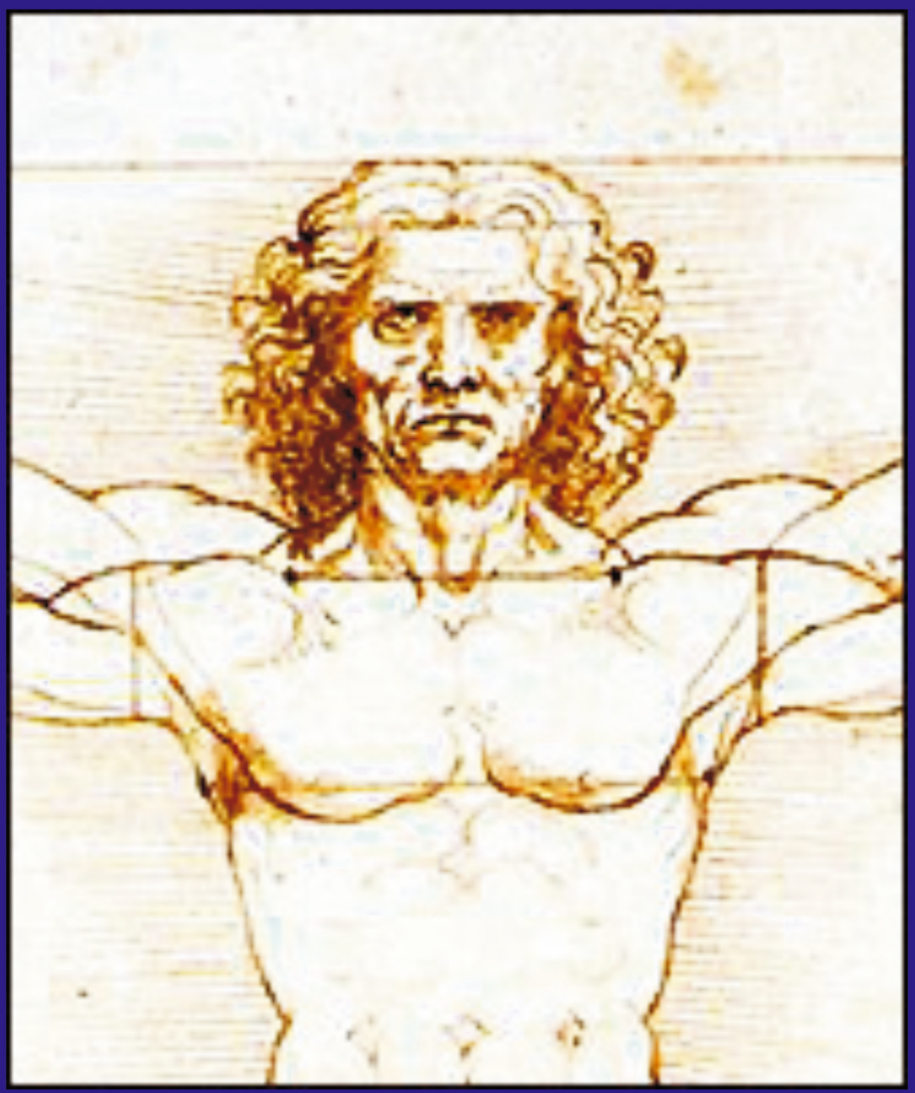
SANAMED

ISSN-1452-662X



Vol 14 (3) 2019.

MEDICAL JOURNAL

SANAMED

ISSN-1452-662X

Izdavač

Udruženje lekara Sanamed, Novi Pazar

ČASOPIS IZLAZI TRI PUTA GODIŠNJE

Adresa uredništva

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Štampa

„OFSET“, Kraljevo

Tiraž

500

Pretplata

Godišnja pretplata: 4500 din. za domaće ustanove; 1500 din. za pojedince; za inostranstvo 75 eura (u dinarskoj protivrednosti po kursu na dan uplate). Pretplatu vršiti na račun 205-185654-03, Komercijalna banka. Za sve dodatne informacije kontaktirati Uredništvo.

SANAMED

ISSN-1452-662X

Publisher

Association of medical doctors “Sanamed”, Novi Pazar

ISSUED THREE TIMES A YEAR

Editorial address

“SANAMED”, St. Palih boraca 52, 36300 Novi Pazar, Serbia
email: sanamednp@gmail.com, www.sanamed.rs

Print

“OFSET”, Kraljevo

Circulation

500

Subscription

Annual subscriptions: 4500 RSD for domestic institutions and 1500 RSD for individuals. For readers abroad, annual subscription is 75 Euro (in Dinar equivalent at the exchange rate on the day of payment). For further instructions and informations, contact Editorial Board.

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SANAMED
2019; 14(3): 235–239
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.349
UDK: 617.711-002
ID: 281762316
Original article

THE EFFECT OF ALLERGIC CONJUCTIVITIS ON CHOROIDAL THICKNESS

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Primljen/Received 02. 08. 2019. god.
Prihvaćen/Accepted 01. 11. 2019. god.

Abstract: **Background:** To examine the effects of allergic conjunctivitis and its treatment upon choroidal thickness (ChT) using topical antihistaminic agents.

Methods: 60 eyes of 30 children and adolescents with allergic conjunctivitis and 60 eyes of 30 healthy controls participated in the study. Inclusion criteria for patient groups were best-corrected visual acuity 20/20 or better, normal intraocular pressure (IOP) and no systemic or ocular diseases other than allergic conjunctivitis. Healthy controls recruited from children and adolescents who had no ocular or chronic systemic disorders and had best-corrected visual acuity 20/20 or better and normal IOP. ChT was measuredby using Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT) before and after treatment by antihistamine agents.

Results: Subfoveal choroidal thicknes mean value was 364.1 ± 63.8 μm in the allergic conjunctivitis group and the first-month values after the treatment were 333.5 ± 52.1 μm. Subfoveal choroidal thickness means value in the control group was 320.6 ± 80.9 μm. There was a statistically significant decrease in ChT after treatment of allergic conjunctivitis patients and there was a significant difference in terms of baseline ChT values between the allergic conjunctivitis group and the control group. There was no significant difference between one month after treatment values and the mean values of the control group.

Conclusions: Our results demonstrate that ChT can increase in allergic conjunctivitis patients and can become normal again with topical antihistamine treatment. In order to support choroidal thickness to be a marker for the diagnosis and follow-up of allergic conjunctivitis, further studies with larger samples and longitudinal studies are needed.

Key words: Allergic conjunctivitis, Antihistamine, Choroidal thickness, Topical eyedrops, Treatment.

INTRODUCTION

Allergic conjunctivitis is one of the most common ocular disorders in pediatric patients and defined as a Type 1 hypersensitivity reaction in which the igE mediated response is involved. There are different types of allergic conjunctivitis such as acute, subacute allergic conjunctivitis, vernal and atopic keratoconjunctivitis. Acute allergic conjunctivitis is a common acute conjunctival reaction in children, which usually develops in spring and summer due to environmental allergens such as pollen (1).

The choroid is a highly vascularized layer of the eye formed of a dense capillary network and nourishes the deep, outer two-thirds of the retina. In a limited number of studies evaluating choroidal thickness (ChT) in children, there are contradictory results reporting that choroidal thickness increases (2) and decreases (3) in healthy children with age. In another study, subfoveal choroidal thickness was thinner in patients with myopia like those in adults (4, 5).

