćenja i koncentracije. *Ginkgo biloba* interreaguje sa omeprazolom, ritonavirom, tolbutamidom, antiepilepticima, aspirinom, diureticima, ibuprofenom, risperidonom, trazodonom, varfarinom [13]. *Ginkgo biloba, Echinacea purpurea* i *Serenoa repens* inhibišu aktivnost citohroma P 450, 3A4, 2D6 i 2D9 i utiču na metabolizam lekova [28]. *Ginkgo biloba* ima prokonvulzivno dejstvo što dovodi do češćih epileptogenih pražnjenja kod pacijenata koji dobijaju preparate na bazi ekstrakta *Ginkgo bilobe* pa sa njihovom primenom treba biti obazriv kod pacijenata sa epilepsijom [29].

Efedra, sibirski žen-šen, gorka narandža i sladić podižu krvni pritisak pa bi sa njihovom primenom trebalo biti obazriv pogotovu kod pacijeneta sa hipertenzijom [14].

Istraživanje sprovedeno u SAD pokazalo je da je 73% odraslih Amerikanaca koristilo dijetetske suplemente; od toga 85% je koristilo multivitamine odnosno multiminerale. Neželjene efekte imalo je 4% korisnika dijetetskih suplemenata a 13,3% njih je neželjene efekte pripisalo multivitaminima ili multimineralima. Veći procenat neželjenih efekata zabeležen je među korisnicima koji su istovremeno uzimali dijetetske suplemente sa propisanim medikamentima [15].

Najveći rizik od interakcije leka i dijetetskih suplemenata imali su pacijenti koji su na antikoagulantnoj terapiji [16].

Zaključak

Veliki broj studenata Univerziteta u Nišu je koristio dijetetske suplemente. Devojke su češće od mladića koristile ove preparate. Ispitanici su koristili dva ili više preparata i to najčešće multivitamine zbog jačanja imuniteta. Studenti nemaju dovoljno informacija o dijetetskim suplementima i najčešće se informišu preko medija i prijatelja. Uglavnom ne poznaju neželjena dejstva dijetetskih suplemenata, a oko polovine smatra da dijetetski suplementi ne mogu imati štetan uticaj po zdravlje.

Dobijanje informacija, koje mogu biti nepouzdane, iz medija i od prijatelja, nepoznavanje neželjenih efekata dijetetskih suplemenata kao i slaba informisanost korisnika dijetetskih suplemenata ukazuje da je potrebno da zdravstveni radnici edukuju javnost, posebno korisnike dijetetskih suplemenata što bi doprinelo adekvatnoj suplementaciji i smanjenju neželjenih dejstava i oštećenja zdravlja među korisnicima dijetetskih suplemenata. Poseban predmet budućih istraživanja bila bi upotreba dijetetskih suplemenata među pacijentima sa hroničnim bolestima i moguće interakcije dijetetskih suplemenata i njihove redovne medikamentozne terapije.

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Rad je primljen 10. IX 2012.
Recenziran 10. X 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:163-169.

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Stručni članak
Professional article
UDK 615.322.012/.014
UDK 615.214.07
DOI: 10.2298/MPNS1304170D

PROCES IZRADE KVALITETNOG FITOPREPARATA NA PRIMERU BILJNOG SEDATIVA

MANUFACTURING PROCESS OF HIGH QUALITY PHYTOPREPARATION ON EXAMPLE OF HERBAL SEDATIVE

Sofija ĐORĐEVIĆ[1], Aleksandra DICKOV[2], Sava PAVKOV[1], Vanja TADIĆ[1], Ivana ARSIĆ[3] i Ana ŽUGIĆ[1]

Sažetak

Uvod. Racionalna fitoterapija je savremeni koncept upotrebe lekova biljnog porekla, nastao iz potrebe da se fitoterapija unapredi, kako bi primena biljnih preparata postala efikasnija i bezbednija. Cilj ovog rada je da se zdravstvenim radnicima približi proces izrade kvalitetnog biljnog preparata po principima dobre proizvođačke i dobre laboratorijske prakse, na primeru biljnog sedativa *Odoval S*® kapsule. **Materijal i metode**. Dizajn ove studije je koncipiran tako da prikaže proces izrade kvalitetnog i bezbednog fitopreparata, od definisanja recepture i postupka izrade biljnog leka, kontrole kvaliteta sirovina, karakterizacije gotovog proizvoda, do ispitivanja stabilnosti aktivnih materija u kapsulama. **Rezultati**. Formulacija fitopreparata, validacija procesa izrade, kontrola kvaliteta i ispitivanja stabilnosti preparata, rezultirali su izradom preparata sa definisanim sadržajem valerijanske kiseline po kapsuli (1 mg/kapsuli). **Diskusija.** Preparat se preporučuje za ublažavnje tegoba nastalih usled hroničnog stresa (uznemirenost, razdražljivost, zamor, odsustvo koncentracije, lupanje srca) kao i kod blagih nesanica. **Zaključak**: U radu je prikazan zaokružen ciklus izrade fitopreparata na primeru novog biljnog sedativa *Odoval S*® kapsule.

Ključne reči: Biljni preparati + terapijska primena; Fitoterapija; Biljni ekstrakti; Aksioznost + terapija; Poremećaji sna i pažnje + terapija; Valerianae radix; Melissae folium

Summary

Introduction. Rational phytotherapy is a modern concept of using plant-originated drugs which has emerged from the need to improve phytotherapy in order to make the use of herbal remedies more efficient and safer. The aim of this study was to give the health-care workers more information on the manufacturing process of high quality phytopreparation following principles of Good Manufacturing Practice and Good Laboratory Practice on the example of herbal sedative, *Odoval S*® capsules. **Material and Methods**. This study was designed to reflect the production process of a high-quality and safe herbal remedy, starting from defining the formulation and the production procedure to the quality control of raw materials, characterization of the final product, and testing stability of active ingredients in the capsules. **Results**. Formulation of the phytopreparation, validation of the production process, quality control and stability testing, all together have resulted in the production of capsules with defined valeric acid content (1 mg valeric acid per capsule). **Discussion**. The preparation is recommended to relieve the symptoms caused by chronic stress (anxiety, irritability, fatigue, lack of concentration, heart palpitations) and for mild insomnia. **Conclusion.** This paper presents the complete cycle of the production of a phytopreparation on the example of a new herbal sedative - *Odoval S*® capsules.

Key words: Plant Preparations + therapeutic use; Phytotherapy; Plant Extracts; Anxiety + drug therapy; Sleep Initiation and Maintenance Disorders + drug therapy; Valerian; Melissa

Uvod

Upotreba lekovitih biljaka u prevenciji i lečenju različitih oboljenja stara je koliko i samo čovečanstvo. Dokumenti neprocenjive vrednosti pokazuju da su lekovito bilje u velikoj meri koristili mnogi narodi kroz čitavu istoriju ljudske civilizacije. Kako je razvoj srpske srednjovekovne medicine bio deo nacionalne kulture, došlo je do stapanja tadašnje medicinske doktrine, koju su učeni ljudi i monasi sticali u stranim medicinskim školama, sa narodnim načinom lečenja [1]. U našoj zemlji i okruženju, mnogi stručnjaci su ostavili dragocena dela iz oblasti farmakognozije: Kušan, Petrović, Pančić, Tucakov, Lukić i dr.

Fitoterapija, kao komplementarni deo farmakoterapije, zauzima značajno mesto u mnogim oblastima savremene medicine. Predstavlja sistem lečenja zasnovan na primeni prirodnih lekovitih sirovi-

Zahvalnica: Autori ovog istraživanja zahvaljuju Ministarstvu prosvete, nauke i tehnološkog razvoja Republike Srbije koje finansijski podržava Projekat III 45017.

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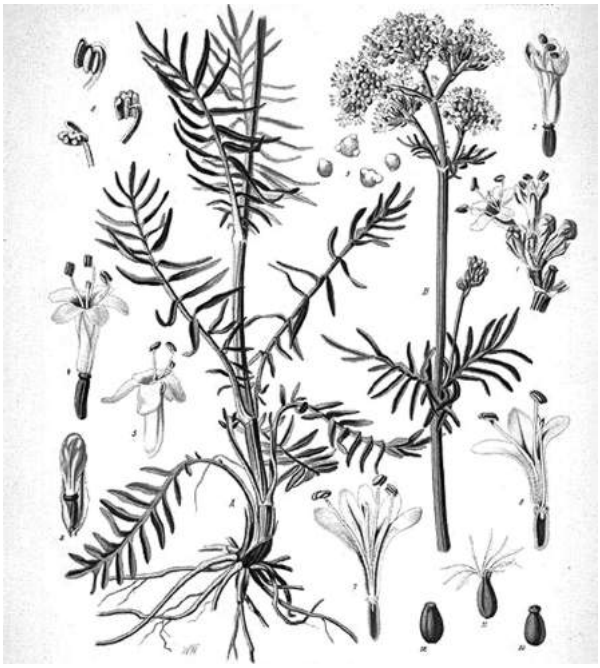
Skraćenice

GABA − γ-aminobuterna kiselina
HPLC − tečna hromatografija visokih performansi
Komisija E – Ekspertska grupa za evaluaciju efikasnosti i delovanja fitopreparata

na (droga) i biljnih lekova (fitopreparata) u svrhu prevencije i lečenja. Biljna droga (*engl. Herbal drug*) je ceo ili usitnjen, osušen deo biljke, alge, gljive ili lišaja koji se koristi zbog svojih lekovitih svojstava. Pored biljnih organa (nadzemni deo biljke u cvetu, list, cvet, koren, kora, plod, seme), drogom se smatraju i biljni eksudati (smole, balzami, gume). Biljni lekovi, fitopreparati ili fitofarmaka (engl. *Herbal medicinal products*) sadrže kao aktivne sastojke isključivo biljne droge ili preparate biljnih droga. Preparati biljnih droga (engl. *Herbal drug preparations*) dobijaju se od droga postupcima destilacije, ekstrakcije, ceđenjem itd. Ovim pojmom obuhvaćeni su sprašeni oblici droga, etarska ulja, masna ulja, tinkture, ekstrakti [2−4].

Racionalna fitoterapija je savremeni koncept primene biljnih lekova, koji je osmišljen u Nemačkoj krajem prošlog veka i ubrzo široko prihvaćen u drugim evropskim zemljama. Nastala je iz potrebe da se fitoterapija unapredi, kako bi biljni preparati bili efikasniji, njihova primena bezbednija i zasnovana na rezultatima kliničkih ispitivanja. Biljni lekovi, koji se koriste u racionalnoj fitoterapiji, pripremaju se od standardizovanih biljnih ekstrakata, poznata je hemijska priroda njihovih aktivnih principa, ispoljavaju dozno-zavisan terapijski efekat, poznati su neželjeni efekati i kontraindikacije i definisanog su i standardnog farmaceutskog kvaliteta [5,6].

Biljni lekovi se koriste preventivno, u terapiji blažih oblika bolesti, ili kao dopunska terapija za lečenje hroničnih oboljenja. Najčešće se primenju kod poremećaja funkcije organa respiratornog, digestivnog, urogenitalnog trakta, blažih i srednjih oblika anksioznosti i depresije, kao i kod različitih promena na koži i sluzokoži. Njihovo lekovito delovanje nastupa postepeno, tako da se maksimalan efekat ispoljava 2-3 nedelje od početka primene [7, 8]. U našoj sredini, biljni lekovi se koriste kroz samomedikaciju, na osnovu odluke pacijenata, ili po preporuci lekara ili farmaceuta. U nekim zemljama Evropske unije, pojedini biljni lekovi pripadaju sistemu primarne zdravstvene zaštite, a u našoj zemlji, kao i u velikom broju drugih zemalja, nalaze se na režimu izdavanja bez lekarskog recepta. Zakon o lekovima i medicinskim sredstvima Republike Srbije navodi da lekovi pored humanog, životinjskog i hemijskog porekla, mogu biti i biljnog porekla. Zakon prepoznaje i definiše biljni lek i tradicionalni biljni lek [9]. U zavisnosti od prirode i količine biljnog ekstrakta, koji je deklarisan kao aktivni sastojak, fitopreparati su klasifikovani i kao dijetetski proizvodi, koji podležu drugim zakonskim propisima [10].



Slika 1. *Valeriana officinalis* L.
Fig. 1. *Valeriana officinalis L.*

Reč „anksiozan” vodi poreklo od latinskog *anxious*. Kod nas je preuzeta iz engleskog jezika, a doslovni prevod znači: biti zabrinut, uznemiren, uplašen. Anksioznost je psihički poremećaj usled koga čovek oseća neprijatnost od neizvesnosti. Anksioznost izvesnog stepena može biti iskustvo koje poznaje svaki čovek, a koje se odnosi na neizvesnost usmerenu prema svakodnevnim životnim situacijama ili nelagodnost od suočavanja sa teškom situacijom. Patološka strepnja, iako može biti uzrokovana spoljnim faktorima, uslovljena je unutrašnjim psihičkim uzrocima. Ona je neproporcionalna realnoj opasnosti ili uopšte nema veze sa njom i umanjuje adaptacione sposobnosti. Anksioznost je patološko stanje obeleženo iracionalnim i prekomernim osećajem straha i strepnje, koji su praćeni znakovima hiperaktivnosti vegetativnog nervnog sistema. Razlikuje se od straha, koji predstavlja odgovor na poznati uzrok − fobija. Anksioznost je difuzan, veoma neprijatan, često nejasan osećaj neprijatnosti, udružen sa jednim ili više telesnih simptoma: praznina u stomaku, pritisak u grudima, lupanje srca, ubrzano disanje, glavobolja, vrtoglavica, „knedla” u grlu, „oduzimanje” ekstremiteta. Stanje se može nazvati anksioznim poremećajem kad je anksioznost snažna, dugotrajna i kada ograničava psihološko i socijalno funkcionisanje. Podaci iz jedne zapadne zemlje sa 25 miliona stanovnika govore da kombinovani anksiozni poremećaji zahvataju 12% građana. Kao grupa, anksiozni poremećaji su najčešći od svih mentalnih poremećaja [11]. Po svemu sudeći, nastanak anksioznih poremaćaja je rezultat kompleksne interakcije genetskih, biološ-

kih, razvojnih i drugih faktora, npr. socioekonomski faktori i stres.

Postoji mnoštvo različitih teorija koje objašnjavaju kako navedeni faktori doprinose razvoju ovog poremaćaja [12,13]. Rano prepoznavanje i adekvatan tretman su imperativi sa ciljem povećavanja kvaliteta života osoba sa anksioznim poremećajima. Adekvatno prepoznavanje i tretman takođe pomažu da se spreče česti sekundarni poremećaji kao što su depresija i zloupotreba alkohola i psihoaktivnih supstancija [14,15]. U lečenju anksioznosti primenjuje se kombinacija psihototerapije i farmakoterapije. Osim klasičnog medicinskog modela preporučuje se higijena spavanja, korekcija ishrane, fizička aktivnost i upotreba lekovitog bilja [16–18].

U savremenoj fitoterapiji, kao sredstva za umirenje i ublažavanje poremećaja spavanja, sa blagim i sedativnim delovanjem, najčešće se primenjuju ekstrakti korena valerijane, lista matičnjaka i šišarica hmelja. Upotrebu ovih biljnih droga je odobrila ekspertska grupa za evaluaciju efikasnosti i delovanja fitopreparata (Komisija E).

U radu su prikazane dve droge čiji ekstrakti ulaze u sastav fitopreparata *Odoval S*® kapsule.