Studies revealed that choroidal thickness was increased in ocular pathologies particularly in central serous chorioretinopathy (CSCR). CSCR is an ophthalmic disease which characterized by pigment epithelial detachment in the neurosensory retina due to increased vascular permeability and hydrostatic pressure and is associated with an increase in choroidal thickness (6-9). In addition, increases in choroidal thickness in many inflammatory diseases with vascular involvement such as Juvenile Systemic Lupus Erythematosus (10), Crohn's Disease (11), Behçet's Disease (12) and

Ankylosing Spondylitis (13) have been determined in previous studies.

Embryologically, eye and brain development are parallel to each other. The retina and the optic nerve are considered part of the central nervous system (CNS). Spectral Optical Coherence Tomography (SD-OCT) is a non-invasive imaging technique that enables in vivo visualization of the eye structures primarily used to monitor retinal changes in glaucoma (14). A method called ***enhanced depth imaging*** *spectral-domain optical coherence tomography* (EDI OCT) has been developed to make possible in vivo cross-sectional imaging of the choroid (15).

Since allergic conjunctivitis is a common inflammatory condition in children, we aimed to investigate the probable relationship between increased choroidal thickness and allergic conjunctivitis. We first aimed to examine whether ChT values showed differences between children and adolescents with allergic conjunctivitisand healthy controls. Our second aim was to investigate the effect of treatment by using topical antihistamine agents on ChT.

METHOD

Sample

The data obtained from the measurements of 60 eyes of 30 children and adolescents with allergic conjunctivitis (study group) and 60 eyes of 30 healthy controls (control group). Patients were admitted to the Ophthalmology outpatient clinic of Ahi Evran University Educational and Research Hospital in February-August 2017. Patients aged 9-17 years who have firstly diagnosed with acute allergic conjunctivitis and haven't received any treatment were included. Healthy controls who admitted to the Child Psychiatry outpatient clinic in the same hospital with minor psychological problems and had no ocular problems were recruited. Allergic conjunctivitis diagnosis was based on detailed history (episodic, seasonal, symptoms consist of itching, burning, watering) and ophthalmic examination by bio-microscope (papillary reaction in upper tarsal conjunctiva or stringy discharge). Patients with allergic conjunctivitis were given emedastine difumarate one drop two times daily after diagnosis and they were advised to stay away from an allergen. Subfoveal choroidal thickness measurements of the patients with allergic conjunctivitis were performed at the first examination and after 1-month than treatment.

Procedure

Children and adolescents with allergic conjunctivitis and healthy controls were evaluated by a specialist in the outpatient clinic of Ophthalmology. Detailed ophthalmologic examination including visual acuity, intraocular pressure measurement was applied to all cases. Patients with visual acuity ≤ 20/20 and any ocular or systemic disease diseases that might affect the choroidal thickness weren't included in the study. All patients who have allergic conjunctivitis underwent SD-OCT examination before and after one-month antihistamine treatment. Then the initial values were compared with one-month after treatment values. The initial and after one-month values were also compared with the control group values.

The research was carried out in accordance with Helsinki declaration rules and informed consent forms of patients were received.

Oct Measurement

Choroidal thickness was evaluated with Spectral-Domain Optical Coherence Tomography (SD-OCT) (software version 6.3.3.0, Heidelberg Engineering Inc., Heidelberg, Germany). This device produces high-resolution images from low infrared light levels. The device contained a superluminescent diode with a wavelength of 870 nm and could obtain 40.000 A-scans per second. The axial and transverse resolutions were 7 and 14 μm, respectively. All examinations were performed between 9:00 a.m. and 12:00 noon, to avoid the effect of diurnal variation on choroidal thickness (16). These measurements were performed at the fovea on EDI-OCT mode which enables in vivo visualization of the choroid (17). Choroidal thickness measurements were performed in both eyes and the mean of the two measurements was evaluated.

Statistical Analysis

All statistical analyses were performed using Statistical Package for Social Sciences-SPSS for IBM, 20.0. Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. ChT values after one-monthof topical antihistamine treatment were compared to the baseline using the paired test; after seeing that all of the continuous variables were normally distributed. The initial and one-month values were compared with the control groupby using student tests.The gender distribution of groups was evaluated by using the Chi-Square test. Statistical significance was accepted as $p < 0.05$.

RESULTS

Thirty children and adolescents with allergic conjunctivitis (17 boys and 13 girls) and 30 healthy controls (16 boys and 14 girls) were included in the study.

Table 1. *Demographics*

		Study group	Control group	p
Gender n (%)	boy girl	17 13	16 14	0.74
Age mean (years)		12 ± 3.5	11,5 ± 4,1	0.48

Table 2. *Subfoveal choroidal thickness value*

	Allergic conjunctivitis - no treatment (Group 1)	Allergic conjunctivitis - Post treatment (Group 2)	Control group (Group3)	P value
Subfoveal Choroidal Thickness (ìm)	364.1 ± 63.8	333.5 ± 52.1	320.6 ± 80.9	*0.04 1 > 2 **0.039 1 > 3 ***0.189 2 = 3

* (Paired sample t test) between baseline and after one month treatment values.
** (Student t test) between baseline and control group
*** (Student t test) between control group an done month after treatment values.

The mean age of study and control groups were 12.4 ± 3.5 years and 11.5 ± 4.1 years, respectively. The groups were similar in terms of age and gender (p = 0.48, p = 0.74) (Table 1).

Sub-foveal choroidal thickness was 364.1±63.8 μm in the allergic conjunctivitis group; the first-month mean values after the treatment were 333.5 ± 52.1 μm. Sub-foveal choroidal thickness means value in the control group was 320.6 ± 80.9. There was a statistically significant decrease in mean ChT value after treatment of allergic conjunctivitis patients (paired sample t-test; p = 0.04) and there was a significant difference between baseline ChT values of allergic conjunctivitis group and control group (student t-test; p = 0.039). There was no significant difference between one-month values after treatment and mean values of the control group (student t-test; p = 0.189) (Table 2). When the choroidal thickness of children and adolescents with allergic conjunctivitis were compared according to gender, the choroidal thickness of boys was found to be higher than girls. However, this difference was not statistically significant (p = 0.357).

DISCUSSION AND CONCLUSION

In this study, we investigated whether there is any difference in terms of choroidal thickness in children and adolescents with acute allergic conjunctivitis. We also examined the effect of conservative and medical treatment on choroidal thickness in children with allergic conjunctivitis.The baseline ChT values of the study group were significantly higher than the control group. And there was a statistically significant decrease in ChT of children and adolescents with allergic conjunctivitis after treatment with topical antihistamine agents.