Valerijana (*Valeriana officinalis L., Valerianaceae*), rasprostranjena je sporadično u našoj zemlji [19]. Drogu čini osušeni rizom sa korenovima *Valerianae radix* **(Slika 1)**. Danas se droga uglavnom dobija iz gajenih biljaka. Koren valerijane se koristio od davnina u tradicionalnoj medicini mnogih naroda, kao sredstvo za ublažavanje poremećaja spavanja, za smanjenje napetosti i kod gastrointestinalnih poremećaja. Pored tradicionalne, droga se koristi i u zvaničnoj medicini. Zbog dokazane terapijske efikasnosti, oficinalna je u mnogim nacionalnim farmakopejama uključujući i evropsku. Pozitivna monografija Komisije E ukazuje na sigurnost i efikasnost njene primene. Prema ovoj monografiji, droga ispoljava sedativno i uspavljujuće delovanje, a koristi se u obliku infuza, tinkture i najčešće suvog ekstakata. Zbog nedovoljnih podataka o bezbednosti primene, preparati na bazi valerijane ne preporučuju se deci mlađoj od dvanaest godina, trudnicama i dojiljama, a treba izbegavati istovremenu primenu sa barbituratima i drugim sedativima, ali i sa alkoholnim pićima. Toksikološka ispitivanja izolata valerijane ili pak pojedinačnih aktivnih sastojaka droge, pokazala su izuzetno nisku toksičnost.

Koren valerijane sadrži veliki broj različitih farmakološki aktivnih jedinjenja, koje se mogu svrstati u nekoliko hemijskih grupa: terpenski sastojci (monoterpenske i seskviterpenske komponente etarskog ulja, estre monoterpenskih iridoidnih alkohola − valepotrijate, monoterpenske biciklične aldehide − baldrinale, biciklične ciklopentenske seskviterpenske kiseline − valerenska, acetoksivalerenska i hidroksivalerenska), derivati fenilpropana (sastojci etarskog ulja, fenilkarbonske kiseline, flavonoidi) i jedinjenja koja sadrže azot (alkaloidi i aminokiseline − tirozin, arginin, glutamin, γ-aminobuterna kiselina-GABA).

I pored brojnih farmakoloških ispitivanja, kako izolovanih pojedinačnih sastojaka droge, tako i različitih ekstrakata, još uvek nije razjašnjeno koja jedinjenja i po kom mehanizmu su odgovorna za sedativno delovanje. Farmakološka aktivnost je najverovatnije posledica sinergističkog delovanja većeg broja prisutnih sastojaka u korenu, kao i njihovih razgradnih produkata. Rezultati dosadašnjih ispitivanja ukazuju da je inhibitorno delovanje na centralni nervni sistem najvećim delom posledica povećanja GABA-ergične aktivnosti. Poznato je da GABA, kao glavni inhibitorni neurotransmiter u centralnom nervnom sistemu, posreduje u inhibiciji stresa i uznemirenosti. Za ukupni vodeni ekstrakt pokazano je, u *in vitro* ispitivanjima, da stimuliše oslobađanje GABA. Koren valerijane takođe sadrži GABA, kao i druge sastojke, za koje je ustanovljeno da se vezuju za $GABA_A$ receptore (valerenska i amino-kiseline). Seskviterpenske kiseline dodatno inhibiraju enzime koji razgrađuju GABA [2,3,20–25].

Valerenska kiselina i njeni derivati specifični su za vrstu *Valeriana officinalis* i njihovo prisustvo nije utvrđeno u drugim vrstama, roda *Valeriana*, koje imaju medicinski značaj. Evropska farmakopeja propisuje postupak ispitivanja prisustva i sadržaja valerenske kiseline i njenih derivata metodama tankoslojne hromatografije (TLC) i tečne hromarografije visokih performansi (HPLC), kao dokaz identiteta i kvaliteta droge *valeriana officinalis*. Takođe, propisuje najmanji sadržaj seskviterpenskih

Slika 2. *Melissa officinalis L.*
Fig. 2. *Melissa officinalis L.*

kiselina, računato kao valerenska za koren valerijane (0,17%) [26−28]. Znači, kvalitet biljne droge i njenih ekstraktivnih preparata, prati se preko sadržaja aktivnih supstancija koje su karakteristične za tu biljnu vrstu i koje su u velikoj meri odgovorne za farmakološke aktivnosti (u ovom slučaju sadržaj seskviterpenskih kiselina računato kao valerenska).

Primena preparata sa korenom valerijane zasniva se na iskustvima tradicionalne medicine, rezultatima hemijskih ispitivanja, eksperimentima na životinjama, kao i brojnim kliničkim ispitivanjima. Najkomforniji način upotrebe je u obliku standardizovanog suvog ekstrakta u formi čvrstih galenskih preparata (kapsule, tablete).

Drogu *Melissae folium* čine osušeni listovi matičnjaka *Melissa officinalis L.*, *Lamiaceae* **(Slika 2)**. U našoj zemlji je sporadično rasprostranjena. Veoma je cenjena lekovita, aromatična i medonosna biljka, pa se najčešće gaji. Prema zahtevima evropske farmakopeje, sadrži najmanje 4% hidroksi derivata cimetne kiseline, izraženo kao rozmarinska kiselina. List matičnjaka sadrži etarsko ulje sa monoterpenskim aldehidima, flavonoide, derivate hidroksicimetne kiseline (kafena, hlorogenska, rozmarinska) i triterpenske kiseline. Prema važećim monografijama preparati na bazi lista matičnjaka koriste se kod uznemirenosti, napetosti, razdražljivosti, kod blažih poremećaja spavanja i kao karminativa [2,3,20–22]. Sedativno delovanje ekstrakta lista matičnjaka potvrđeno je na eksperimentalnim životinjama. Mehanizam delovanja nije sa sigurnošću utvrđen.

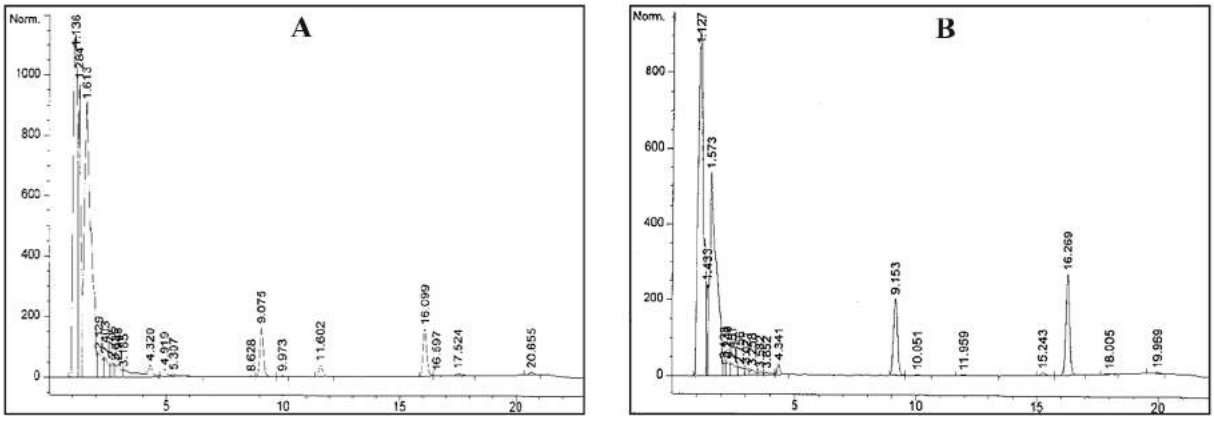
Pregledom literature i sagledavanjem stanja na našem i inostranom tržištu, ustanovljeno je da postoji izvestan broj preparata u čvrstim oblicima (tablete, kapsule) sa ekstraktom korena valerijane. U njima je definisana samo količina ekstrakta po tableti/kapsuli, bez tačnog sadržaja valerenske kiseline, odnos količine upotrebljene droge prema dobijenom suvom ekstraktu, a ponegde je naznačen i ekstragens. Rote liste [29] navode preparate sa različitom količinom suvog ekstrakta korena valerijane (45−441,35 mg po tableti/kapsuli), sa različitim odnosom količine korišćene droge prema dobijenom suvom ekstraktu (4−7, 4 : 1), i 70% etanolom kao ekstragensom. Postoji i manji broj preparata u kojima je suvi ekstrakt valerijane kombinovan sa ekstraktima lista matičnjaka i šišarica hmelja. U našim apotekama nalazi se manji broj fitopreparata na bazi korena valerijane ili kombinacije sa drugim biljnim ekstraktima. *Persen forte* kapsule (*Persen* dražeje) − 1 tvrda kapsula/dražeja sadrži 125 mg (50 mg) suvog ekstrakta korena valerijane (5−7 : 1), 25 mg suvog ekstrakta lista matičnjaka (5−8 : 1) i 25 mg suvog ekstrakta lista nane (5−9 : 1); *Cefan-1* kapsula sadrži 441,3 mg suvog ekstrakta korena valerijane; *Zirkulin valerijane* − 1 kapsula ima 160 mg ekstrakta valerijane i 40 mg suvog ekstrakta šišarica hmelja.

Cilj ovog rada je da se predstavi proces izrade kvalitetnog biljnog preparata po principima dobre proizvođačke i laboratorijske prakse, na primeru biljnog sedativa *Odoval S*® kapsule, koji je standardizovan na sadržaj valerenske kiseline po kapsuli. Namera je, da se kroz razvoj formulacije i kontrolu kvaliteta fitopreparata, prezentuje ispunjenost osnovnih postulata, kako bi se biljni lek koristio u racionalnoj fitoterapiji (izrađen od standardizovanih biljnih ekstrakata, definisan sadržaj aktivne materije, validiran proces izrade, da je tačno doziran).

Materijal i metode

Dizajn ove studije je koncipiran tako da prikaže proces izrade kvalitetnog a samim tim i bezbednog fitopreparata na primeru biljnog sedativa *Odoval S*® kapsule, koji se nalazi u proizvodnom programu Instituta za proučavanje lekovitog bilja „Dr Josif Pančić" iz Beograda, od definisanja recepture i postupka izrade biljnog leka, kontrole kvaliteta korena valerijane i lista matičnjaka, standardizacije i kontrole kvaliteta njihovih suvih ekstrakata, formulacije i kontrole kvaliteta mase za kapsuliranje, karakterizacije gotovog proizvoda, do ispitivanja stabilnosti aktivnih materija u kapsulama.

Princip metode određivanja seskviterpenskih kiselina, izraženo kao valerenska kiselina u korenu va-



Grafikon 3. A) HPLC hromatogram standarda valerenske kiseline; B) HPLC hromatogram *Odoval S*® kapsula
Graph 3. *A) HPLC chromatogram of valeric acid standard; B) HPLC chromatogram of Odoval S® capsules*

lerijane, suvom ekstraktu korena valerijane, masi za kapsuliranje i u kapsulama, zasniva se na HPLC metodi primenom eksternog standarda [28]. Analize se izvode na HPLC aparatu (HP 1090M), opremljenom DAD detektorom. Kao referentni rastvor koristi se standardizovani ekstrakt valerijane (0,45% valerenske kiseline) koncentracije 20 mg/ml (**Grafikon 3a**).

Suvi ekstrakt korena valerijane izrađen je metodom dvostruke ekstrakcije u cirkularnom ekstraktoru (linija UTVA), upotrebom 70% etanola kao ekstragensa, postepenim uparavnjem rastvarača, pažljivim sušenjem ugušćenog ekstrakta i mlevenjem dobijenog suvog ekstrakta u fini prah. Suvi ekstrakt lista matičnjaka izrađuje se po definisanom procesu jednostruke cirkularne ekstrakcije, a dalji postupci dobijanja ekstrakta su identični kao i za ekstrakt korena valerijane.

Masa za kapsuliranje izrađuje se definisanim redosledom mešanja suvih ekstrakata i pomoćnih materija u „Y" mešalici i prosejavanjem granulata do dobijanja ujednačenog stepena usitnjenosti. Izrada kapsula vrši se na poluautomatskoj kapsulirki „Multigel". Da bi se utvrdila stabilnost sadržaja aktivne materije u kapsulama, radi definisanja roka upotrebe preparata, praćen je sadržaj valerenske kiseline u kapsulama čuvanim na sobnoj temperaturi (22 ± 2° C) u toku 18 meseci [28–30]. Sve aktivnosti su sprovodene u laboratorijama i proizvodnim pogonima Instituta.

Rezultati

Institut za proučavanje lekovitog bilja „Dr Josif Pančić" iz Beograda, kao renomirana ustanova iz ove oblasti, u svom proizvodnom programu ima nekoliko preparata na bazi korena valerijane: monokomponentni čaj, čajne mešavine, biljne kapi – tinkture. Zainteresovanost pacijenata za korišćenje valerijane primenom komfornijih i bezbednih farmaceutskih oblika, dala je ideju da se napravi novi fitopreparat − kapsule sa standardizovanim ekstraktom valerijane kao nosiocem farmakološkog delovanja.

Formulacija preparata počinje pregledom literature i sagledavanjem stanja biljnih sedativa na tržištu. Kako postoje preparati u čvrstim formama sa ekstraktom korena valerijane, u kojima je definisana samo količina ekstrakta po tableti/kapsuli, bez tačnog sadržaja valerenske kiseline, namera je bila da se formuliše i proizvede kvalitetan biljni sedativ koji je definisan sadržajem aktivne materije po kapsuli, a ne samo količinom suvog ekstrakta.

Sledeći korak u formulaciji fitopreparata je odabir one količine ekstrakta po kapsuli koja zadovoljava preporučenu dnevnu dozu i odabir suvog ekstrakta lista matičnjaka kao druge delujuće komponente, ali u količini koja ne zahteva posebnu analitiku. Zvanične monografije za *Valeriana radix* [2,20–22], navode da su preporučene pojedinačne doze za suvi ekstrakt, ekvivalentne sa 2-3 g droge. Maksimalna dnevna doza je četiri pojedinačne doze. Polazeći od mogućnosti tehnološkog postupka izrade suvog ekstrakta u Institutu, napravljen je ekstrakt valerijane sa 0,5% valerenske kiseline. Uzimajući u obzir farmakopejski podatak da koren valerijane mora da sadrži najmanje 0,17% seskviterpenskih kiselina, odabrana je receptura po kojoj kapsula prosečne mase 470 mg, sadrži 200 mg suvog ekstrakta korena valerijane, što odgovara 1 mg valerenske kiseline po kapsuli, 10 mg suvog ekstrakta lista matičnjaka i pomoćne materije, koje omogućavaju dobru homogenizaciju mase za kapsuliranje.

Validacija procesa izrade omogućuje dobijanje fitopreparata standardnog kvaliteta. Droga koja se koristi za izradu suvog ekstrakta mora da odgovara farmakopejskim zahtevima u pogledu sadržaja aktivne komponente. Suvi ekstrakt valerijane izrađuje se validiranim procesom, koji obezbeđuje sadržaj valerenske kiseline od 0,5%. Takođe, i suvi ekstrakt lista matičnjaka se izrađuje definisanim procesom koji omogućava dobijanje ekstrakta čiji je odnos količine upotrebljene droge prema dobijenom suvom ekstraktu 4−7,4 : 1. Masa za kapsuliranje (granulat) priprema se po specifikovanoj proceduri. Kapsuliranje granulata je validirano, da masa 1 kapsule bude 470 mg, što obezbeđuje prisustvo 200 mg suvog ekstrakta korena valerijane i 10 mg ekstrakta lista matičnjaka. Ovako definisan proces izrade fitopreparata, omogućava da 1 kapsula sadrži 1 mg ± 10% valerenske kiseline. Režim doziranja, od dve a maksimalno četiti kapsule dnevno, uklapa se u preporučenu dnevnu dozu.

Kontrola kvaliteta se sprovodi po definisanim parametrima (specifikacijama) i validiranim analitičkim metodama. Ispitivanje kvaliteta korena valerijane, obuhvata identifikaciju, određivanje procenta vlage, pepela, stranih primesa, određivanje valerenske kiseline i mikrobiološku ispravnost. Kontrola kvaliteta suvog ekstrakta korena valerijane obuhvata određivanje procenta vlage i stepena usitnjenosti, sadržaj aktivne materije, kao i mikrobiološku ispravnost. Masa za kapsuliranje se ispituje na sadržaj valerenske kiseline i mikrobiološku ispravnost. Finalni proizvod se ispituje na broj kapsula u pakovanju, prosečnu težinu jedne kapsule, raspadljivost kapsula, HPLC identifikaciju i kvantitativnu analizu sadržaja valerenske kiseline po kapsuli **(Grafikon 3b)** i kompletnu zdravstvenu ispravnost.

Ispitivanje stabilnosti preparata proveravano je određivanjem sadržaja valerenske kiseline u *Odoval S*® kapsulama, tokom čuvanja u periodu do 18 meseci. Sadržaj seskviterpenskih kiselina, izraženo kao valerenska kiselina, u granicama je farmakopejskih zahteva (± 10%).

Diskusija

U ovoj studiji su predstavljene aktivnosti koje su prethodile izradi kvalitetnog, originalnog biljnog sedativa, koncipiranog da njegova primena bude dozno-zavisna a samim tim i kontrolisana.

Poštujući osnovne principe izrade preparata u modernoj fitoterapiji, proizveden je *Odoval S*® kapsule, biljni preparat za održavanje mentalne ravnoteže [5]. Odabrani su ekstrakti koji imaju dugu tradiciju primene za ovo indikaciono područje. Aktivni sastojci ekstrakta korena valerijane imaju povoljno dejstvo na ublažavanje uznemirenosti i razdražljivosti kao i slabosti srca nastale usled nervoze, olakšavaju uspostavljanje prirodnog ritma spavanja. Ekstrakt lista matičnjaka potencira delovanje valerijane [3,7,20−22,31−33].

S obzirom da formulacija novog fitopreparata počinje pregledanjem literature i sagledavanjem stanja na tržištu, ustanovljena je originalna receptura. Svi procesi izrade kapsula definisani su i validirani. Kontrola kvaliteta, koja počinje od biljnih sirovina a završava se kontrolom kapsula, obezbeđuje standardni kvalitet fitopreparata. Stabilan sadržaj aktivne materije u suvom ekstraktu obezbeđuje definisan sadržaj valerenske kiseline po kapsuli preparata, što garantuje sigurnu terapijsku dozu u roku trajanja preparata [34]. Originalnost preparata se ogleda i u tome, što je u kapsuli definisan sadržaj aktivne materije, a ne masa delujućeg suvog ekstrakta.

Preparat se preporučuje za ublažavnje tegoba nastalih usled hroničnog stresa (uznemirenost, razdražljivost, zamor, odsustvo koncentracije, lupanje srca) kao i kod blagih nesanica. Koristi se dva puta dnevno po jedna kapsula (pola sata do sat pre spavanja), a može i do četiri puta dnevno, čime se ostvaruje preporučena dnevna doza. Preparat se ne sme davati deci mlađoj od 12 godina. Takođe se ne sme koristiti u toku trudnoće i dojenja.

Zaključak

U radu je prikazan zaokružen ciklus izrade fitopreparata, na primeru novog biljnog sedativa *Odoval S*® kapsule, od formulacije, preko izrade, kontrole kvaliteta i ispitivanja stabilnosti aktivne materije u kapsulama, kako bi se odredio rok trajanja preparata. Dakle, ispunjeni su osnovni kriterijumi, koje treba da zadovolji biljni lek, kako bi se koristio u racionalnoj fitoterapiji: da je izrađen od standardizovanih biljnih ekstrakata (standardizovani suvi ekstrakt korena valerijane sa 0,5% seskviterpenskih kiselina izraženo kao valerenska kiselina, validiranim procesom izrade), da je hemijska priroda aktivnih sastojaka poznata (hemijskim analizama se identifikuje i prati sadržaj aktivnih sastojaka kako u polaznim sirovinama, tako i u finalnom proizvodu), da se tačno dozira (sadržaj aktivne materije po kapsuli je definisan na 1 mg) i da je biljni lek stabilan u roku trajanja (u roku od 18 meseci na sobnoj temperaturi sadržaj aktivne materije u kapsulama je stabilan).

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Rad je primljen 22. V 2012.
Recenziran 2. VII 2012.
Prihvaćen za štampu 20. X 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:170-176.

PRIKAZI SLUČAJEVA
CASE REPORTS

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Prikaz slučaja
Case report
UDK 616-003-091.8/-092:611.93
UDK 616-006.6:611.93
DOI: 10.2298/MPNS1304177T

CARCINOMA DEVELOPING IN A BRANCHIAL CYST

KARCINOM NASTAO U BRANHIJALNOJ CISTI

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Summary

Introduction. The malignant transformation of the branchial cysts epithelium is rare and it represents separate entity called branchiogenic carcinoma. **Case report.** A 55-year-old male with fluctuating mass localized on the right side of the neck, was admitted to the Department of Maxillofacial Surgery, General hospital in Vrbas where cystic tumor 3 cm in its greatest dimension with friable, dark red wall below the front edge of the sternocleidomastoid muscle was revealed. The wall of the tumor was composed of lymphoid tissue with germinal centers. The internal surface of the cyst was lined with thin layered squamous epithelium that showed a transition from the normal, followed by the atypical epithelium, and the in situ carcinoma to the part corresponding to a poor differentiated invasive squamous carcinoma. Following the diagnosis of suspected branchiogenic carcinoma a radical neck dissection was performed. No elements of the tumor had been found in the sampled materials taken from striated muscle tissue, salivary gland tissue and reactive lymph nodes (n = 24). The patient was presented to Oncology Consilium, and radiotherapy was implemented. **Conclusion**. The definitive diagnosis must be based on histological features. A five-year monitoring of the patient is necessary to rule out cervical metastasis of this tumor. It is necessary for a five-year follow-up to rule out cervical metastasis of the tumor.

Key words: Carcinoma, Squamous Cell; Branchioma; Cyst; Epithelial Cells; Cell Transformation, Neoplastic; Head and Neck Neoplasms; Male; Middle Aged

Sažetak

Uvod. Maligna transformacija epitela branhijalne ciste je retka i predstavlja poseban entitet nazvan branhiogeni karcinom. **Prikaz slučaja.** Muškarac, star 55 godina sa fluktuirajućom masom na desnoj strani vrata, primljen je na Odeljenje maksilofacijalne hirurgije Opšte bolnice u Vrbasu gde se nakon incizije ispod prednje ivice sternokleidomastoidnog mišića ukazao cistični tumor najvećeg dijametra 3 cm trošnog, tamnocrvenog zida, koji je histološki bio izgrađen od limfoidnog tkiva sa širokim germinativnim centrima na koje naleže pločastoslojevit epitel koji je pokazivao spektar promena od normalnog, preko atipičnog do dela koji je odgovarao invazivnom loše diferentovanom skvamoznom karcinomu. Nakon postavljene dijagnoze suspektnog branhiogenog karcinoma urađena je radikalna disekcija vrata i tada u materijalu koji je odgovarao poprečnoprugastom mišićnom tkivu, tkivu pljuvačne žlezde i reaktivno izmenjenim limfnim čvorovima (n=24) nije bilo elemenata tumora. Slučaj ovog pacijenta iznet je konzilijumu, te mu je ordinirana zračna terapija. **Zaključak**. Definitivna dijagnoza branhiogenog karcinoma nakon kompletne ekscizije mora biti bazirana na histološkoj slici. Neophodno je petogodišnje praćenje pacijenta kako bi se isključile cervikalne metastaze ovog tumora.

Ključne reči: Skvamozni karcinom; Branhijalna cista; Cista; Epitelne ćelije; Maligna transformacija; Karcinomi glave i vrata; Muško; Uzrast, 45-64 godina

Introduction

Branchial cysts belong to the lateral neck cyst type, resulting from proliferation of epithelial remnants of the second branchial arch or the cervical sinus. They co-appear with angulus mandibulae, spread along the front edge of the sternocleidomastoid muscle (SCM) to the clavicle, and can also be found in the parotid and the submandibular gland. Although they have no contact with the external environment, there is a case which illustrates the communication with the Eustachian tube [1]. Branchial cysts usually occur in the second and third decade of life, they grow slowly and fluctuate and they are filled with liquid or semiliquid content with cholesterol crystals. Micro-

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Abbreviations
SCM –sternocleidomastoid muscle
BC – branchiogenic carcinoma

scopically, they are coated with the thin multilayered cylindrical or a squamous epithelium without mitotic activity and nuclear atypia. The epithelium overlaps intimately the lymphoid tissue with wide germinal centers [2]. The malignant transformation of epithelium as a separate entity was first described by Von Volkmann in 1882, who named it branchiogenic carcinoma (BC), which has sparked many controversies in the medical and scientific literature since then [3-5].

Case report

A 55-year-old male was admitted to the Department of Maxillofacial Surgery due to a painful swelling on the right side of the neck which had been treated with antibiotics for seven days. Physical examination revealed the presence of a fluctuating mass localized at the anterior edge of the SCM. The skin covering the mass was unchanged and the patient had no other complaints. The ultrasonographic finding described a cystic change about 32 mm in its largest diameter, hypoechoic with the thin wall and posterior acoustic enhancement. No enlarged regional lymph nodes were present. Computer tomography of the neck showed a well circumscribed, homogeneously low density unilocular cyst with the thin wall. The biochemical analyses of blood showed the dominance of leukocytosis. A collar cut was performed under endotracheal anesthesia. Below the front edge of the SCM a cystic tumor was revealed no greater than 3 cm in diameter extending from the back of the musculus digastricus, along the front side of the SCM all the way to the internal jugular vein. During the course of manipulation, the cystic tumor was opened in several places, and the purulent content was emptied. Macroscopically, the tumor wall was friable, dark red, and histologically it was composed of lymphoid tissue with wide germinal centers. The internal surface of the cyst was lined with the thin layered squamous epithelium which showed a transition from the normal (**Fig. 1**), followed by the atypical epithelium (**Fig. 2**), and the in situ carcinoma to the part corresponding to a poor differentiated invasive squamous carcinoma. The tumor parenchyma was built of polygonal cells with the hyperchromic nuclei arranged in the solid sheets and linear cords, of scant acidophilic cytoplasm, and vivid mitotic activity (**Fig. 3**). The tumor stroma was a vascular connective tissue, permeated with lymphocytes, plasma cells and granulocytes.

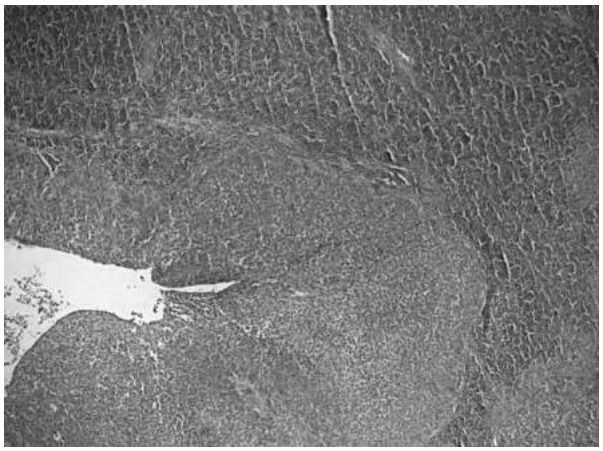

Fig. 1. The wall of cyst lined with squamous epithelium which rests on the lymphoid tissue (HEx20)
Slika 1. *Zid ciste izgrađen od skvamoznog epitela koji se naslanja na limfoidno tkivo (HE x 20)*

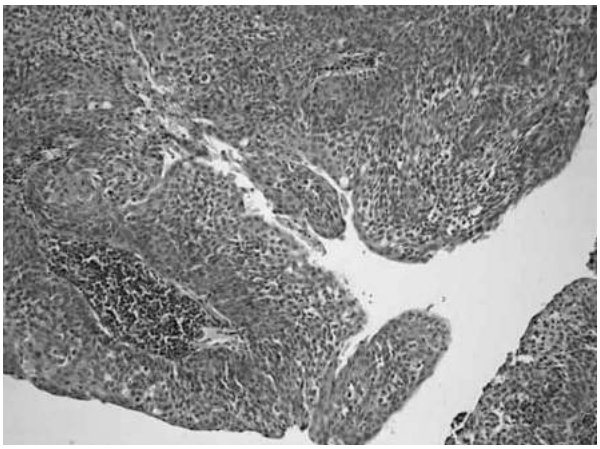

Fig. 2. Atypical squamous cells within the wall of cyst (HEx20)
Slika 2. *Atipične skvamozne ćelije u zidu ciste (HE x 20)*

A radical neck dissection was performed after the diagnosis of suspected branchiogenic carcinoma had been made. No elements of a tumor were found in the samples which corresponded to the transversely striated muscle tissues, salivary gland tissue and reactively altered lymph nodes (n = 24). The patient was presented for the oncology consultation, and was prescribed radiotherapy. The patient is monitored regularly and the check-ups have not revealed the presence of metastatic tumor so far.

Discussion

Lateral neck cysts of adults are usually benign [6,7]. Among these cysts, branchial cysts are relatively common, as confirmed by the analysis of our material collected over 10 years, when eight patients were diagnosed to have them. Although they usually occur in the second and third decade of life, they can also be found in elderly patients. If the patient is older than 40, solitary cystic neck lesions raise suspicion of cancer, particularly metastatic occult nasopharyngeal carcinoma, tongue carcinoma or papillary thyroid cancer and very rarely BC [2,6-8]. Even though Lester et al. argue that there is no BC [6],

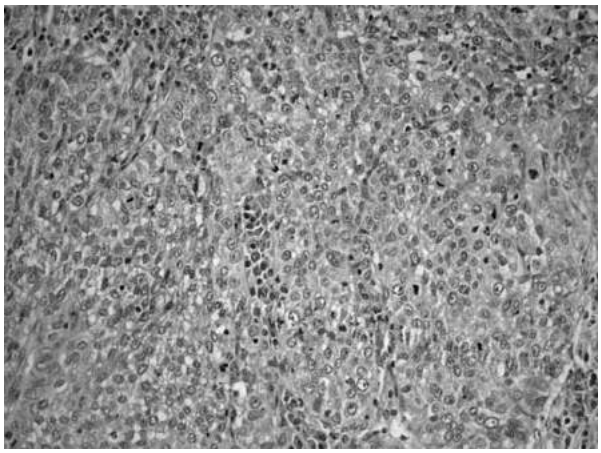

Fig. 3. Expressed mitotic activity of tumor cells (HEx40)
Slika 3. *Izražena mitotska aktivnost tumorskih ćelija (HEx40)*

Martin and colleagues confirmed the presence of BC in 18 patients after they had examined 250 cases [7]. According to Katori et al., BC is 2.5 times more common in men [10]. That this is a rare form of cancer is confirmed in our case study, given that there is only one recorded case in our material.

Martin et al. proposed the criteria for diagnosing BC in 1950: the anatomical localization of cystic tumor mass (from the tragus along the front side of the SCM to the clavicle), the histological appearance of cystic masses has to be in accordance with tissues descendent from the gill arch, and the periodic monitoring of the patient and survival for five years after the diagnosis of BC was made [9].

Khafif et al. expanded these criteria stating that the cyst epithelium shows a transition from the normal, followed by the atypical epithelium, and the in situ carcinoma to invasive squamous carcinoma. Unlike Martin et al., Khafif et al. believe that the five-year monitoring does not play a major role in making diagnosis of BC with regard to many of the patients receiving postoperative radiotherapy, which may affect the potentially present metastatic carcinoma; there is also a possibility of an entirely new primary tumor developing during the period of five years or afterwards. In the period from 1951 and 1988 they reviewed 67 cases of branchyal cysts according to their criteria and the presence of BC was determined in only 10 patients. The diagnosis of BC has been made in 25 cases following these criteria since 1988 [11].