In a study conducted by Yenigun et al. evaluated whether there were any differences in choroidal thickness between allergic rhinitis patients and healthy controls. The mean sub-foveal choroidal thickness was 367.49 ± 92.73 μm in patients with allergic rhinitis and the mean sub-foveal choroidal thickness in patients without allergic rhinitis was 327.62 ± 72.39 μm. In parallel with our study, they found this difference was statistically significant (18). Previous studies indicated that choroidal alterations were determined in several ocular or systemic diseases associated with inflammation. In two adult patients with posterior sclerosis, choroidal thickness measured by OCT was found thickened in the active phase of the disorder and thinned after treatment. The authors suggested that recurrent inflammation of the sclera could induce atrophic changes. In two different studies from the Far East, sub-foveal choroidal thickness measured by EDI-OCT of patients with posterior uveitis due to Behçet's disease was increased in the acute phase of the disease and decreased after the relief of the acute phase. They showed sub-foveal choroidal thickness was correlated with retinal vascular leakage revealed by fluorescein angiography (12, 19). In a case report presents a patient diagnosed with sarcoidosis and having unilateral, multifocal choroidal granuloma, it was revealed that choroidal thickness decreased by steroid treatment (20). In another study examining choroidal changes in toxoplasma cases with retino-choroidal lesions, it was found that choroidal thickness was higher in the acute phase of the disease and was determined normally in the follow-up (21).

Another finding in our study was that boys had higher choroidal thickness than girls. However, this difference was not statistically significant. In a study from Denmark, the sub-foveal choroidal thickness of 1323 healthy children aged 11 to 12 years was measured by using EDI-OCT. It has been determined that the sub-foveal choroidal thickness was higher in fe-

males than in males but the difference wasn't significant (22).

In our study, the sample size was small, so studies with a larger sample are needed to confirm our findings and to fully clarify the mechanism of increased choroidal thickness with allergic conjunctivitis. To track allergic conjunctivitis activity and evaluate the effectiveness of the treatment, choroidal thickness measures can be utilized.

Abbreviations

ChT — choroidal thickness
CSCR — central serous chorioretinopathy
CNS — central nervous system
SD-OCT — Spectral Optical Coherence Tomography
EDI OCT — enhanced depth imaging spectral-domain optical coherence tomography

Acknowledgment: None

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authorship Statement: TA, DA wrote the manuscript. TA, MY designed the study, TA, DA and MY contributed to data collection. TA and DA performed the statistical analysis and interpretation of the results. All authors read and approved the final manuscript.

Licensing

Sažetak

UTICAJ ALERGIJSKOG KONJUKTIVITISA NA DEBLJINU HOROIDEE

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Cilj: Ispitati efekte alergijskog konjunktivitisa i njegovog lečenja korišćenjem topikalnih antihistaminskih lekova na debljinu horoidee (ChT).

Metode: U istraživanju je učestvovalo 30 dece i adolescenata sa alergijskim konjunktivitisom kao i 30 zdravih kontrola. Kriterijumi za uključivanje pacijenata u istraživanje bili su najbolja korigovana vidna oštrina 20/20 ili bolje, normalan intraokularni pritisak (IOP), i odsustvo sistemskih ili drugih očnih bolesti osim alergijskog konjunktivitisa. Zdrave kontrole su podrazumevale decu i adolescente bez očnih ili hroničnih sistemskih bolesti i koji su imali najbolju korigovanu vidnu oštrinu 20/20 ili bolje i normalan IOP. ChT je merena pomocu EDI-OCT (Enhanced Depth Imaging Optical Coherence Tomography) pre i posle tretmana antihistaminicima.

Rezultati: Srednja vrednost subfovealne horoidalne debljine bila je 364.1 ± 63.8 μm u grupi sa alergijskim konjunktivitisom, a vrednost nakon prvog meseca tretmana bila je 333.5 ± 52.1 μm. Srednja vrednost subfovealne horoidalne debljine u kontrolnoj grupi bila je 320.6 ± 80.9 μm. Došlo je do značajnog smanjenja ChT nakon lečenja pacijenata sa alergijskim konjunktivitisom i postojala je statistički značajna razlika u odnosu na početne vrednosti ChT između grupe sa alergijskim konjunktivitisom i kontrolne grupe. Nije bilo značajne razlike između srednjih vrednosti ChT nakon jednomesečnog lečenja i srednjih vrednosti kontrolne grupe.

Zaključak: Naši rezultati pokazuju da ChT može porasti kod pacijenata sa alergijskim konjunktivitisom i ponovo može postati normalna usled lokalnog lečenja antihistaminicima. Kako bi se podržalo to da horoidalna debljina bude marker za dijagnozu i praćenje alergijskog konjunktivitisa, dodatna istraživanja sa većim uzorcima i longitudinalne studije su potrebne.

Ključne reči: alergijski konjunktivitis, antihistamin, horoidalna debljina, topikalne kapi za oči, lečenje.

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SANAMED
2019; 14(3): 241–246
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.352
UDK: 616.155.2-053.31
ID: 281827596
Original article

THROMBOCYTOPENIA AS ONE OF THE REASONS OF PROLONGED STAY IN THE NEONATAL INTENSIVE CARE UNIT

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Primljen/Received 25. 07. 2019. god.

Prihvaćen/Accepted 02. 10. 2019. god.

Abstract: The aim of this paper was to present the occurrence and severity of thrombocytopenia, with intracranial and another bleeding in neonates with sepsis, analyze the risk factors for the development of thrombocytopenia and compare it with the length of hospitalization in the Neonatal Intensive Care Unit (NICU). Thrombocytopenia is a platelet count <150 x 109/L and is common in newborns during hospitalization in the NICU. In the early days of life, the most common causes of thrombocytopenia in newborns are conditions that lead to fetal hypoxia, intrauterine growth failure, maternal hypertension, and sepsis. In this study were included all newborns with thrombocytopenia, who were hospitalized in NICU, Children's Disease Clinic, University Clinical Centre in Tuzla, from 01. 01. 2014 to 01. 01. 2019.

In our results, 379 newborns had severe, 337 moderate, and 127 milder forms of thrombocytopenia, without a statistically significant difference in the incidence of thrombocytopenia between groups of neonates born < 37 GW and ≥ 37 GW. Sepsis was the most common cause of thrombocytopenia, 300 children had early sepsis and 190 late. We found the statistically significant difference in intracranial hemorrhage of the second degree and pulmonary hemorrhage among neonates born < 37 GW in relation to newborns born ≥ 37 GW. A statistically significant effect of length of stay of our neonates in the Department of Neonatal Intensive Therapy and morbidity was shown in relation to the lower gestational age and lower platelet counts.

Conclusion: Timely diagnosis of the cause and development of thrombocytopenia with adequate and effective treatment can reduce the mortality and morbidity of newborns with perinatal risk for neonatal thrombocytopenia.

Key words: thrombocytopenia, newborn, sepsis, neonatal intensive care unit.

INTRODUCTION

Thrombocytopenia by definition is reduced platelet count < 150 x 109/L and frequent finding in neonates during hospitalization in the Neonatal Intensive Care Unit (NICU) (1). Despite a large number of studies, thrombocytopenia in the newborn is still in the focus of interest, due to possible complications resulting from a reduced number of platelets, such as various bleeding, especially intracranial and necrotizing enterocolitis, with possible fatal outcome (2).

In the first days of life, the most common causes of thrombocytopenia in neonates are antibodies mediated by platelet destruction, intrauterine growth retardation, and maternal hypertension, along with other factors associated with chronic fetal hypoxia. Antibodies mediated by platelet destruction are further classified into neonatal alloimmune thrombocytopenia when the mother's antibodies recognize fetal platelets as foreign and destroy them. However, it also could be a passive transfer of maternal autoantibodies that are produced in the mother due to the existence of an autoimmune disease, such as systemic lupus or immune thrombocytopenic purpura, when the platelets are also destroyed.

One of the main causes of thrombocytopenia in NICU is sepsis, during which middle-to-severe thrombocytopenia occurs in the period from 24 to 48 hours from the first signs of infection (3). Congenital infections, the causative agents of toxoplasmosis, measles, cytomegalovirus, herpes simplex virus, and fungal infections are also possible causes of thrombocytopenia in the neonatal period.

The thrombocytopenia pathogenesis and platelet count in neonatal sepsis have not yet been fully clarified, nor did the exact number of platelets, by which bleeding occurs. A possible mechanism of bleeding is damage to the blood vessel endothelium that activates the reticuloendothelial platelet damage system. Throm-

bocytopenia occurs when it is a higher consumption than platelet production, with the particular role of reduced serum thrombopoietin (1).

Thrombocytopenia, that occurs within the first 72 hours of birth is early, compared to late, which occurs after 72 hours of birth. In relation to the platelet count, it may be severe form < 30 x 109/L, a moderate form of 31 to 100 x 109/L, and a milder form of 101 to 150 x 109/L (4, 5).

The aim of this paper was to present the occurrence and severity of thrombocytopenia, with intracranial and another bleeding in neonates with sepsis, analyze the risk factors for the development of thrombocytopenia and compare it with the length of hospitalization in the Neonatal Intensive Care Unit.

SUBJECTS AND METHODS

All newborns with thrombocytopenia, who were hospitalized in the Department of Neonatal Intensive Care Unit, the Clinic for Children's Diseases, University Clinical Centre in Tuzla, in the period from 01. 01. 2014 to 01. 01. 2019 were included in this study. Data are collected from the history of neonatal disease. The research was approved by the Ethics Committee, University Clinical Centre in Tuzla.

Data on hypertension, the number and the order of pregnancy, and the way of ending the delivery were collected from the mother's history of the disease. Maternal hypertension was defined when systolic blood pressure was higher than 140 mmHg, diastolic 90 mmHg or more, in more than two measurements, or once measured with values greater than 160/110 mmHg.

The children's history of the disease has been reported data of gestational age, birth weight, gender, day of occurrence and duration of thrombocytopenia,severe bleeding and length of hospitalization.

Of the hematological data for each child, the initial platelet count was observed in the occurrence of sepsis and the lowest number of platelets over the duration of the sepsis. The clinical diagnosis of sepsis was confirmed by a positive finding of blood culture.

The exclusion criteria of this study were for newborns, who had a good general condition in the first 24 hours, with the excluded clinical diagnosis of sepsis, and were moved to another department, or had a contaminated blood culture, i.e. positive blood culture, without an increase in C- reactive protein and no antibiotic treatment in the first 72 hours.

All data were statistically processed and displayed using tables and images. The standard methods of descriptive statistics were used in the analysis. Absolute numbers and percentages were used to describe categorical data. The mean value ± standard deviation, or median, was used to describe numerical data. Statistical data analysis was carried out using the statistical program SPSS (version 17, StatSoft, Tulsa, USA).

RESULTS

This study included 843 newborns with thrombocytopenia, 536 (41.3%) born < 37 GW (week of gestation), and 307 (27%) born ≥ 37 GW. The prevalence of thrombocytopenia in preterm births was 6.5% (843/1296) compared to the previous 5 years. Most of our neonates, 489 (58.6%) had early thrombocytopenia. There was no statistically significant difference in the incidence of thrombocytopenia between groups of neonates born < 37 GW and ≥ 37 GW. Table 1 isthe epidemiological date of newborns with thrombocytopenia born < 37 GW and born ≥ 37 GW (Table 1).

In our study, 379 newborns had severe, 337 moderate, and 127 milder forms of thrombocytopenia (Figure 1).

Table 2 shows the perinatal data of neonates with thrombocytopenia. The average mother's age of children with thrombocytopenia born < 37 GW was 24 ± 3.2, while for children born ≥ 37 GW was 28.2 ± 4.1 years. Hypertension had 61.8% of mothers in the group

Table 1. *Newborns with thrombocytopenia born < 37 GW and ≥ 37 GW*

Birth year	Total number of births (<37 GW / > 37 GW)	Newborns with thrombocytopenia born < 37 GW		Newborns with thrombocytopenia born ≥ 37 GW	
		(n; %)	Time of sepsis onset (early/late)	(n; %)	Time of sepsis onset (early/late)
2014	195 (130/65)	78 (40%)	50/28	40 (20.5%)	29/11
2015	180 (111/69)	87 (48.3%)	50/37	35 (19.4%)	19/16
2016	247 (149/98)	105 (42.5%)	75/30	60 (24.3%)	30/30
2017	332 (182/150)	116 (35%)	70/46	82 (25%)	40/42
2018	342 (172/170)	150 (44%)	85/65	90 (26.3%)	41/49
Ukupno	1296 (747/522)	536 (41.3%)	330/206	307 (27%)	159/128

Table 2. *Perinatal data of neonates with thrombocytopenia*

Perinatal data	Number of newborns with thrombocytopenia born < 37 GW	Number of newborns with thrombocytopenia born ≥ 37 GW
Mother's age (years)	24 ± 3.2 (14-47)	28.2 ± 4.1 (15-45)
Mother's hypertension	310 (57.8%)	190 (61.8%)
Number of pregnancy	2 (1-5)	2 (1-6)
Multiple pregnancy	92 (17.2%)	34 (11%)
Intrauterine growth of retardation	173 (32.3%)	148 (48.2%)
Caeserian section	328 (61.2%)	170 (55.9%)
Age of gestation (week of gestation)	30 ± 3.9 (24-36)	38.2 ± 2.1 (37-42)
Birth weight (gram)	1010 ± 234 (455-2500)	3550 ± 456 (2950-5010)
Gender (male/female)	80:55 (15:10%)	150:197 (49:64%)
Apgar score after 1 minute	4 (0-9)	6 (0-9)
Apgar score after 5 minute	8 (0-9)	9 (0-9)

*Data is represented by a number as n (%) or median (space)

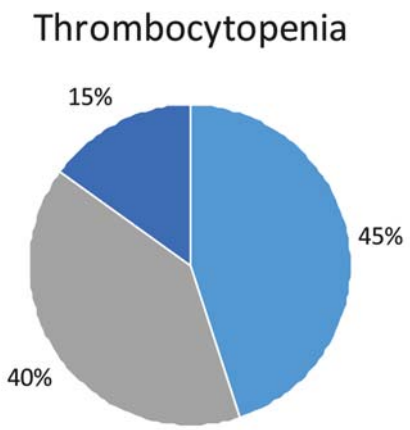
Table 3. *Causes of thrombocytopenia in neonates*

Causes of thrombocytopenia	Number of newborns with thrombocytopenia born < 37 GW	Number of newborns with thrombocytopenia born ≥ 37 GW	P values
Sepsis	300 (55.9%)	190 (62%)	0.268
Early onset of sepsis	180 (33.5%)	120 (39%)	0.112
Late onset of sepsis	120 (22.3%)	70 (11%)	0.534
Perinatal asphyxia	530 (98%)	268 (87.2%)	0.065
Necrotizing enterocolitis	88 (16.4%)	10 (30.7%)	0.068
Chromosomal abnormalities	13 (2.4%)	20 (6.5%)	0.876