The differential diagnosis is broad, extensive, and includes both serious and benign etiologies. Differentials and other problems to be considered are cystic hygroma, dermoid cyst, glomus tumor of the head and neck, lipomas, liposarcoma, metastatic squamous cell carcinoma, glandular cysts, lymphadenopathy, dermoid tumor of the neck, ranula, laryngocele, parathyroid gland adenoma**,** thyroglossal duct cyst, hemangioma of soft tissue etc.[12,13].

The diagnosis of lateral neck cysts containing malignant epithelium is a great challenge and is made only after the complete excision of cyst [14]. The definitive diagnosis of BC must be based on histological features. A five-year monitoring of the patient is necessary to rule out metastasis of this tumor [15].

The treatment of choice is the wide tumor ablation with the radical neck dissection, whereas chemotherapy and radiotherapy are recommended when the invasion of surrounding tissues is evident. BC has a high mortality rate, up to 48%, and the prognosis depends on the degree of differentiation of tumor tissue, mitotic activity, extensiveness and lymphovascular invasion [16,17].

Clinical and radiological monitoring of our patient, as well as histopathological findings after the radical neck dissection performed in the second act, excluded the existence of metastatic carcinoma, and thence a definitive diagnosis of BC was made.

Conclusion

Branchiogenic carcinoma is a rare tumor which is difficult to diagnose preoperatively. Bearing in mind the fact that there are restrictions on the criteria of the diagnosis of branchiogenic carcinoma, and that metastatic carcinoma was not revealed by a number of diagnostic procedures in our patient, who was sent to radiotherapy postoperatively, it seems possible to make the diagnosis of BS in this case at this moment. The diagnosis is to be fully confirmed after meeting the last Martin criteria, i.e. the five-year monitoring and follow-up.

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Rad je primljen 6. IV 2012.
Recenziran 17. VIII 2012.
Prihvaćen za štampu 20. X 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:177-180.

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Prikaz slučaja
Case report
UDK 616.831-009.11-053.2:159.9-055.2
DOI: 10.2298/MPNS1304181K

ODNOS MAJKE PREMA DETETOVOJ DIJAGNOZI CEREBRALNE PARALIZE

MOTHERS' RESOLUTION OF THEIR CHILDREN'S DIAGNOSIS OF CEREBRAL PALSY

Tatjana KRSTIĆ[1,3], Vojislava BUGARSKI[1,2], Nina BRKIĆ[3] i Biljana OBRADOVIĆ[1,3]

Sažetak

Uvod. Proces adaptacije i prihvatanja detetove dijagnoze cerebralne paralize zahteva roditeljsku kognitivnu i emocionalnu obradu traume izazvane saznanjem detetove dijagnoze. Roditelji koji su prihvatili detetovo stanje označavaju se kao 8prihvatajući". Nasuprot njima, 8neprihvatajući" roditelji ne prihvataju realnost detetovog stanja i nisu prevazišli krizu izazvanu saznanjem detetove dijagnoze. Neprihvatajući status ima negativne implikacije na dete, roditelje i njihov odnos. **Prikazi slučajeva.** Dati su prikazi slučaja dve majke, čija deca imaju dijagnozu cerebralne paralize. Prvi slučaj prikazuje prihvatajuću majku koja je uspela da prevlada početni šok i oseti olakšanje od perioda kada je saznala detetovu dijagnozu. Nasuprot tome, drugi slučaj prikazuje 8neprihvatajuću" majku kod koje nema značajnih promena u mislima i osećanjima od perioda kada je saznala detetovu dijagnozu. Preokupirana je ljutnjom i pokušajem da minimizira detetov problem. **Diskusija.** Intervju o reagovanju na dijagnozu i Klasifikacioni sistem za intervju o reagovanju na dijagnozu omogućuju prepoznavanje majčinog odnosa prema detetovoj dijagnozi cerebralne paralize. Diskutovano je o karakteristikama majčinog prihvatajućeg i neprihvatajućeg odnosa. **Zaključak.** Roditeljski odnos prema dijagnozi je ključni za uspešnu adaptaciju na podizanje dece sa smetnjama u razvoju, kao i ispunjavanje zahteva roditeljske uloge. Važno je da se prepoznaju roditeljska razmišljanja i osećanja u pogledu detetovog stanja da bi se psihoterapeutske intervencije usmerile prema populaciji vulnerabilnih roditelja.

Ključne reči: Cerebralna paraliza; Majka; Dete; Dijagnoza; Psihološka adaptacija; Ponašanje; Izražavanje emocija; Psihoterapija

Summary

Introduction. The process of adaptation and acceptance of a child's diagnosis of cerebral palsy requires from parents to process the trauma caused by this knowledge cognitively and emotionally. Parents who manage to come to terms with their children's condition are labeled as resolved. As opposed to them, unresolved parents do not accept the reality of their children's condition and fail to overcome the crisis caused by knowledge of the child's diagnosis. Unresolved status has negative implications for the child, the parents and their relationship. **Case Reports.** Two case reports of mothers whose children have been diagnosed to have cerebral palsy are given. The first case shows a resolved mother who managed to overcome the initial shock and started to feel a sense of relief from the period when she found out the child's diagnosis. In contrast, another case shows an unresolved mother with no significant changes in thoughts and feelings from the time since she learned the child's diagnosis. She was preoccupied with anger and attempted to minimize the child's problem. **Discussion.** Interviews on reaction to diagnosis and reaction to diagnosis classification system allow identification of mothers' resolution of their children's diagnosis of cerebral palsy. The characteristics of resolved and unresolved maternal status are discussed. **Conclusion.** Parental resolution of diagnosis is essential for the successful adaptation to raising children with disabilities, as well as meeting the requirements of the parental role. It is important to recognize parental cognitions and feelings regarding the child's condition in order to direct psychotherapeutic interventions towards vulnerable population of parents.

Key words*:* Cerebral Palsy; Mother; Child; Diagnosis; Adaptation, Psychological; Behavior; Expressed Emotion; Psychotherapy

Uvod

Dijagnoza koja ukazuje da dete ima smetnje u razvoju izaziva kod roditelja doživljaj tuge, koji je sličan iskustvu ljudi koji tuguju nakon što je preminula neka njima bliska osoba. Taj proces tuge nije uvek jednostavno odrediti. Jedna od komplikacija jeste prepoznavanje onoga za čime roditelji tuguju. Fizički, njihovo dete nije izgubljeno, tako da roditelji tuguju za svojim nadama koje su bile usmerene na rođenje „perfektnog deteta" [1]. Fraza „tuga zbog gubitka perfektnog deteta" često se koristi za opisivanje procesa u kome roditelji menjaju svoje predstave očekivanog deteta i prihvataju sliku svog deteta sa hroničnim zdravstvenim poteškoćama [2]. Postoje razlike u okolnostima i vremenu saznavanja detetove dijagnoze, pa su tako deca sa Daunovim sindromom uvek prepoznata na samom rođenju, dok je kod zdravstvenih problema kao što su cerebralna paraliza (CP), autizam, mišićna distrofija stanje mnogo manje određeno na sasvim ranom uzrastu [3]. Bez obzira kada su saznali detetovu dijagnozu, roditelji o tom periodu govore kao o periodu krize kada se narušava porodična dinamika,

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Skraćenice

CP − cerebralna paraliza
SSS − srednja stručna sprema
AS − Apgar skor
KR − koeficijent razvoja

menjaju se očekivanja u vezi sa detetom, roditelji osećaju krivicu ili tragaju za uzrokom detetovog stanja, a njihova samopercepcija kao efikasnih zaštitnika i staratelja je promenjena [2].

Proces prilagođavanja i prihvatanja detetovog stanja zahteva roditeljsku kognitivnu i emocionalnu obradu doživljenog iskustva. Kognitivno, oni moraju da razumeju implikacije detetove dijagnoze. Emocionalno, moraju doživeti, prihvatiti i izraziti osećanje razočarenja, žalosti, tuge, ljutnje i krivice da bi mogli shvatiti značenje informacije da njihovo dete ima ometenost u razvoju [4]. Prema detetovoj dijagnozi roditelji razvijaju različit odnos, pri čemu možemo razlikovati roditelje koji prihvataju dijagnozu kod svog deteta i one koji ne uspevaju u tome. Roditelji koji prihvataju detetovu dijagnozu imaju realističan pogled na detetovo zdravstveno stanje i sposobnosti, te prepoznaju promenu u svojim osećanjima u odnosu na vreme kada su saznali detetovu dijagnozu. Nasuprot njima, roditelji koji ne prihvataju dijagnozu nisu napredovali od početne krize koja je nastupila nakon saznanja detetove dijagnoze. Oni ostaju fokusirani na doživljaj kada su saznali dijagnozu u emocionalno preplavljujućem ili ljutitom stavu, ili poriču uticaj dijagnoze na sebe da bi se sačuvali od konfrontiranja sa bolnim emocijama [2].

Cerebralna paraliza je jedna od najčešćih fizičkih smetnji koja utiče na funkcionalni razvoj dece i često je udružena sa stanjima kao što su mentalna retardacija i epilepsija [5,6]. S obzirom na kompleksnu prirodu CP i brojne teškoće u prihvatanju dijagnoze, cilj ovih prikaza jeste da predstavimo različite vidove majčinog odnosa prema detetovoj dijagnozi.

Prikaz prvog slučaja

Majka deteta je stara 32 godine, srednje stručne spreme (SSS), živi u bračnoj zajednici. Ima dečaka koji je uzrasta 2 godine i 8 meseci. Rođen je iz prve trudnoće. Porođaj je dugo trajao, od poteškoća u toku porođaja majka navodi samo podatak da je odojčetu pupčana vrpca bila obmotana oko vrata. Dobijeni Apgar skor (AS) deteta na rođenju bio je 9/10 i roditelji su bili uvereni da je detetovo zdravstveno stanje dobro. U prvim mesecima detetovog života bilo je problema prilikom hranjenja odojčeta jer je zabacivalo glavu, ali majka tome nije pridavala veći značaj. Na uzrastu od 6 meseci u Razvojnom savetovalištu (kada odojče nije reagovalo na zvuk zvonceta i izvrtalo se pri postavljanju u sedeći položaj) pedijatar ukazuje majci da ono ima značajnije zdravstvene probleme i da su neophodna dalja ispitivanja. Majčine prve reakcije su bile izrazita zbunjenost i strah. Zatim slede detaljna dijagnostička ispitivanja i terapijske procedure. Na uzrastu od 20 meseci je postavljena dijagnoza CP. Premda majka navodi da je sumnjala da dete ima ozbiljniji problem jer je kašnjenje u razvoju i njoj postalo uočljivo, ipak doživljava emotivni šok, a svoje stanje opisuje kao „mentalnu i fizičku oduzetost". U tom periodu je bila izuzetno razdražljiva i plačljiva. Kao olakšavajuću okolnost navodi potpunu podršku koju ima od supruga.

Dete od odojčadskog perioda prati i psiholog, a rezultati psihološkog ispitivanja ukazuju na veoma izraženo kašnjenje u psihomotoričkom razvoju. Na uzrastu od 2 godine i 8 meseci primenom Skale za procenu psihomotoričkog razvoja deteta dobija se koeficijent razvoja (KR) = 35 [7,8]. Tada je s majkom sproveden i Intervju o reagovanju na dijagnozu [9] gde se jasno uočava početni emotivni šok i teškoće u funkcionisanju nakon saznanja detetove dijagnoze. Iako su i dalje prisutni periodi pojačane tuge i „vraćanja" u prošlost, ta tuga ne preokupira njeno funkcionisanje i odnos prema detetu. Sama majka uviđa veliku promenu u svojim osećanjima i razmišljanjima od perioda u vreme saznanja detetovih problema i postavljanja konačne dijagnoze do danas. Sada značajno mirnije i staloženije prihvata informacije koje dobija o detetu i počinje da oseća zadovoljstvo pri njegovom, čak i minimalnom napredovanju. Majčine odgovore u Intervjuu su kodirali [10] ispitivači i dva nezavisna kodera, koji su procenili da je majka prihvatila dijagnozu svog deteta. Tokom hospitalizacija, majka aktivno učestvuje u grupama za roditelje gde nakon dužeg vremena otvoreno počinje da ispoljava svoja osećanja i razmišljanja u vezi sa detetom.

Prikaz drugog slučaja

Majka deteta je stara 30 godina, SSS, živi u harmoničnoj bračnoj zajednici. Ima dvoje dece, od kojih je stariji dečak, uzrasta 6 godina, zdrav. Drugo dete je devojčica koja je rođena iz komplikovane trudnoće u 34. nedelji gestacije, AS 7/8. Majka navodi da nije obaveštena da dete ima neke zdravstvene probleme, niti su roditelji sumnjali u to. Navodi da im je jedino bio upadljiv detetov dugotrajni plač koji je počeo u drugom mesecu. Kada je odojče bilo staro osam meseci pedijatar ukazuje da ono ima zdravstveni problem, a to saznanje kod majke izaziva bes.

Dete od osmog meseca prati psiholog. Na uzrastu od 2 godine i 11 meseci rezultati psihološkog ispitivanja ukazuju na izrazito usporen psihomotorički razvoj KR = 39 [7,8]. Tada je majka intervjuisana Intervjuom o reagovanju na dijagnozu. Uočeni su jasno perzistiranje besa i izražena ljutnja, prvenstevno prema medicinskom osoblju. Detetovu dijagnozu CP saznali su na uzrastu od 22 meseca. Majka je to sa nevericom primila, a i sada nalazi mnoštvo nelogičnih objašnjenja kako to

„ipak nije prava cerebralna paraliza već cerebralna paraliza tipa jedan". Majka izveštava da je u prvom momentu po saznanju detetove dijagnoze veoma žalila i sebe i svoje dete. U odnosu na taj period, ona ne uviđa promenu u svojim razmišljanjima i osećanjima, već ukazuje na izraženu nervozu, teško priča o osećanjima, povremeno deluje konfuzno i uznemireno. Uporna je u pokušaju da minimizira detetov problem *(„Ona ne odudara od druge dece, u stvari odudara, ali ne vidi se to baš toliko").* Ispitivač i dva nezavisna kodera su kodirali majčine odgovore koristeći Klasifikacioni sistem za intervju o reagovanju na dijagnozu [10] i usaglasili se da majka nije prihvatila detetovu dijagnozu, a kao supkategoriju njenog odnosa prema dijagnozi ističu preokupiranost ljutnjom. Ta ljutnja zaokuplja veći deo njenih razmišljanja i emotivnog odnosa u vezi sa detetovim zdravstvenim stanjem, onemogućavajući joj da se adekvatno usmeri na svoje dete, njegove potrebe (prvenstveno emotivne) i njihov odnos.

Diskusija

Intervju o reagovanju na dijagnozu razvijen je sa ciljem ispitivanja roditeljskog odnosa prema detetovoj dijagnozi hronične bolesti ili smetnje u razvoju. Suštinski, Intervjuom ispitujemo prevazilaženje traume povezane sa saznanjem roditelja o dijagnozi njihovog deteta. Prvi predstavljeni slučaj prikazuje majku koja je prihvatila, a drugi majku koja nije prihvatila detetovu dijagnozu. Premda su početna reagovanja obe prikazane majke upućivala na traumu i značajne teškoće usled saznanja o postojanju detetovih zdravstvenih problema, odnosno konačne dijagnoze CP, njihov kognitivni i emotivni odnos prema tom saznanju se nakon toga razvijao u različitim smerovima. Istraživanja takođe ukazuju da pri saznanju detetove dijagnoze koja upućuje na hronične probleme, roditeljska emotivna ispoljavanja ukazuju na šok, neprihvatanje, nevericu, tugu [2,4]. Navodi se i da je za prevazilaženje početnog šoka potrebno da prođe period od najmanje 6 meseci i u tom periodu se i ne preporučuje uključivanje roditelja u grupni terapijski rad [4]. Kao što je prikazano u prvom slučaju majke koja je uspela da prihvati stanje svog deteta, ona kao i drugi „prihvatajući" roditelji povremeno ima periode vraćanja tuge i bolnih osećanja, ali je suštinsko da ta osećanja nisu preokupirajuća kao na početku i da roditelji koriste različite strategije koje im vremenom olakšavaju prihvatanje detetove dijagnoze [11]. Prihvatanje nije uvek potpuno: većina roditelja ukazuje na povremena vraćanja tuge, „lečenje" fantazijama i to naročito u vreme oko godišnjih odmora i periodima kada se očekuju određene razvojne promene kod deteta [2]. Ključno u određivanju roditeljskog odnosa jeste promena (izvesno olakšanje) koju roditelji počinju da osećaju i kao što se u prikazu prve majke vidi, ona počinje da uživa čak i u minimalnim napredovanjima svog deteta. Ono što je važno naglasiti jeste da roditelji koji prihvate detetovo stanje realno sagledavaju njegove mogućnosti i sopstvenu starateljsku ulogu [4]. Nasuprot njima, roditelji koji ne prihvataju dijagnozu doživljavaju distres kada brinu o svom detetu što smanjuje njihovu emotivnu prijemčivost i otežava prepoznavanje detetovih potreba [12,13]. Prikaz druge majke ukazuje na njenu preokupiranost ljutnjom, naročito usmerenu prema zdravstvenom osoblju, čak i onima koji aktuelno pomažu njenom detetu. Pored preokupiranosti ljutnjom, prepoznate su i druge supkategorije neprihvatajućeg roditeljskog odnosa, kao što su emocionalna preplavljenost, depresivno regovanje, kognitivne distorzije [2].

Zaključak

Saznanje da dete ima cerebralnu paralizu traumatsko je za roditelje i oni na različite načine percipiraju i prihvataju stanje svog deteta pokušavajući da se kognitivno i emotivno nose sa neželjenom i stresnom situacijom. Potrebno je pomoći porodici da razume i emotivno obradi saznanje da njihovo dete ima cerebralnu paralizu, koja predstavlja stanje koje je trajno i koje se neće izlečiti. Ukoliko roditelji uspeju da prevaziđu svoje početne reakcije tuge oni mogu bolje da razumeju stanje svog deteta, njegove sposobnosti i ograničenja, kao i da uspešno usklade svoju starateljsku ulogu s detetovim potrebama. Roditeljsko prihvatanje dijagnoze je neophodno da bi se porodica uspešno adaptirala na podizanje deteta sa smetnjama u razvoju. Stoga je prepoznavanje roditeljskog odnosa prema detetovoj dijagnozi veoma važno za praktični rad sa roditeljima kako bi se psihoterapeutske intervencije usmerile na poboljšanje funkcionisanja porodice. S obzirom da su roditelji (posebno oni koji ne prihvataju detetovo stanje) dece sa cerebralnom paralizom pod pojačanim stresom uslovljenim zahtevima detetove bolesti (emocionalnim, fizičkim, finansijskim), ne sme se potceniti važnost psihoterapijskog rada kako bi im se pomoglo u realnom prihvatanju stanja svog deteta i adaptaciji na njega.

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Rad je primljen 13. VI 2012.
Recenziran 29. VI 2012.
Prihvaćen za štampu 20. X 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:181-184.

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Prikaz slučaja
Case report
UDK 616.381-78-06
DOI: 10.2298/MPNS1304185D

INKAPSULIRAJUĆA PERITONEUMSKA SKLEROZA – PRIKAZ SLUČAJA

ENCAPSULATING PERITOENAL SCLEROSIS – CASE REPORT

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Sažetak

Uvod. Inkapsulirajuća peritoneumska skleroza je moguća, ozbiljna, životno ugrožavajuća komplikacija lečenja peritoneumskom dijalizom. **Prikaz slučaja 1.** Bolesnica je hitno hospitalizovana zbog kliničke slike inkapsulirajuće peritoneumske skleroze u zapaljenskom stadijumu: febrilnost, subokluzija, pozitivan zapaljenski sindrom (Le 20 K/µl, CRP 217 mg/l) i jako zamućen peritoneumski efluent (Le 3,3 K/µl) uz sterilnu kulturu. Faktori rizika za razvoj inkapsulirajuće peritoneumske skleroze bili su devet prethodnih epizoda peritonitisa kao i višegodišnje korišćenje hipertonih dijaliznih rastvora. Dijagnoza je potvrđena kompjuterskom tomografijom. Ordinirani su joj tamoksifen i pronizon i odgovor na terapiju bio je pozitivan. Međutim, i pored kontrole inkapsulirajuće peritoneumske skleroze, smrtni ishod nastao je posle osam meseci usled tuberkuloze pluća sa znacima popuštanja srca. **Prikaz slučaja 2.** Klinička slika je takođe odgovarala inkapsulirajućoj peritoneumskoj sklerozi u zapaljenskom stadijumu, a identifikovani faktori rizika bili su dugogodišnje lečenje peritoneumskom dijalizom (100 meseci) i epizoda teškog peritonitisa sa infekcijom tunela. Prvi znak inkapsulirajuće peritoneumske skleroze bio je hemoragičan ascites, koji je viđen pri ponovnom pokušaju plasiranja Tenkofovog (*Tenckhoff*) katetera. Dijagnoza je potvrđena CT nalazom. U terapiju je uveden tamoksifen (tbl. 10 mg 2 x 2). Nakon 14 meseci od otpusta bolesnik sem anemije, slabog apetita i zamaranja, negira druge tegobe. **Zaključak.** Tokom lečenja bolesnika peritoneumskom dijalizom uvek treba misliti na komplikaciju u vidu inkapsulirajuće peritoneumske skleroze koju nije uvek lako prepoznati. Blagovremena dijagnoza uz upotrebu kortikosteroida i tamoksifena u prvom, a samo tamoksifena u drugom slučaju bila je delotvorna u kontroli i sprečavanju napredovanja bolesti.

Ključne reči: Peritonealna fibroza; Peritonealna dijaliza; Peritonitis; Faktori rizika; Dijagnoza; Terapija

Summary

Introduction. Encapsulating peritoneal sclerosis is a possible, serious, life-threatening complication of peritoneal dialysis therapy. **Case 1.** A female patient was hospitalized for clinical signs of encapsulating peritoneal sclerosis in the inflammatory stage with fever, intestinal occlusion, positive inflammatory syndrome (Le 20 K/µL, CRP 217 mg/L) and highly turbid peritoneal effluent (Le 3.3 K/µL) with sterile culture. Risk factors for the development of encapsulating peritoneal sclerosis were nine previous episodes of peritonitis and long-term use of high osmolality dialysis solution. The diagnosis was confirmed by computed tomography findings. During the course of therapy, the patient had a good response to Tamoxifen and prednisone. Although encapsulating peritoneal sclerosis was well controlled, the patient died after eight months due to tuberculosis of the lungs with signs of heart failure. **Case 2.** The clinical presentation also corresponded to encapsulating peritoneal sclerosis in the inflammation stage, and the identified risk factors were the long-term treatment with peritoneal dialysis (100 months) and an episode of peritonitis with tunnel infection. The first sign of encapsulating peritoneal sclerosis was hemorrhagic ascites, which was observed when the peritoneal catheter was being replaced. The diagnosis was confirmed by computed tomography findings. He was treated with Tamoxifen (10 mg 2x2 tbl). Except anemia, poor appetite and fatigue, the patient denied any other symptoms after 14 months of therapy. **Conclusion.** During peritoneal dialysis, one should always think about encapsulating peritoneal sclerosis which is not always easy to recognize. Timely diagnosis with the use of corticosteroids and Tamoxifen in the first and Tamoxifen in the second case were effective in controlling and preventing dise- ase progression.

Key words: Peritoneal Fibrosis; Peritoneal Dialysis; Peritonitis; Risk Factors; Diagnosis; Drug Therapy

Uvod

Inkapsulirajuća peritonumska skleroza (IPS) je životno ugrožavajuća moguća komplikacija lečenja peritoneumskom dijalizom (PD) [1−3]. Prevalencija IPS varira između 0,7 i 3,7%, pri čemu raste sa vremenom provedenim na PD (0,7−6,4% posle 5 godina do čak 17,2% posle 15 godina) [1]. Dijagnoza IPS bazira se na kliničkim simptomima i znacima kao i na specifičnom, ali ne i patognomoničnom radiološkom i patohistološkom nalazu [4]. Karakteristike IPS na snimcima kompjuteriovane tomografije (CT) su zadebljanje i kalcifikacija peritoneumske membrane, zadebljanje crevnog zida, strikture i di-

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Skraćenice

IPS	– inkapsulirajuća peritoneumska skleroza
CT	– kompjuterizovana tomografija
HD	– hemodijaliza
PD	– peritoneumska dijaliza
CAPD	– kontinuirana ambulantna peritoneumska dijaliza
PET	– test peritoneumske ekvibrilacije

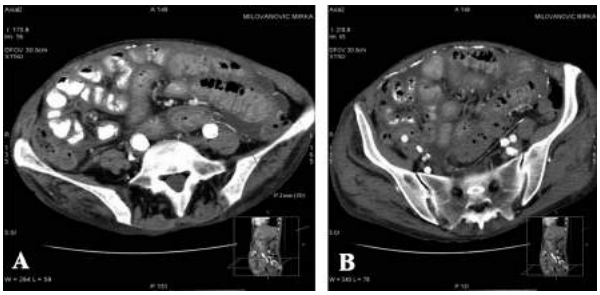
latacije creva, kao i „učaurene" kolekcije tečnosti [4]. U radu su prikazana dva slučaja razvoja inkapsulirajuće peritoneumske skleroze.

Prikaz slučaja 1

Bolesnica, 1955. godište, otpočela je lečenje kontinuiranom ambulantnom peritoneumskom dijalizom (CAPD) oktobra 1998. godine usled hipertenzivne nefroskleroze. U periodu od avgusta 2002. do juna 2004. godine, bolesnica je imala 9 epizoda peritonitisa: jedna kultura negativna i 8 epizoda izazvanih Gram-pozitivnim bakterijama (*St. Aureus i St. Epidermidis*). Nakon šeste epizode peritonitisa u novembru 2003. godine registrovana je promena u transportnim karakteristikama peritoneumske membrane (hipervolemija, smanjenje 24-satne ultrafiltracije). Avgusta 2006. bolesnica je hospitalizovana zbog čestih prolivastih stolica i bolova pod levim rebarnim lukom. Nalaz ultrazvučnog pregleda abdomena ukazivao je na stazu crevnih vijuga u levoj polovini trbuha, a na nativnom snimku abdomena uočeni su manji nivoi u projekciji tankog creva. U laboratorijskim analizama zabeležene su povišene vrednosti tumorskih markera i pozitivan zapaljenski sindrom: CEA 12,8 ng/ml, CA 19-9 194 U/ml, Le 16,9 K/µl, CRP 41,4 mg/l. Kako na CT snimku abdomena nisu nađeni kriterijumi za IPS, urađena je endoskopska retrogradna holangiopankreatografija sa papilotomijom zbog progresivnog porasta vrednosti tumorskih markera (CEA 24,2 ng/ml; CA-19-9 584 U/ml) i proširenih intrahepatičnih žučnih puteva (uz pozitivan ishod). Tokom 2007. godine došlo je do daljeg smanjenja 24-satne ultrafiltracije i test peritoneumske ekvilibracije (PET) pokazao je da je bolesnica brz transporter. Jula 2008. bolesnica je hitno hospitalizovana zbog edema pluća, te joj je plasiran centralni vaskularni kateter za hemodijalizu. Istovremeno, javila se febrilnost, subokluzija i pozitivan zapaljenski sindrom (Le 20 K/µl, CRP 217 mg/l), kao i jako zamućen peritoneumski efluent (Le 3,3 K/µl) uz sterilnu kulturu. Ovog puta, na CT snimku abdomena (septembar 2008.) viđena je slobodna tečnost denziteta ascitesa u svim delovima intraperitoneumske šupljine kao i peritoneum difuzno prožet kalcifikacijama **(slike 1A i 1B)**. Kod bolesnice je postavljena dijagnoza IPS, a lečenje je nastavila hemodijalizama (HD) na implantiranoj vaskularnoj protezi. Ordiniran je tamoksifen 20 mg/dan i pronizon 10 mg/dan i upućena je u matični centar na dalje lečenje oporavljena i bez subjektivnih tegoba. Do februara 2009. godine bolesnica je lečena savetovanom terapijom, koja je obustavljena zbog dijagnostifikovane tuberkuloze pluća i započeta je četvorostruka tuberkulostatska terapija. Međutim, i pored kontrole IPS, u martu 2009. godine došlo je do smrtnog ishoda sa znacima popuštanja srca.

Prikaz slučaja 2

Bolesnik, 1947. godište, hospitalizovan je jula 2002. godine sa ispoljenim uremijskim sindromom usled hipertenzivne nefroskleroze. S obzirom na ablaciju retine i amaurozu od 1984. godine supruga je obučena za izvođenje asistirane CAPD metode sa glukoznim rastvorima. Prva epizoda peritonitisa bila je avgusta 2002. godine izazvana bakterijom *St. Aureus* koja je uspešno sanirana. Do 2010. bolesnik je bio stabilan, a u aprilu iste godine, i pored redovnog lečenja, registrovana je sideropenijska anemija i hipervolemija uz smanjenje diureze sa 1 500 na 300 ml/24 h. PET test je pokazao da je bolesnik prosečno brz transporter, te mu je i dijalizna preskripcija promenjena (2 x 1,36%, 1 x 2,27% svi rastvori glukozni od 2,5 x l i *extraneal* u noćnoj izmeni). Ordinirana mu je supstitucija preparatima gvožđa, transfuzije koncetrovanih eritrocita i povećana je doza agenasa stimulacije eritropoeze. Druga epizoda peritonitisa javila se januara 2011. godine (Le u efluentu 1,1 K/µl), udružena sa infekcijom tunela (*St. Aureus*) uz znake sistemske infekcije (Le 13,8 K/µl, CRP 155 mg/l). Bolesniku je predloženo indikovano vađenje katetera, što je odbio i započeta je dvostruka intraperitoneumska administracija antibiotika. Ipak, nakon 7 dana, zbog slabog odgovora na terapiju (Le u efluentu 1,0 K/µl, CRP 123 mg/l) kateter je izvađen i nastavljeno je *i. v.* ordiniranje antibiotika, plasiran je centralni venski kateter i otpočeta je hemodijaliza. Zbog insistiranja bolesnika da dalje lečenje nastavi peritoneumskom dijali-



Slika 1. Snimak abdomena kompjuterizovanom tomografijom kod bolesnika sa inkapsulirajućom peritoneumskom sklerozom
A. Nivoi koji označavaju subokulziju
B. Kalcifikacije parijetalnog peritoneuma
Fig. 1. *Computed tomography of abdomen of a patient with encapsulating peritoneal sclerosis*
A. Gas-fluid lines indicate intestinal sub-occlusion
B. Calcifications of parietal peritoneum

zom, nakon 3 nedelje ponovo mu je hirurškom tehnikom (mini-laparatomijom infraumbilikalne regije) plasiran Tenkofov (*Tenckhoff*) kateter. Na CT abdomena viđena je slobodna tečnost oko jetre i slezine i ispred vijuga tankog creva (denziteta 20 HU − gušća tečnost), atipično raspoređena, stekao se utisak da je inkapsulirana. Postavljena je dijagnoza IPS i bolesniku je krajem februara 2011. kreirana fistula na podlaktici leve ruke. Polovinom marta 2011. bolesnik je otpušten kući, a dalje lečenje je nastavljeno hemodijalizom. U terapiju mu je uveden tamoksifen (tbl. 10 mg 2 x 2). Nakon 14 meseci i pored povećanja doze stimulatora eritropoeze i dalje postoji izražena anemija. Sem slabog apetita i zamaranja, negira druge tegobe sem redukcije telesne mase za 16 kg. Na kontrolnom ultrazvučnom pregledu abdomena nema znakova evolucije bolesti, dok su parametri inflamacije mirni (Le 6,8 K/µl, CRP 5,9 mg/l).