Table 4. *Hemorrhagic diathesis in neonates with thrombocytopenia*

haemorrhage	Number of newborns with thrombocytopenia born < 37GW	Number of newborns with thrombocytopenia born ≥ 37GW	p
Intracranial haemorrhage grade I	54 (10%)	30 (9.7%)	0.322
Intracranial haemorrhage grade II	250 (46.7%)	250 (81.4%)	0.040*
Intracranial haemorrhage grade III	32 (5.9%)	37 (12%)	0.644
Cutaneus bleeding	98 (18.2%)	60 (19.5%)	0.342
Pulmonal haemorrhage	169 (31%)	20 (6.5%)	0.003*
Haematuria	2 (0.3%)	1 (0.3%)	0.675
Gatrointestinal haemorrhage	23 (4,2%)	10 (3%)	0.546

of births ≥ 37GW. In both groups, children with thrombocytopenia were from second pregnancy, and in the group of children < 37 GW, 17.2% were from multiple pregnancies. Although 48.2% of children with thrombocytopenia who was born ≥ 37 GW had an intrauterine delay in growth, the incidence of cesarean section was greater in the birth group ≥ 37 GW. Newborns with thrombocytopenia in the group < 37 GW are born in 30 ± 3.9 GW, with a birth weight of 1010 ± 234 grams, and in the group ≥ 37 GW at 38.2 ± 2.1 GW and 3550 ± 456 grams. The higher incidence of males was seen in the group of children < 37 GW and lower Apgar score.



* Severe thrombocytopenia 45% (platelets < 30 x 109/L), moderate 40% (platelets 31 to 100 x 109/L), mild 15% (platelets > 101 to 150 x 109/L).

Figure 1. *Thrombocytopenia in our neonates*

The causes of neonatal thrombocytopenia are shown in Table 3. Sepsis was the most common cause of thrombocytopenia, 300 children had early sepsis and 190 late. Thrombocytopenia was associated with sepsis, necrotizing enterocolitis, perinatal asphyxia, and chromosomal abnormalities, with no statistically significant difference between neonates born <37 or ≥ 37 GW.

In Table 4, the rates of intracranial and another bleeding of neonates with thrombocytopenia in relation to gestational age are shown. We found the statistically significant difference in intracranial hemorrhage of the second degree (p = 0.04) and pulmonary hemorrhage (0.003) among neonates born < 37 GW in relation to newborns born ≥ 37GW.

A two-factor analysis of the variance of neonates with thrombocytopenia has shown the effect of the platelet count and gestational age on the length of hospitalization in the NICU and the state of morbidity (Figure 2). Newborn infants are divided by gestational age into two groups (1group < 37 GN, 2 groups ≥ 37 GN) and platelet counts (group 1 < 30 x 109/L, group 2 from 31 to 100 x 109/L, and 3rd group 101 to 150 x 109/L). The effect of interaction between gestational age and platelet count was not statistically significant, F (2,290) = 1.44, p = 0.74. A statistically significant influence of the length of stay in NICU and morbidity of newborns in relation to younger gestational age and lower platelet count F (0.873) = 2.91, p = 0.002 was determined.

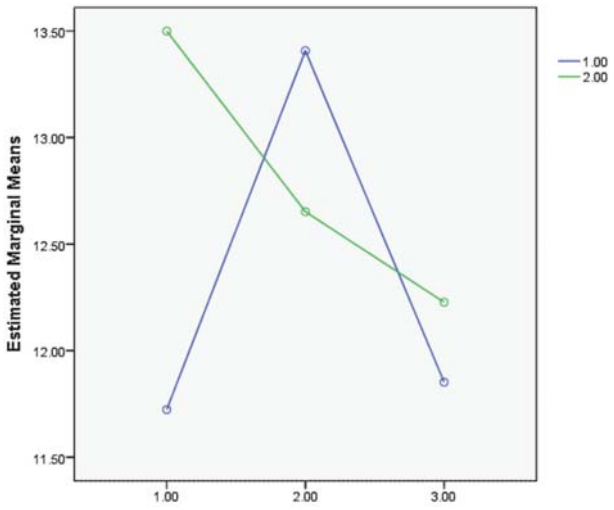


Figure 2. *Effect of the platelet count and gestational age on the length of hospitalization in NICU of the neonates with thrombocytopenia*

DISCUSSION

Thrombocytopenia in the neonatal period is a common problem. During our research, it was recorded in more than half of newborns (68.3%). In 45% of newborns, severe thrombocytopenia has been diagnosed. Most of our neonates, 489 (58.6%) had early thrombocytopenia, but without a statistically significant difference in the incidence of thrombocytopenia between groups of neonates born < 37 GN and ≥ 37 GN. The Dutch authors presented similar results in their research (6).

The average of mother's age of children with thrombocytopenia born < 37 GN was 24 ± 3.2, while for children born ≥ 37 GN was 28.2 ± 4.1 years. Hypertension had 61.8% of mothers in the group of children born ≥ 37 GN. In both groups, children with thrombocytopenia were from second pregnancy. In the group of children < 37 GN, 17.2% were from multiple pregnancies. A higher percentage of 48.2% of children with thrombocytopenia born ≥ 37 GN had intrauterine growth retardation, while a higher incidence of cesarean sections had newborns in the group of ≥ 37 GN. Newborns with thrombocytopenia in the group < 37 GN are generally born in 30 ± 3.9 GN, with a birth weight of 1010 ± 234 grams, and in the group ≥ 37GN at 38.2 ± 2.1 GN and 3550 ± 456 grams. The higher incidence of males was seen in the group of children < 37 GN and lower Apgar score. According to the data of a large retrospective cohort study (7), Resch et al. proved that neonatal thrombocytopenia is directly related to maternal hypertension and the elderly age of birth, also more frequent in prematurely born children, with lower birth weight and lower Apgar scores, which we had during our research.

Thrombocytopenia was associated with sepsis, necrotizing enterocolitis, perinatal asphyxia, and chromosomal irregularities, with no statistically significant difference between neonates born <37 GN or ≥ 37. Bleeding was diagnosed in 443 (50%) infants. The incidence of caesarean section in newborns with sepsis

and thrombocytopenia can be explained by the higher incidence of maternal hypertension and the risk of birth naturally. It is known that maternal hypertension, in addition to being a risk factor for the development of neonatal thrombocytopenia, is a possible risk factor for intrauterine growth retardation. Also, maternal hypertension leads to fetal hypoxia and causes suppression of fetal megakaryocytopoiesis and platelet production. According to a study by British authors (8) and central venous catheters, they cause mechanical damage to the blood vessel, which directs the flow of blood in the other direction into the vascular wall sections that damage the megakaryocytopoiesis process.

Inthe newborns with thrombocytopenia intracranial, bleeding in the skin, pulmonary and gastrointestinal bleeding and hematuria were often, but statistically, a significant difference was found in intracranial hemorrhage of the second degree ($p = 0.04$) and pulmonary hemorrhage (0.003) among neonates born < 37 GN in relation on newborns born ≥ 37 GN.

The association between the number of platelets and clinically manifest bleeding complications is still not fully clarified. The incidence of association of major manifest bleeding and severe thrombocytopenia in several different authors ranges from 15% to 50% (9, 10). The risk of occurrence of manifest bleeding is associated with lower gestational age, but a small number of platelets is not yet an indicator or measure of severe manifest bleeding in a child (10, 11).