Diskusija

Etiologija IPS još uvek je nedovoljno jasna, ali se veruje da je multifaktorska. Široko je prihvaćena teorija Honde i Oda, takozvana *two hit* teorija, prema kojoj su potrebna dva stimulusa za nastanak IPS [5]. Prvi stimulus je oštećenje peritoneumske membrane uzrokovano dijaliznom procedurom (bioinkopatibilni dijalizni rastvori, plastisizeri, rekurentni peritonitisi, uremija). Drugi stimulus, takozvani *okidač* može biti epizoda teškog peritonitisa, inflamacija, naglo prekidanje PD zbog prevoda na HD ili transplantacija bubrega, abdominalna hirurška intervencija. Nakamato je mišljena da je raznovrsnost kliničke slike IPS posledica činjenice da bolest napreduje kroz četiri stadijuma [6]. Prvi, pre-IPS stadijum karakteriše gubitak ultrafiltracione sposobnosti, hipoproteinemija i kalcifikacije peritoneuma. Drugi stadijum je zapaljenski stadijum i karakteriše ga febrilnost, gubitak telesne mase, gubitak apetita, dijareja, povišene vrednosti CRP i leukocitoza. Treći stadijum je inkapsulirajući ili progresivni stadijum, karakteriše ga nestajanje inflamacije i pojava simptoma i znakova ileusa (muka, povraćanje, abdominalni bol, opstipacija, abdominalne mase, ascites). Četvrti stadijum je stadijum ileusa i karakterišu ga anoreksija, potpuni ileus i prisustvo abdominalne mase. Iako su ultrazvučni i nativni snimak značajni, najveću dijagnostičku vrednost ima CT abdomena koja ukazuje na adhezije, kalcifikacije peritoneuma, strikture i dilatacije creva kao i učaurene kolekcije [6,7].

U prvom prikazanom slučaju, klinička slika je odgovarala IPS u zapaljenskom stadijumu. Faktori rizika za razvoj IPS bili su devet prethodnih epizoda peritonitisa kao i višegodišnje korišćenje hipertonih dijaliznih rastvora, a dijagnoza je potvrđena CT nalazom. U drugom prikazanom slučaju, klinička slika je takođe odgovarala IPS u zapaljenskom stadijumu, a identifikovani faktori rizika bili su dugogodišnje lečenje PD (100 meseci) i epizoda teškog peritonitisa sa infekcijom tunel. Prvi znak IPS bio je hemoragijski ascites, mada je povećana potreba za agensima simulacije eritropoeze uz loše korigovanu anemiju možda bio najraniji znak početka ove komplikacije. Iako u oba prikazana slučaja nije rađena biopsija peritoneumske membrane i histološki pregled, dijagnoza je postavljena na osnovu kliničke slike i CT nalaza. Pored prekida PD i prevođenja bolesnika na HD − preporuke za lečenje IPS u Japanu su objavili 2005. godine Kawaguchi i dr. i prema ovim autorima, terapija treba da zavisi od stadijuma bolesti [7]. U pre-IPS stadijumu treba koristiti preventivne mere kao što je upotreba biokompatibilnih rastvora. U zapaljenskom stadijumu ordiniranje prednizolona 20 do 30 mg po danu je preporučeno sa inicijalnom pulsnom terapijom metilprednizolonom ili bez nje. U stadijumu ileusa, preporučuje se hirurško lečenje, laparatomija i enteroliza. Prikazi slučajeva i manje studije ukazuju na korist od primene tamoksifena u prevenciji i lečenju IPS u dozama od 10 do 40 mg/dan [6,8]. U oba prikazana slučaja postojao je pozitivan efekat na primenjenu terapiju.

Zaključak

U lečenju inkapsulirajuće peritoneumske skleroze primarno je rano postavljanje dijagnoze i aktivno započinjanje lečenja. Imunosupresija i upotreba antifibrotika je logičan pristup da bi se smanjila inflamacija i prevenirala inkapsulacija i napredovanje bolesti do stadijuma ileusa. Upotreba kortikosteroida i tamoksifena u prvom, a samog tamoksifena u drugom slučaju bila je delotvorna u kontroli bolesti i sprečavanju napredovanja bolesti do inkapsulirajućeg stadijuma.

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Rad je primljen 31. VII 2012.
Recenziran 18. X 2012.
Prihvaćen za štampu 20. X 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:185-188.

ISTORIJA MEDICINE
HISTORY OF MEDICINE

Univerzitet u Novom Sadu
Medicinski fakultet, Novi Sad

Istorija medicine
History of medicine
UDK 61(38)(091)

ZNAMENITI LEKARI IZ PROŠLOSTI – ORIBAZIJE IZ PERGAMONA

FAMOUS PHYSICIANS FROM THE PAST – ORIBASISUS FROM PERGAMUM

Želimir MIKIĆ

Sažetak

Uvod. Grčki lekar Oribazije iz Pergamona (današnji grad Bergama u zapadnoj Turskoj) (c. 320−400) bio je jedan od najpoznatijih lekara i ličnosti svog doba. **Životni put**. Oribazije je studirao medicinu u Aleksandriji, bio je lični lekar i prijatelj rimskog imperatora Julijana, te veoma važan političar tog perioda, ali iznad svega ostao je upamćen kao najznačajniji medicinski pisac i istoričar medicine. **Spisateljski rad.** Oribazije je napisao zamašno enciklopedijsko delo u 70 knjiga, od kojih je ostalo sačuvano 25, nazvano „Medicinska zbirka" (*Collectiones Medicae*) u kome je prikupio veliki broj izvoda (grč. *epitome*) iz radova pisaca iz oblasti medicine starog veka. Kasnije je napisao još dva značajna dela: „Sinopsis Eustahiju" (*Synopseos ad Eustahium*), posvećen njegovom sinu koji je takođe bio lekar, te „Knjigu Eunapijusu" (*Libri ad Eunapium*), posvećenu njegovom prijatelju, filozofu Eunapijusu, u 4 sveske u kojima je dao enciklopedijski prikaz tzv. *kućnih lekova*, tj. lekova za laike. Pored toga, napisao je još nekoliko knjiga koje nisu ostale sačuvane. Njegova dela bila su prevedena na latinski još u 5. veku, a kasnije, u srednjem veku, prevođena su i štampana u Evropi („Sinopsis Eustahiju" publikovan je 1554.) dok je modernije, kritičko izdanje prevoda grčkog teksta njegovih sačuvanih dela, bilo objavljeno u Nemačkoj od 1926. do 1933. **Zaključak.** Veliki značaj Oribazijevih dela je u tome da je u njima ostao sačuvan za potomstvo veliki broj saznanja i iskustva brojnih antičkih lekara koji bi inače ostali izgubljeni i zaboravljeni. Osim toga, ovi apstrakti (epitomi), nisu bili doslovno prepisani, nego su kritički razmotreni i razvrstani na enciklopedijski način. Zbog toga se Oribazije s pravom može smatrati prvim piscem medicinske enciklopedije u istoriji medicine.

Ključne reči: Istorija medicine; Antička istorija; Poznate ličnosti; Enciklopedija kao tema

Summary

Introduction. Greek physician Oribasius from Pergamum (today's Bergama in western Turkey) (c. 320-400) was one of the most important physicians and personalities of his time. **The life and Career.** Oribasisus studied medicine at Alexandria. Although he was the personal physician and friend of the Roman emperor Julian the Apostate, and a very important political figure of that period, he has been remembered as a most important medical writer and historian of medicine. **Medical Writing.** His major work, written in 70 books (only 25 of these survived), was the "Collectiones Medicae" which contains massive compilation of excerpts (*epitomai*) from the writings of older medical writers of the ancient world. Later on, he produced the "Synopsis for Eustathius" (*Synopseos ad Eustathium)* for his son Eustathius, who was also a physician. Oribasius dedicated a large work to his friend, the philosopher Eunapius: *"Libri ad Eunapium"*, a kind of medical encyclopaedia in four volumes with a collection of easily procured medicines compiled for laymen. Several more of his writings are known to have been entirely lost. The works of Oribasius were translated in Latin as early as the fifth century, and later, in the medieval times his books were published in Europe (the "Synopsis for Eustathius" was published in 1554), while the critical edition of his works translated from Greek texts was published in Germany in 1926 - 1933. **Commentary and Conclusion.** The special importance of the Oribasius' works is that they have preserved a number of excerpts from many medical authors of antiquity whose writings would otherwise have been lost. Besides, these extracts *(epitomai*) were not entirely verbatim, they were looked upon critically and sorted out in an encyclopaedic manner. Because of that Oribasius is rightly considered to be the first writer of a medical encyclopaedia in the history of medicine.

Key words: History of Medicine; History, Ancient; Famous Persons; Encyclopedias as Topic

Uvod

Oribazije iz Pergamona bio je jedan od najistaknutijih antičkih grčkih lekara iz IV veka n. e. koji je, pored svog burnog i bogatog života, ostao najviše upamćen po spisateljskom radu, tako da se on smatra jednim od najznačajnijih antičkih medicinskih pisaca i istoričara medicine, te jednim od prvih, ako ne i prvim enciklopedistom u istoriji medicine.

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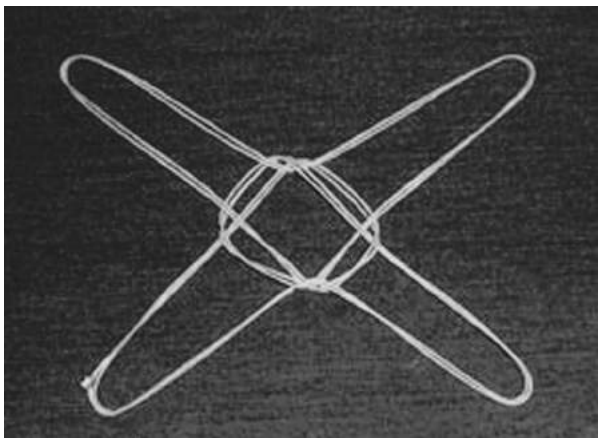
Životni put

Oribazije iz Pergamona ili Pergama (*Oribasius* ili *Oreibasius Pergamenus*) rođen je oko 320−325. g. n. e. [1−5] u gradu Pergamon ili Pergam (*Pergamum*) (danas grad Bergama u Zapadnoj Turskoj, oko 25 km istočno od obale Egejskog mora) [6] u uglednoj porodici grčkog porekla, koji su, u religioznom smislu, najverovatnije bili pagani. Činjenice da je grad Pergamon, u kome je rođen i čuveni grčki lekar Galen (129–200. g. n. e.) [7], bio poznat kao jedan od centara sa bogatom kulturnom tradicijom, a isto tako i kao važan medicinski centar u to doba, svakako su uticale na Oribazija u izboru buduće profesije, odnosno u donošenju odluke da se posveti medicini. Verovatno je da je Oribazije započeo studije medicine u svom rodnom gradu [8,9], ali je veći deo studija proveo u Aleksandriji, najpoznatijem centru medicine u to doba, gde je učio kod čuvenog grčkog lekara Zenoa (*Zeno*) sa Kipra koji mu je bio mentor [10]. Oribazije je po završetku studija radio kao dvorski lekar na dvoru imperatora Konstancija II (*Constantius II*) (živeo 317−361, bio imperator 337−361) [5,11] u čijoj pratnji je bio kada je oko 350. Konstancije II posetio imperatorsko imanje i tvrđavu Macelum (*Macellum*) u Kapadokiji, u centralnoj Maloj Aziji, gde su prisilno bili smešteni na školovanje njegovi bliski rođaci (braća od strica), prinčevi Gal (*Gallus*) i Julijan (*Iulianus*) i gde je Oribazije upoznao mladog, trinaestogodišnjeg Julijana, budućeg imperatora [5,12]. Nešto kasnije, oko 351., u Nikomediji (današnji grad Izmir na istočnoj obali Mramornog mora, na oko 100 km istočno od Istanbula), Oribazije se ponovo sreo sa Julijanom rekavši mu da je napustio mesto dvorskog lekara i pozvao ga da dođe u njegov rodni grad Pergamon, gde se u to vreme nalazila najveća biblioteka na svetu posle one u Aleksandriji, te da tamo nastavi studije, što je Julijan i učinio i gde se među njima razvilo veliko i trajno prijateljstvo [5]. Po prelasku Julijana u Efes, Oribazije mu se pridružio u tom gradu, te pored prijateljstva, postao je i njegov lični lekar. Kada je Julijan 355. proglašen za Cezara u Galiji (zapadnom delu carstva) pozvao je u svoju stalnu pratnju starog prijatelja Oribazija koji se odazvao i odmah mu se pridružio u Galiji (današnja Francuska) [5] kao njegov lični lekar, prijatelj i savetnik, te upravnik Julijanove biblioteke [8,9]. Od tada je Oribazije stalno bio u najužem Julijanovom krugu, učestvovao u njegovom proglašenju za Augusta 360. i pratio ga na važnom pohodu sa vojskom na istok, gde je trebalo da dođe do presudne bitke za presto sa imperatorom Konstancijem II, do čega međutim nikada nije došlo zbog iznenadne bolesti i smrti Konstancija II 361. posle čega je Julijan (*Iulianus*) bio priznat za jedinog cara − imperatora Rimskog carstva. Kao velikog prijatelja i čoveka od poverenja, imperator Julijan je postavio Oribazija za kvestora (*quaestor*) u Konstantinopolju, čime je on postao najvažniji činovnik centralne uprave, jer je to bilo jedno od najznačajnijih mesta u imperiji na koje je postavljana ličnost koja je bila odgovorna za finansije, administraciju i sudstvo u celom carstvu [13]. Pored toga, Oribazije, čiji je politički uticaj nesumnjivo bio veoma velik, učestvovao je i u organizaciji kulturnih programa, uključujući i restauraciju paganskih religija, naročito helenističke paganske religije za šta se imperator Julijan veoma zalagao i zbog čega je ostao zabeležen u istoriji kao Julijan Apostata (Julijan Otpadnik) [5,8,14]. Tokom 363. imperator Julijan je preduzeo veliki vojni pohod protiv Persije, a u njegovoj najužoj pratnji stalno je bio i Oribazije. Kada je Julijan prilikom jedne akcije bio teško ranjen kopljem nepoznatog porekla u trbuh koje je probilo donji deo jetre i creva, Oribazije, kao njegov lični lekar ga je aktivno lečio, podrazumevajući verovatno ispiranje rane crnim vinom, te hiruršku intervenciju u vidu zašivanja oštećenih creva i drugih struktura [9,12]. Međutim, trećeg dana posle povređivanja došlo je do velikog krvarenja i imperator Julijan je umro. Nakon smrti Julijana i promene vlasti, Oribazije, kao i ostale pristalice Julijana, bio je proteran iz Rimskog carstva, ali ga je imperator Valens, koji je vladao kao imperator Istočnog dela carstva od 364. do 378. [2,9], nakon izvesnog vremena pomilovao i dozvolio mu da se vrati i nastani u Konstantinopolju, a potom mu je vraćeno i njegovo imanje. Tada se oženio bogatom Konstantinopoljkom sa kojom je imao četvoro dece, a njegov sin Eustahije (*Eustathius*) takođe se posvetio medicini i bio poznati lekar. Oribazije je umro oko 400-403. [1-5].

Spisateljski rad

Oribazije iz Pergamona započeo je svoju spisateljsku delatnost dosta rano a po savetu, ili tačnije, na zahtev njegovog prijatelja Julijana. Prvi rad bila je knjiga u vidu kolekcije izabranih izvoda ili epitoma (*epitomai*) iz Galenovih radova, knjiga koja je kasnije izgubljena i iz nje je ostao sačuvan samo predgovor [8,15]. Nakon toga Oribazije je napisao najveće svoje delo, nazvano „Medicinska zbirka" (*Collectiones Medicae* ili, grčki, *Latrikai synagogai*, koje je predstavljalo veliku kompilaciju izvoda ili tzv. epitoma iz dela najznačajnijih medicinskih pisaca iz ranijih perioda, u 70 knjiga, od kojih je samo 25 sačuvano [1,2,15,16]. Vrednost ovog dela je u tome što je na taj način ostao sačuvan veliki broj izvoda iz zapisa starijih autora koji bi inače bili potpuno izgubljeni. Među njima je npr. i prikaz hirurškog poveza za imobilizaciju slomljene donje vilice, koju je opisao grčki lekar Heraklas iz 1. veka n. e. kao *Plinthios Brokhos* **(Slika 1)** [2]. Ovaj hirurški povez opisan je u 48. knjizi Oribazijevih *Collectiones medicae* pod naslovom: „Od Heraklasa". Iako su ovi epitomi primarno bili zapisi starijih autora, oni nisu bili jednostavna kolekcija starih zapisa, oni nisu bili doslovno prepisani, nego su zapravo bili u formi kritičkih prikaza ranijih radova starijih pisaca, po-



Slika l. Povez za imobilizaciju slomljene donje vilice (*Plinthios Brokhos*) koju je opisao grčki lekar Heraklas u 1. veku n. e. i čiji opis je ostao sačuvan zahvaljujući Oribazijevim delima

Fig. 1. *A sling for the immobilisation of fractured jaws (Plinthios Brokhos) as described by Greek physician Heraklas from the first century, which was preserved thanks to Oribaisus' works*

kazujući na taj način, kako autorovo široko poznavanje te materije, tako i razumevanje rada njegovih prethodnika [15]. Oba ova dela bila su posvećena njegovom prijatelju imperatoru Julijanu Apostati [15]. U svojoj kasnijoj karijeri, nakon izgnanstva posle Julijanove smrti, Oribazije je, koristeći materijal iz prethodnih dela (*Collectiones Medicae*), napisao još dve knjige. Prva je bila „Sažet pregled" ili „Sinopsis Eustahiju" (*Synopseos ad Eustahium*), posvećen njegovom sinu Eustahiju, u kome je dao sažet pregled ranijeg dela, kao neku vrstu priručnika za svog sina koji je takođe bio lekar [8,15,17]. Drugo delo bilo je posvećeno njegovom prijatelju filozofu Eunapiju (*Eunapius*) i naslovljeno kao „Knjige Eunapijusu" (*Libri ad Eunapium*) u 4 sveske [8,9,16] u kojima je autor dao enciklopedijski prikaz medicinskih problema i tzv. „kućnih lekova" tj. lekova za laike [1,8,9,15]. Pored navedenih dela poznato je još nekoliko njegovih napisa iz medicine koji su izgubljeni: „Za zbunjenog lekara", „O bolestima", „Anatomija creva", a izvan medicine „O kraljevskoj vladavini" čiji je jedino naslov ostao poznat [8]. U svojim delima Oribazije se u velikoj meri bavio hirurškim problemima **(Slika 2)**, a posebno problemom uroloških operacija [18].

Oribazijevi „Medicinski zapisi" pisani su na grčkom jeziku, ali su već u 5. veku bili prevedeni na latinski, jer su privukli veliku pažnju Zapadnog rimskog carstva, a njegova sačuvana dela štampana su u Evropi već u srednjem veku i to, pojedini delovi, u Francuskoj 1554. **(Slika 3)** [17], a prevod pojedinih njegovih sačuvanih dela objavljen je u Francuskoj 1851−1876. Najveći broj njegovih dela objavljen je u Evropi u prvoj polovini XX veka [16], a moderno, kritičko izdanje grčkog teksta objavljeno je kao *Oribasii Collectionum medicarum reliquiae* u Nemačkoj od 1928. do 1933., te *Synopsis ad Eustahium* i *Libri ad Eunapium* 1926. takođe u Nemačkoj [1,16]. Savremeni prevod 1−4. knjige „Medicinskih kompilacija" na engleski jezik, sa uvod-

Slika 2. Hirurški instrumenti iz rimskog doba koje je opisao Oribazije

Fig. 2. *Surgical instruments from the Roman period described by Oribasius*


ORIBASII SAR-
DIANI SYNOPSEOS
AD EVSTATHIVM FI-
LIVM LIB. NOVEM:
QVIBVS tota medicina in compendium redacta continetur.
IOANNE *Baptiſta Raſario Nouarenſi medico interprete.*
PARISIIS.
In officina Audoëni Parui, ad Lilij inſigne, via Iacobea.
1554.

Slika 3. Primerak knjige koju je Oribazije napisao za svog sina Eustahija: *Sinopsis Eustahiju*, a koja je publikovana 1554. godine

Fig. 3. *A copy of the book "Synopsis for Eustathium", written by Oribasisus for his son Eustathius, published in 1554*

nikom i komentarima, pod naslovom „Dijetalna ishrana za jednog imperatora" (*Dieting for an Emperor*) objavljen je 1997. godine [19].

Zaključak

Veliki broj sačuvanih i prevednih dela Oribazija iz Pergamona nesumnjivo ukazuju na to da je on bio jedan od najznačajnijih medicinskih pisaca kasnog antičkog doba. Njegov način pisanja bio je enciklopedijskog karaktera pa se može s pravom zaključiti da je on bio jedan od prvih, ako ne i prvi pisac medicinske enciklopedije u istoriji medicine. Iako je značajan broj njegovih dela izgubljen, ipak, iz onih dela koja su sačuvana za potomstvo i kasnije prevedena, možemo se informisati o stanju medicine u antičko doba, te o mnogim značajnim lekarima tog perioda, čime je Oribazije iz Pergamona ostavio neizbrisiv trag, a njegov doprinos istoriji medicine bio je i ostao veoma velik i dragocen.

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Rad je primljen 18. X 2012.
Recenziran 31. X 2012.
Prihvaćen za štampu 20. XII 2012.
BIBLID.0025-8105:(2013):LXVI:3-4:189-192.

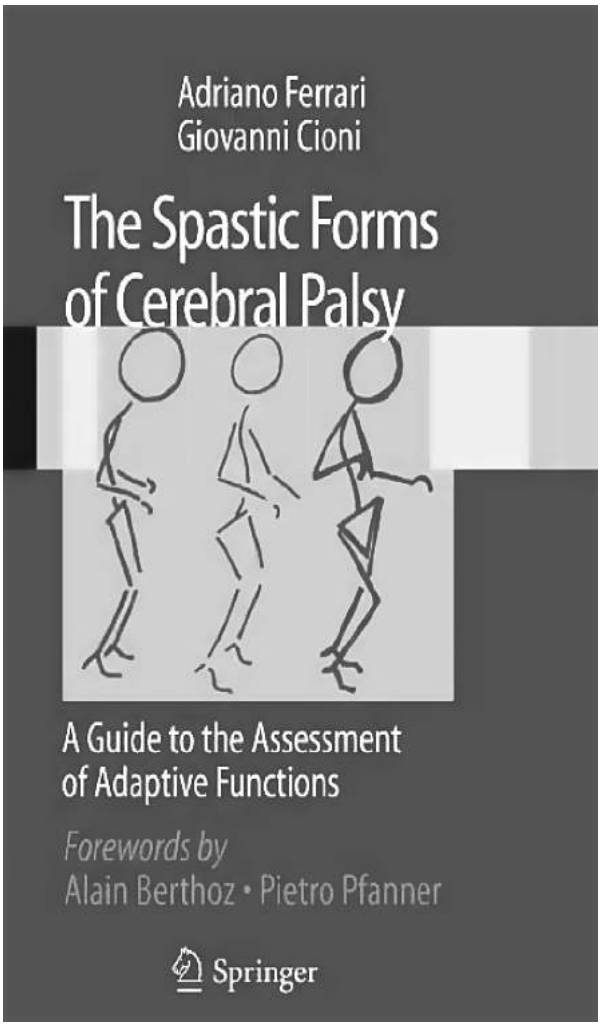
PRIKAZI KNJIGA
BOOK REVIEWS

Ferrai A, Cioni G. The Spastic Forms of Cerebaral Palsy A Guide to the Assessment of Adaptive Functions *(Spastična forma cerebralne paralize Vodič za merenje (evaluaciju) adaptivnih funkcija*). Italija: Springer−Verlag; 2010.

Knjiga „Spastična forma cerebralne paralize. Vodič za merenje (evaluaciju) adaptivnih funkcija" prema oceni recenzenata veoma je korisna a njena originalnost ogleda se u jasnom fokusu različitih problema cerebralne paralize (CP) predstavljenih sa više aspekata – interpretacije prirode bolesti (funkcionalne dijagnoze), preko problema u vezi sa prognozom do rehabilitacije. Knjiga na 359 strana predstavlja mehanizme cerebralne paralize i moguće pristupe ovom oboljenju. Svakako se može reći da predstavlja bogat izvor informacija za stručnjake različitih profila. Oruginalnosti su doprinele nove ideje, kao i interaktivni DVD uz knjigu. Sa aspekta specijalne edukacije i rehabilitacije značajnost knjige ogleda se u sagledavanju razumevanja povezanosti kognitivnog, perceptivnog, socijalnog i motoričkog ponašanja. Dosad je, vrlo često, motorna patologija povezivana isključivo sa mišićnim deficitima.

Posledice i informacije desetogodišnjeg istraživanja i rada, predstavljene u ovoj knjizi, kao i druga aktuelna istraživanja, treba da budu osnov dizajniranja novih rehabilitacionih metoda. Jedan od autora, Giovanni Cioni, univerzitetski je profesor, direktor kliničkog departmana koji se bavi dečjom neurologijom, psihijatrijom i rehabilitacijom u italijanskom naučnom biomedicinskom istraživačkom institutu. Drugi autor, Andriano Ferrari, osnivač je i direktor važnog specijalizovanog bolničkog centra koji funkcioniše na nacionalnom nivou, koji je baza inovativnih rehabilitacionih programa za decu. Autori su kroz svoj rad integrisali sve aspekte cerebralne paralize u teorijske modele i kliničke procedure.

Knjiga je podeljana na tri dela i sastoji se od 16 poglavlja. U prvom delu je predstavljenja priroda cerebralne paralize koja polazi od detekcije i prvih opisa, odnosno od perioda Johna Littla do sada ali je ujedno i vodič u interpretaciji cerebralne paralize gde se jasno navode definicije cerebralne paralize. U drugom delu knjige obrađene su funkcionalne analize koje polaze od ranih prediktivnih znakova CP kod novorođenčadi, sagledavanja motoričkih poremećaja, peceptivnih deficita, poremećaja organizovanosti praksije, vizuelnih i vizuelno-motornih poremećaja i neuropsihološke evaluacije. Jedno posebno poglavlje u ovom delu je posvećeno emocionalanim, bihevioralnim i socijalnim poremećajima kod dece i adolescenata sa



CP. U trećem delu knjige prikazana je klasifikacija spastičnih sindroma i kliničkih formi.

Cerebralna paraliza je trajno stanje, ali ne i nepromenjivo, nastalo oštećenjem centralnog nervnog sistema te predstavlja heterogenu skupinu simptoma, a manifestuje se na više organa i sistema. Najčešći su poremećaji posture i motoričkih veština praćeni intelektualnim, emocionlanim i senzornim poremećajima. Detekcija i opisi cerebralne paralize datiraju još iz viktorijanskog doba ali prvi značajniji doprinos i opis bolesti nastaju kao rezultat rada engleskog ortopeda Johna Littla 1862. godine koji je opisao spastičnu displegiju.

Interesovanje za CP raste nakon II svetskog rata. Američka akademija za CP osnovana je 1947. godine. Phelps je bio prvi predsednik. Prva deficinija od 1957. godine vrlo je slična navedenoj i do danas se

nije mnogo promenila. Rosenbaum i saradnici su 2007. godine cerebralnu paralizu opisali kao grupu poremećaja u razvoju pokreta i posture, koja prouzrokuje ograničenje aktivnosti, koja je neprogresivnog karaktera, nastala kao posledica oštećenja mozga perinatalno ili postnatalno. Oni navode da su motorički poremećaji često udruženi sa senzornim poremećajima, kognitivnim, komunikacionim, perceptivnim i poremećajima ponašanja. U ovoj definiciji se motorički poremećaji klasifikuju kao „prateći". Kako se menjaju definicije CP tako se menja i pristup rehabilitaciji, što je za profesionalce u praksi izuzetno važno. U knjizi se navodi tradicionalna klasifikacija CP koja uključuje podelu na spastičnu kvadriplegiju, spastičnu diplegiju, spastičnu hemiplegiju, ataksičnu formu, distoničnu formu, atetotičnu formu i horeo-atetotičnu formu CP. Ovakva sistematična klasifikacija je korisna za klasifikaciju kliničkih slika i za epidemiološke studije, ali nije korisna u postavljanju rane dijagnoze. Može se reći da se ovim načinom klasifikovanja, ne prepoznaje promena tokom razvoja (jedna forma može da bude zamenjena drugom i sl.). Godine 2000. mreža *Surveillance of Cerebral Palsy in Europe*, koju čini 14 centara u 8 zemalja, predložila je jednostavniju klasifikacju, koja izbegava razliku između diplegije i tetraplegije već diferencira bilateralnu od unilateralne spastične forme. Zbog potrebe da klasifikaciona metodologija uzme u obzir i funkcionalne veštine deteta, *CanChild* (kanadska grupa) predložila je klasifikacioni sitem funkcionalnim merama grube motorike – *Gross Motor Function Measure* (GMFM). U skorije vreme (2002. godine) klasifikacioni sistem baziran na manipulativnim funkcijama i manuelnim sposobnostima (*Bimanual Fine Manipulation Functional Clasiffication* − BFMFC i *Manual Ability Classification System* − MACS) je u upotrebi. Usmerenost pažnje na idealne modele klasifikacije CP je značajna jer klasifikacija bi trebalo da bude korisna i za prognozu ali i za organizaciju rehabilitacionih tretmana. U ovoj knjizi mogu se sagledati najnovije informacije koje će svakako biti korisne u izboru načina klasifikacije dece sa CP.

Jedna od dodatnih vrednosti ove knjige jeste i opisivanje prednosti i nedostataka u predočavanju problema roditeljima koji imaju dete sa CP i značaju njihovog uključivanja u sam proces rehabilitacije. Autori prepoznaju značaj rane dijagnostike i intervencije i navode načine opservacije novorođene dece sa faktorima rizika još u inkubatorima.

Kao što je u uvodnom delu istaknuto, autori čitaocima približavaju i informacije o uticaju razumevanja relacije poremećaja percepcije i pokreta i obrnuto. Nekorektan/neadekvatan – informacije. Korektan pokret podrazumeva korektne dostupne perceptivne informacije.

Na slikovitom primeru stavljanja ruke u džep i razlikovanju novčića od ključa koji podrazumeva perceptivnu rekogniciju (taktilnu, termalnu, ...), prepoznavanje objekta koji istražujemo jasno se vidi važnost percepcije u izvođenju pokreta. Iz navedenog se vrlo lako može razumeti zašto deca sa CP mogu imati poremećaj senzorne funkcije, koji ne mora direktno da potiče od prisustva specifične lezije u centralnom nervnom sistemu, već može biti rezultat prikupljanja informacija neophodnih za motoričku kontrolu, zbog nepostojanja kapaciteta u izvođenju neophodnih specijalizovanih pokreta.

Poremećaje praksičke organizovanosti kod dece sa CP opisao je još Steinthal 1781. godine. Posebna pažnja je posvećena terminu razvojna dispraksija, koji je u upotrebi od 1960. godine. DSM IV razvojnu dispraksiju klasifikuje u razvojni poremećaj koordinacije a ICD 10 klasifikacija u specifičan razvojni poremećaj motoričkih funkcija.