In several different studies, the association between thrombocytopenia and gram-negative sepsis was found (12, 13). The number of platelets is significantly lower in gram-negative sepsis and sepsis caused by fungi, compared with gram-positive sepsis. According to research by Ahmed F et al. the duration of thrombocytopenia in gram-positive sepsis is also lower compared to gram-negative (14). The pathogenesis of thrombocytopenia in neonatal sepsis has not yet been fully clarified. Thrombocytopenia should be a predictor of the severity of sepsis, the more gram-negative than gram-positive, as it causes intravascular disseminated coagulopathy (12). An important mechanism of action of endotoxin in gram-negative bacteria is important.

During our research, a statistically significant difference was found on the length of stay in NICU and morbidity of neonates compared to younger gestational age and lower platelet counts, as was confirmed by other authors in their research (13, 14, 15).

However, further and more detailed research is needed to help determine the exact number of platelets as a predictor of possible bleeding and prevention of sepsis and mortality in newborns, as well as longer hospitalization in the NICU.

CONCLUSION

Thrombocytopenia is often diagnosed in the neonatal period. Most episodes are mild or moderate and usually pass without major clinical consequences for the newborn. However, severe thrombocytopenia also causes serious consequences and is associated with longer hospitalization and more frequent child mortality. Early birth, sepsis, and perinatal asphyxia are the most common causes of neonatal thrombocytopenia. A timely diagnosis of the cause of thrombocytopenia with adequate and effective treatment can reduce the mortality and morbidity of newborns with perinatal risks for the development of neonatal thrombocytopenia.

Abbreviations

NICU — Neonatal Intensive Care Unit
GW — week of gestation

Acknowledgment: None

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

TROMBOCITOPENIJA KAO JEDAN OD RAZLOGA PRODUŽENE HOSPITALIZACIJE NA ODELJENJU NEONATALNE INTENZIVNE NEGE

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Cilj ovog rada je bio uporediti pojavu i težinu trombocitopenije, uz intrakranijalno i druga krvarenja kod novorođenčadi sa sepsom, te analizirati faktore rizika za nastanak i razvoj trombocitopenije i dužine hospitalizacije na Odeljenju neonatalne intenzivne terapije.

Trombocitopenija je broj trombocita < 150 x 109/L i čest je nalaz kod novorođenčadi tokom hospi-

talizacije na Odeljenju neonatalne intenzivne terapije. U prvim danima života najčešći razlozi trombocitopenije kod novorođenčadi su stanja koja dovode do fetalne hipoksije, intrauterinog zastoja u rastu, majčina hipertenzija i sepsa. U ovo istraživanje su uključena sva novorođenčad sa trombocitopenijom, koja su bila hospitalizovana na Odeljenju neonatološke intenzivne terapije, Klinike za dečije bolesti, JZU UKC Tuzla, u periodu od 01. 01. 2014. do 01. 01. 2019. godine.

Rezultatima smo pokazali da je 379 novorođenčadi imalo tešku, 337 umerenu, a 127 blaži oblik trombocitopenije, bez statistički značajne razlike u učestalosti trombocitopenije između grupa novorođenčadi rođenih < 37 GN i >37 GN. Sepsa je bila najčešći razlog trombocitopenije, 300 dece je imalo ranu, dok 190 kasnu sepsu. Kod novorođenčadi rođene < 37 GN u odnosu na novorođenčad rođenu > 37 GN nađena je statistički značajna razlika kod intrakranijalnog krvarenja drugog stepena i plućnog krvarenja.Utvrđen je statistički značajan uticaj dužine boravka na Odeljenju neonatalne intenzivne terapije i morbiditeta novorođenčadi u odnosu na mlađu gestacijsku dob i niže vrednosti trombocita.

Zaključak: Pravovremeno dijagostikovanje razloga nastanka trombocitopenije uz adekvatno i pravovremeno lečenje može smanjiti smrtnost i morbiditet novorođenčadi sa perinatalnim rizicima za nastanak neonatalne trombocitopenije.

Ključne reči: trombocitopenija, novorođenčad, sepsa, Neonatalna Intenzivna terapija.

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SANAMED
2019; 14(3): 247–252
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.360
UDK: 616.12-089; 616.12-008.31-085.817
ID: 281773580
Original article

COMPARING THE OUTCOMES OF ROUTINE AND SELECTIVE EPICARDIAL PACING WIRE PLACEMENT: A SINGLE-CENTER EXPERIENCE OF 237 PATIENTS

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Primljen/Received 02. 09. 2019. god. Prihvaćen/Accepted 12. 10. 2019. god.

Abstract: **Objective:** Recently, the use of epicardial pacing wires (EPW) has become the standard of care for patients undergoing open-heart surgery (OHS) at many cardiovascular surgery centers. However, the routine use of EPWs after OHS is increasingly questioning due to their potentially lethal complications and limited efficacy. Here, we aimed to investigate the impact of EPW placement on in-hospital mortality and to compare the frequency of the EPW related complications in patients receiving routine or selective EPW placement after elective OHS.

Methods: A total of 237 patients undergoing OHS in our clinic (ORDU UNİVERSTY TRAİNİNG AND RESEARCH HOSPİTAL) were enrolled in this study. Study subjects were randomly assigned to one of the groups: Routine or selective EPW placement. In the latter, EPWs were placed according to the presence of intraoperative bradycardia with hemodynamic compromise, nodal or junctional arrhythmias, atrioventricular block or ventricular tachycardia.

Results: There were 95 patients (40 %) receiving routine EPW and 142 (60%) patients receiving selective EPW. Active pacing was performed or required in 13 patients (5.4%). Five of them were in routine EPW group and 8 were in the selective EPW group ($p = 0.902$). Active pacing requirement was similar in coronary artery bypass grafting and valvular surgery (5% vs. 9%, $p = 0.712$, respectively). Permanent pacing was required in any of the subjects. Complications related to EPW occurred in 17 patients receiving routine EPW and 2 patients receiving selective EPW ($p < 0.001$). Routine EPW implantation was significantly correlated with the development of the complications ($r = 0.309$, $p < 0.001$).

Conclusion: Our findings indicate that the number of patients requiring temporary pacing after OHS is quite low and implementing an EPW is associated with potentially hazardous complications. Selective EPW placement compared to routine EPW placement is associated with fewer postoperative complications.

Key words: Open heart surgery, epicardial pacing wire, complication.

INTRODUCTION

Conduction disturbances due to surgical manipulations, myocardial edema, hypothermia, and cardioplegia solutionare frequently encountered following open-heart surgery (OHS) (1). Many of the patients undergoing open-heart surgery, therefore, receive epicardial pacing wires (EPW) to avoid unforeseen complications such as conduction disturbances. Overdrive pacing or electrical cardioversion applied through EPWs might also be useful in the treatment of atrial and ventricular tachyarrhythmia developing after OHS (2, 3).

During the procedure, pacing electrodesare loosely sutured onto the epicardial surface of the right ventricle and/or right atrium and are approximated to the skin through the anterior chest wall before chest closure (4). These wires remain on the epicardial surface for several days and are then removed if stable cardiac conduction has been established.

The use of EPWs has become the standard of care for patients undergoing OHS in many cardiovascular surgery centers. Although the efficacy of implanting an EPW has been established in patients undergoing valvular operations (5), the routine use of EPWs after OHS is increasingly being questioned due to potentially lethal complications and the limited efficacy of EPWs in coronary artery bypass grafting (CABG). In addition, implementation of EPWs as a routine procedure increases the risks for several complications in-

cluding hemothorax, tamponade due to atrial and/or ventricular lacerations, saphenous vein graft injury, and unsuccessful removal of wiring (retained wire). These potentially lethal complications discourage surgeons when considering routine EPW placement in subjects with a lower risk for conduction abnormalities (6-9).

The purpose of the present study was to investigate the impact of EPW placement on in-hospital mortality and to compare the frequency of EPW related complications in patients receiving routine or selective EPW placement after elective OHS.

MATERIAL AND METHODS

The present study was conducted on adult patients (> 18 years) referred to a tertiary center for OHS between January 2018 and August 2018. A preoperative 12-lead electrocardiogram was used to identify preexisting conduction problems. Patients requiring emergent surgery and those with atrioventricular conduction abnormalities at admission were not included in this study. No patients were excluded on the basis of coronary anatomy, the number of grafts needed, or ventricular function. Informed consent was obtained from all patients and the study protocol was approved by the Institutional Ethical Committee (no:2018-e.1800178793). All surgical procedures were performed by the same surgical team and all EPWs were implanted by the same primary surgeon. Study subjects were randomly assigned to one of the groups: 1) The routine EPW group consisted of patients receiving an EPW independent of the clinical implication, 2) The selective EPW group was comprised of patients who received EPW immediately prior to chest closure as per the surgeon's discretion with regard to the occurrence of any of the following conditions: bradycardia with hemodynamic compromise, nodal or junctional arrhythmia, atrioventricular block, or ventricular tachycardia. All procedures were carried out with a median sternotomy with cardiopulmonary bypass. Moderate systemic hypothermia (32 °C) and topical cardiac hypothermia were used to reduce the temperature. Antegrade blood cardioplegia was used in the majority of the procedures. Data regarding age, sex, medical history electrocardiographic data and echocardiographic data (left ventricular ejection fraction[LVEF]), were collected prospectively for all patients. EPWs (Johnson & Johnson, Somerville, NJ) were sutured either on the ventral or on the diaphragmatic surface of the right ventricle. Dopamine (4 mg/kg/min) was administered toward the end of cardiopulmonary bypass to improve ventricular function and enhance atrioventricular conduction, in all patients. Intraoperative details and EPW related complications were monitored for all patients throughout their hospitalization. Temporary venous pacing equipment was on stand-by during the in-hospital course of patients that were deemed to be candidates for temporary pacing during their postoperative course. ECGs were obtained every 12 hours postoperatively and evaluated by two independent blinded cardiologists, for pacing requirement.

Statistical analysis

Statistical analyses were carried out using SPSS for Windows, version 17 (SPSS, Chicago, IL, USA). The normal distribution of continuous variables was studied with the Kolmogorov-Smirnov test. Continuous variables are presented as mean ± standard deviation and categorical variables as a percentage. For group comparisons, the Student t-test was used for continuous variables, and Chi-square tests were used for categorical variables. Pearson and Spearman correlation analyses were performed to identify the variables that were significantly associated with pacing requirements. A p-value lower than 0.05 was accepted to be statistically significant.

RESULTS

A total of 237 patients (mean age 59 ± 11years, 64 % male) undergoing OHS at our clinic were enrolled in this study. There were 95 patients (40%) receiving routine EPW and 142 (60%) patients receiving selective EPW. In the selective EPW group, 12 of the subjects received an EPW due tothe intraoperative presence of conduction disturbances or ventricular tachycardia. There were no significant differences between the two groups with respect to age, sex, preoperative atrial fibrillation, smoking, diabetes and LVEF value (Table 1).

The two groups were similar with respect to cross-clamp time, by-pass time, inotrope requirement and the type of operation performed. Active pacing was performed in 13 patients (5.4%). Five of these patients were in the routine EPW group and 8 were in the selective EPW group ($p = 0.902$). Active pacing requirement was similar in CABG and valvular surgery (5% vs. 9%, $p = 0.712$, respectively). Temporary transvenous pacing was performed only in 3 subjects in the selective EPW group due to the postoperative occurrence of advanced AV conduction. Permanent pacing was not required in any of the subjects (Table 2). Complications related to EPW occurred in 17 patients receiving routine EPW and 2 patients receiving selective EPW ($p < 0.001$). The majority of EPW related complications in the routine EPW group were associated with bleeding during EPW implantation and all were controlled with standard measures and resolved spontaneously. Cardiac tamponade developed in 2 patients and 1 pati-

Table 1. *Demographic features and LVEF values of the study population*

	Routine EPW n = 95	**Selective EPW n = 142**	**p value**
Age (years)	60 ± 9	58 ± 11	0.340
Sex (male)	63 (66 %)	89 (63 %)	0.584
Atrial Fibrillation (n)	8 (8 %)	11 (8 %)	0.852
Diabetes (n)	37 (39 %)	69 (48 %)	0.182
Smoking (n)	61 (64 %)	90 (63 %)	0.972
LVEF (%)	47 ± 6	48 ± 6	0.212

Data are presented as mean ± standard deviation. EPW: epicardial pacing wire, LVEF: left ventricular ejection fraction

Table 2. *Intraoperative details, pacing requirement and complications in regard to groups*

	Routine EPW n = 95	**Selective EPW n = 142**	**p value**
Cross-clamp time (minutes)	59 ± 10	58 ± 12	0.418
By-pass time (minutes)	108 ± 17	105 ± 11	0.068
Surgical procedure CABG (n) MVS (n) AVR (n)	 85 (89%) 7 (7%) 2 (2%)	 118 (83%) 12 (8%) 8 (6%)	 0.263 0.764 0.185
Ascending Aorta Surgery (n)	1 (1%)	4 (3%)	0.354
Inotrope duration (hours)	48 ± 12	50 ± 15	0.658
EPW implantation (n)	95 (100%)	12 (8%)	< 0.001
Requirement for active pacing (n)	5 (5%)	8 (6%)	0.902
Complications (n) Bleeding (n) Tamponade (n) Reopening (n)	17 (18 %) 14 (15 %) 2 (2 %) 1 (1 %)	2 (1 %) 2 (1 %) 0 0	< 0.001 < 0.001 0.055 0.176
Mortality (n)	4 (4 %)	6 (4 %)	0.987

Data are presented as mean ± standard deviation.AVR: aortic valve replacement, EPW: epicardial pacing wire, MVS: mitral valve surgery

ent underwent reopening in the routine EPW group. In the postoperative period, 5 deaths were encountered in the routine EPW group and 6 deaths in the selective EPW group ($p = 0.987$, Table 2). Furthermore, there was a low but significant correlation between routine EPW implantation and complication development ($r = 0.309$, $p < 0.001$).

DISCUSSION

The present study aimed to investigate whether EPW placement has any impact on in-hospital mortality or development of EPW related complications in patients undergoing OHS. Our findings demonstrate that the mortality rate is similar in patients receiving routine or selective EPW placement. Moreover, EPW related complications are fewer in patients undergoing selective EPW placement. Our results also show that only a small proportion of patients, particularly those undergoing valvular surgery, require temporary pacing which indicates that the avoidance of routine EPW placement in patients undergoing CABG should be considered.