Posebno poglavlje je posvećeno vizuelnim i okulomotornim poremećajima. Vizuelne funkcije donedavno su bile bazirane na pregledu oftalmologa. Sada se koriste i drugi načini pregleda i interesovanje raste i za druge aspekte vida – vizuelno polje, vizuelna pažnja, optokinetički nistagmus i kolorni vid. Opravdano je posvećeno jedno poglavlje u knjizi navedenim poremećajima i zbog činjenice da je vizuelni deficit kod oko 50% dece sa CP registrovan a poznato je da vid igra krucijalnu ulogu u motoričkom, kognitivnom i funkcionlanom razvoju.

Neuropsihološka evaluacija je početna tačka u definisanju rehabilitacionih programa – istakli su autori. Incidencija mentalne retardacije (MR) kod dece sa CP je veća nego u opštoj populaciji. Epidemiološki podaci govore o prisutnosti kognitivnih poremećaja u 30−60% slučajeva. Incidencija MR se razlikuje u zavisnosti od forme CP. Češća je kod diskinetičke, diplegične i hemiplegične forme nego kod tetraparetične i ataksične. Prisutnost epilepsije je frekventnija kod tetrapareze i hemiplegije. Učestalost epislepsije kod dece sa CP sa očuvanom inteligencijom iznosi 15%, dok kod dece sa CP i MR izražena je u 60% slučajeva.

Faktori koji se odnose na leziju (vreme, lokalizacija, veličina, unilateralna ili bilateralna) imaju relevantnu ulogu u psihološkom ishodu kod dece sa CP. Faktori koji utiču na psihološki ishod: MR, epilepsija, karakter lezija, poremećaj vizuelnih funkcija i prisutnst psihijatrijskih poremećaja. Prisutnost pomenutih psihijatrijskih poremćaja kod dece sa CP iznosi 25−60%. U praćenju kognitivnog razvoja dece sa CP koriste se brojne skale, te su autori naveli zamerke na pojedine jer daju kvantitativne markere i zahtevaju očuvane manuelne sposobnosti. Preporuka autora je da u kognitivnoj evaluaciji dece sa motoričkim poremećajima treba zahtevati performansu gde očuvanost egzekucije nije esecijalna, gde postoji fleksibilnost tipa materijala i stimulus situacije, da se sve adaptira različitim motoričkm karakteristikama svakog pojedinog deteta i da se izbaci merenje brzine egzekucije.

Intenzivni tretmani, rekurentne hospitalizacije, loše socijalne mogućnosti i dr. rezultiraju niskim samopoštovanjem i deficitom u razvoju socijalnih veština na šta autori u knjizi takođe ukazuju.

U poslednjem delu knjige su navedeni klinički aspekti klasifikacije. Autori, tokom svog dugogodišnjeg rada i metaanalizom naučne i stručne literature, slažu se da je CP razvojna, te i dijagnoza treba da bude razvojna i mora uzeti sve činjenice u obzir, razmatrajući prirodu cerebralne paralize. Dobar način za klasifikaciju CP je kroz analizu posture i pokreta (sa kinezoiološke tačke gledišta) i kvantiteta (merenja). Do sada se najviše primenjivala topografska klasifikacija (geografski prikazana distribucija motornog oštećenja).

U knjizi je posebno poglavlje posvećeno disperceptivnim formama. Među bebama prevremeno rođenim sa bilateralnim motornim oštećenjem, postoji grupa sa jedinstvenom kombinacijom kliničkih karakteristika, koje mogu reprezentovati specifičnu grupu unutar CP kategorije pod terminom *disperceptive*. Predložena je nova klasifikacija diplegija, kvadriplegija i hemiplegija.

Posle svakog potpoglavlja navedena je literatura koju su autori koristili. U najvećem broju slučajeva radi se o referencama iz poslednjih 10 godina, a nisu retkost ni reference iz 2010. godine, dakle, godine u kojoj je knjiga izdata. Ovo dovoljno govori o želji autora da stavi na uvid stručnoj javnosti najnovije podatke iz oblasti o kojima su pisali.

Na kraju knjige dat je veoma bogat indeks pojmova i naziva koji se pominju u tekstu sa naznakom stranice na kojoj se nalaze, što znatno olakšava korišćenje knjige. Uz već pomenutu originalnost, preglednost, sadržajnost, aktuelnost i jasnoću izraza kojom je napisana, treba napomenuti da je ova knjiga, u prvom redu, namenjena stručnjacima iz oblasti medicine i specijalne edukacije i rehabilitacije. Međutim, ona se može preporučiti kao korisno štivo i različitim profilima stručnjaka (psiholozima, pedagozima i drugima) koji se u svom poslu, na bilo koji način, susreću sa osobama sa cerebralnom paralizom.

Dr Sanela Slavković
Prof. dr Špela Golubović

SAOPŠTENJA REDAKCIJE
EDITORIAL OFFICE ANNOUNCEMENTS

SPISAK STUDENATA NA DOKTORSKIM STUDIJAMA TOKOM 2012. GODINE

Ime i prezime	*Studijski program*	*Datum odbrane*
1. DROBAC MILAN	Klinička medicina	27. januar 2012.
2. ZARIĆ BOJAN	Klinička medicina	9. februar 2012.
3. DEMEŠI DRLJAN ČILA	Klinička medicina	16. mart 2012.
4. BRESTOVAČKI BRANISLAVA	Klinička medicina	16. mart 2012.
5. SPASOJEVIĆ SLOBODAN	Klinička medicina	23. mart 2012.
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11. STOJANOVIĆ MILOŠ	Klinička medicina	23. april 2012.
12. PREVEDEN TOMISLAV	Klinička medicina	25. april 2012.
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15. NIKOLIĆ IVAN	Klinička medicina	12. juni 2012.
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17. KOVAČEVIĆ NADICA	Klinička medicina	15. juni 2012
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19. GRUJIĆ NEVENA	Klinička medicina	5. juli 2012.
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21. OLUJIĆ MAJA	Klinička medicina	8. oktobar 2012.
22. SRDANOVIĆ ILIJA	Klinička medicina	8. oktobar 2012.
23. POPOVIĆ GORDANA	Klinička medicina	11. oktobar 2012.
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25. RAJOVIĆ JELKA	Klinička medicina	19. oktobar 2012.
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27. RADOVANOVIĆ DRAGANA	Klinička medicina	23. oktobar 2012.
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29. GOLUŠIN ZORAN	Klinička medicina	10. decembar 2012.
30. POPOV TANJA	Klinička medicina	18. decembar 2012.
31. KNEŽEVIĆ VIOLETA	Klinička medicina	28. decembar 2012.

SPISAK STUDENTA KOJI SU ODBRANILI DOKTORSKU DISERTACIJU

Ime i prezime	*Datum odbrane*
1. HARHAJI VLADIMIR	8. mart 2012.
2. BULJČIK ČUPIĆ MAJA	13. mart 2012.
3. KUKAVICA DARINKA	12. april 2012.
4. RADEKA GORDANA	6. juni 2012.
5. TOMIĆ NAGLIĆ DRAGANA	15. juni 2012.
6. ŠAHMAN ZAIMOVIĆ MAJDA	2.oktobar 2012.
7. BOGDANOVIĆ JOVO	12. oktobar 2012.
8. JOVANOVIĆ MLADEN	26. oktobar 2012.
9. KOVAČEVIĆ BRANKA	14. decembar 2012.
10. OBRADOVIĆ DUŠANKA	20. decembar 2012.
11. NIĆIFOROVIĆ ŠURKOVIĆ OLJA	21. decembar 2012.
12. TATJANA KURUCIN	24. decembar 2012.

SPISAK STUDENATA HA DIPLOMSKIM AKADEMSKIM STUDIJAMA

Ime i prezime	*Studijski program*	*Datum odbrane*
1. HERIN RANKO	Hirurgija	25. januar 2012.
2. JANKOVIĆ JELENA	Pedijatrija	26 juni 2012.
3. SEKULIĆ BOJAN	Ginekologija i opstetricija	16. juli 2012.
4. PETROVIĆ PREDRAG	Interna medicina	24. septembar 2012.
5. MIRONICKI MELISA	Interna medicina	24. septembar 2012.
6. NIKOLIĆ BORISLAVKA	Interna medicina	26. septembar 2012.
7. GRUJIĆ DUŠAN	Interna medicina	26. septembar 2012.
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9. LIKIĆ TANJA	Interna medicina	5. decembar 2012.

SPISAK STUDENATA HA MAGISTARSKIM STUDIJAMA

Ime i prezime	*Studijski program*	*Datum odbrane*
1. VASILEVSKA LAZAREVIĆ ANA	Farmakologija sa toksikologijom	12. april 2012.
2. BOBNAR RENATA	Fiziologija	20. decembar 2012.

LEKARI MEDICINE I STOMATOLOGIJE I ZDRAVSTVENI SARADNICI KOJI SU POLOŽILI SPECIJALISTIČKI I SUPSPECIJALISTIČKI ISPIT NA MEDICINSKOM FAKULTETU U NOVOM SADU TOKOM 2012. GODINE

Ime i prezime	*Studijski program*	*Datum odbrane*
1. AVRAMOV PREDRAG	Radioloplja	30. januar 2012.
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17. VOJVODIĆ DRAGAN	Nefrologija	25. april 2012.
18. VRANEŠEVIĆ DRAGICA	Neurologija	28. juni 2012.
19. VUJAČIĆ TATIANA	Pedijatrija	14. novembar 2012.
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21. VUKOVIĆ IVANA	Stomatološka protetika	20. decembar 2012.
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30. DOLINAJ VLADIMIR	Anesteziologija sa reanimacijom	16. oktobar 2012.
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32. ĐORĐEVIĆ RELJA	Perinatologija	17. decembar 2012.
33. ĐUKIĆ STEKIĆ MARICA	Opšta medicina	18. decembar 2012.
34. ĐURĐEVIĆ NINA	Klinička genetika	8. februar 2012.
35. ERDELJAN BRANISLAVA	Urgentna medicina	24. septembar 2012.
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37. ŽIVANOVIĆ PEĐA	Fizikalna medicina i rehabilitacija	14. juni 2012.
38. ZLATANOVIĆ LJILJANA	Anesteziologija sa reanimacijom	12. decembar 2012.
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126. HOLI GABOR	Urgentna medicina	7. novembar 2012.
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UPUTSTVO AUTORIMA

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1. Uvodnici (editorijali) – do 5 stranica. Sadrže mišljenje ili diskusiju o nekoj temi važnoj za Časopis. Uobičajeno ih piše jedan autor *po pozivu*.

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4. Prethodna saopštenja – do 4 stranice. Sadrže naučne rezultate čiji karakter zahteva hitno objavljivanje, ali ne mora da omogući i ponavljanje iznetih rezultata. Donosi nove naučne podatke bez detaljnijeg obrazlaganja metodologije i rezultata. Sadrži sve delove originalnog naučnog rada u skraćenom obliku.

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Priprema rukopisa

Propratno pismo

– Mora da sadrži svedočanstvo autora da rad predstavlja originalno delo, kao i da nije objavljivan u drugim časopisima, niti se razmatra za objavljivanje u drugim časopisima.

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Za pisanje teksta koristiti *Microsoft Word for Windows*. Tekst treba otkucati koristeći font *Times New Roman*, na stranici formata A4, proredom od 1,5 (i u tabelama), sa marginama od 2,5 cm i veličinom slova od 12 pt. Rukopis treba da sadrži sledeće elemente:

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– prikaz slučaja: uvod, prikaz slučaja i zaključak;

– pregled rada: uvod, odgovarajući podnaslovi koji odgovaraju onima u tekstu rada i zaključak.

U nastavku navesti do deset ključnih reči iz spiska medicinskih predmetnih naziva (*Medical Subjects Headings, MeSH*) Američke nacionalne medicinske biblioteke.

3. Sažetak na engleskom jeziku. Sažetak na engleskom jeziku treba da bude prevod sažetka na srpskom jeziku, da ima istu strukturu i da sadrži do 250 reči, bez upotrebe skraćenica.

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– Koristiti mere metričkog sistema prema Internacionalnom sistemu mera (*International System Units – SI*). Temperaturu izražavati u Celzijusovim stepenima (°C), a pritisak u milimetrima živinog stuba (mmHg).

– Ne navoditi imena bolesnika, inicijale ili brojeve istorija bolesti.

Uvod sadrži precizno definisan problem kojim se bavi studija (njegova priroda i značaj), uz navođenje relevantne literature i sa jasno definisanim ciljem istraživanja i hipotezom.

Materijal i metode treba da sadrže podatke o načinu dizajniranja studije (prospektivna/retrospektivna, kriterijumi za uključivanje i isključivanje, trajanje, demografski podaci, dužina praćenja). Statističke metode koje se koriste treba da budu jasne i detaljno opisane.

Rezultati predstavljaju detaljan prikaz podataka dobijenih tokom studije. Sve tabele, grafikoni, sheme i slike moraju da budu citirani u tekstu, a njihova

numeracija treba da odgovara redosledu pominjanja u tekstu.

Diskusija treba da bude koncizna i jasna, sa interpretacijom osnovnih nalaza studije u poređenju sa rezultatima relevantnih studija publikovanim u svetskoj i *domaćoj* literaturi. Navesti da li je hipoteza istraživanja potvrđena ili opovrgnuta. Izneti prednosti i ograničenja studije.

Zaključak u kratkim crtama mora da odbaci ili potvrdi pogled na problem koji je naveden u Uvodu. Zaključci treba da proizilaze samo iz vlastitih rezultata i da ih čvrsto podržavaju. Uzdržati se uopštenih i nepotrebnih zaključivanja. Zaključci u tekstu moraju suštinski odgovarati onima u Sažetku.

5. Literatura. Literatura se u tekstu označava arapskim brojevima u uglastim zagradama, prema redosledu pojavljivanja. Izbegavati veliki broj citata u tekstu. Za naslove koristiti skraćenice prema *Index Medicus*-u (http:// www.nlm.nih.gov/tsd/serials/lji.html). U popisu citirane literature koristiti Vankuverska pravila koja precizno određuju redosled podataka i znake interpunkcije kojima se oni odvajaju, kako je u nastavku dato pojedinim primerima. Navode se svi autori, a ukoliko ih je preko šest, navesti prvih šest i dodati et al.

Članci u časopisima:

∗ *Standardni članak*

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

∗ *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.

∗ *Volumen sa suplementom*

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

∗ *Sveska sa suplementom*

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.

∗ *Sažetak u Časopisu*

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

Knjige i druge monografije:

∗ *Jedan ili više autora*

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

∗ *Urednik(ci) kao autor*

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

∗ *Poglavlje u knjizi*

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

∗ *Rad u zborniku radova*

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.

∗ *Kompjuterski dokument (file)*

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

6. Prilozi (tabele, grafikoni, sheme i fotografije).

Dozvoljeno je najviše šest priloga!

– Tabele, grafikoni, sheme i fotografije dostavljaju se na kraju teksta rukopisa, kao posebni dokumenti na posebnim stranicama.

– Tabele i grafikone pripremiti u formatu koji je kompatibilan sa programom *Microsoft Word for Windows.*

– Slike pripremiti u JPG, GIF TIFF, EPS i sl. formatu

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

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

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

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

– Ukoliko se koriste tabele, grafikoni, sheme ili fotografije koji su ranije već objavljeni, u naslovu navesti izvor i poslati potpisanu izjavu autora o saglasnosti za objavljivanje.

– Svi prilozi biće štampani u crno-beloj tehnici. Ukoliko autori žele štampanje u boji potrebno je da snose troškove štampe.

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

8. Dodatne obaveze

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

Društvo lekara Vojvodine
Vase Stajića 9
21000 Novi Sad
Tel. 021/521 096; 063/81 33 875
E-mail: dlv@neobee.net

INFORMATION FOR AUTHORS

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2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

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6. Case reports – up to 6 pages – deal with rare casuistry from practise important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

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The covering letter:

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

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The manuscript:

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

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

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

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

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

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

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

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

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

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

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

– 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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