Placement of EPW onto the atrial or ventricular epicardial surface has become a standard procedure in many surgical centers since its introduction in the1960's (10). Surgical manipulations and tissue edema occurring after heart surgery may predispose myocardial tissue to transient conduction and rhythm disturbances which commonly develop after the release of the aortic cross-clamp (11, 12). Placement of an EPW constitutes a simple and effective method in the treat-

ment of various conduction disorders that occur after cardiac surgery (13, 14, 15). However, with the advance in surgical techniques and the equipment used in these procedures, open heart surgery is currently less time consuming and tissue manipulation is less prominent, which has led clinicians to question the necessity of routine EPW placement. The most common type of conduction disturbance after OHS is reportedly sinus bradycardia which very rarely warrants the use of temporary pacing in the presence of other options. In a recent trial conducted on 374 patients undergoing OHS, the development of second and third-degree atrioventricular block which usually necessitates temporary pacing was observed in only 7.3 % of the subjects, most commonly in those undergoing valvular operations (16). Similar to these findings, in a study of 564 patients undergoing CABG and receiving an EPW according to the intraoperative presence of conduction disturbances, the authors reported that 5.5% of patients received EPWs intraoperatively and only 3 patients who had not received EPWs further required temporary transvenous pacing (17). In another large prospective cohort study of 1047 patients undergoing CABG, 770 of the subjects received an EPW before the completion of the surgery, and complete AV block requiring ventricular pacing developed in only two patients (18). These studies recognized that routine EPW placement is not required after CABG.

In addition, the short-term reliability of EPW placement might be limited due to wire dislodgement or failure of AV sensing and increasing capture thresholds (19). Moreover, some rare but potentially hazardous complications associated with EPWs including cardiac strangulation, lacerations to coronary grafts or ventricles, hemothorax, tamponade and infections related to retained wires have been reported (20, 21). In a review written by Khorsandi et al., the authors stated that the overall rate of complete AV block was around 2.4% in OHS. This finding shows that only 1 out of 42 routinely-placed EPWs are instrumental in preventing a complete heart block, which warrants the implementation of measures to reduce the number of EPWs used after OHS. Therefore, we believe surgeons should perform a meticulous evaluation of risk factors and should weigh the benefits against risks when making the decision for EPW placement in order to prevent potential complications (22).

Our findings confirm that routine EPW placement is associated with a high frequency of EPW related complications which are potentially lethal. In our study, the active pacing requirement was relatively low (5%), similar to previous reports. The routine administration of inotropic agents towards the end of the procedure might have decreased the incidence of sinus bradycardia and first-degree atrioventricular block. With this background in mind, we believe that the routine implementation of EPWs in patients undergoing OHS has no advantage over the selective approach. Meticulous intraoperative monitoring and placement of EPWs with evidence of intraoperative conduction and rhythm disturbances might prevent the overuse of EPWs and thus complications related to EPWs.

CONCLUSION

In summary, our results indicate that the number of patients requiring temporary pacing after OHS is quite low and routine EPW placement is associated with increased complications. Selective EPW placement compared to routine EPW placement is associated with fewer postoperative complications. Therefore, we suggest the utilization of EPWs only in patients experiencing intraoperative conduction disturbances and using transvenous pacemakers when necessary in the remaining patients.

Abbreviations

EPW — epicardial pacing wires
OHS — open heart surgery
CABG — coronary artery bypass grafting
LVEF — left ventrikul ejection fraction

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

POREĐENJE REZULTATA RUTINSKOG I SELEKTIVNOG POSTAVLJANJA EPIKARDIJALNOG PEJSINGA: ISKUSTVA JEDNOG CENTRA OD 237 PACIJENATA

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Cilj: U poslednje vreme je u mnogim centrima za kardiovaskularnu hirurgiju upotreba epikardijalnog pejsinga postala standard nege za pacijente koji su podvrgnuti operaciji na otvorenom srcu. Međutim, rutinska upotreba EPW-a nakon operacije na otvorenom srcu se sve više dovodi u pitanje zbog svojih potencijalno smrtonosnih komplikacija i ograničene efikasnosti. Ovde smo želeli da istražimo uticaj EPW na bolnički mortalitet i da uporedimo učestalost komplikacija povezanih sa EPW kod pacijenata koji dobijaju rutinski ili selektivni EPW nakon elektivne operacije na otvorenom srcu.

Metode: Ukupno 237 pacijenata koji su bili podvrgnuti operaciji na otvorenom srcu u našoj klinici (Univerzitetska bolnica za obuku i istraživanje Ordu) bilo je uključeno u ovo istraživanje. Ispitanici iz istraživanja bili su nasumično raspoređeni u jednu od grupa: rutinski ili selektivni EPW plasman. U poslednjoj, EPW su postavljani prema prisustvu intraoperativne bradikardije sa ugroženom hemodinamikom, nodalnim ili junkcionim aritmijama, atrioventrikularnim blokom ili ventrikularnom tahikardijom.

Rezultati: 95 pacijenata (40%) je dobilo rutinski EPW, a 142 (60%) selektivni EPW. Aktivni pejsing je izvršen ili bio neophodan kod 13 pacijenata (5,4%). Pet njih je bilo u rutinskoj EPW grupi, a osam u selektivnoj ($p = 0.902$). Zahtevi za aktivnim pejsingom su bili slični kod bajpasa koronarnih arterija i operaciji zalistaka (5% naspram 9%, $p = 0,712$). Komplikacije povezane sa EPW zabeležene su kod 17 pacijenata koji su dobili rutinski EPW i dva pacijenta koji su dobili selektivni EPW ($p < 0.001$). Rutinska implementacija EPW-a je bila značajno povezana sa razvojem komplikacija ($r = 0.309$, $p < 0.001$).

Zaključak: Naši nalazi pokazuju da je broj pacijenata kojima je potreban privremeni pejsing nakon operacije na otvorenom srcu prilično nizak i da je primena EPW-a povezana sa potencijalno opasnim komplikacijama. Selektivno postavljanje EPW-a u poređenju sa rutinskim povezano je sa manjim brojem postoperativnih komplikacija.

Ključne reči: operacija na otvorenom srcu, epikardijalni pejsing, komplikacija.

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SANAMED
2019; 14(3): 253–258
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.361
UDK: 617.77-089
ID: 281839884
Original article

RESULTS OF SURGICAL TECHNIQUES APPLIED IN BLEPHAROPTOSIS

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Primljen/Received 02. 09. 2019. god. Prihvaćen/Accepted 10. 10. 2019. god.

Abstract: **Objective:** Our aim was to analyze the success rates of patients who underwent levator aponeurosis or frontal suspension with silicone tube surgery due to blepharoptosis according to the elevator function (LF) and to compare our results with the literature.

Material and Methods: We included twenty-five eyes of 47 patients who had levator aponeurosis or frontal suspension with silicone tube surgery in this study. The patients were grouped as good, moderate, and poor according to their LF. Good and moderate patients had levator aponeurosis while poor patients had frontal suspension with silicon tube surgery. The follow-up period after surgery was 2 to 36 months. The results were evaluated with margin reflex distance (MRD) which greater than 2 mm was considered as successful, between 1 and 2 mm was satisfactory, and less than 1 mm was unsuccessful. Also, patients required revision surgery was considered as unsuccessful.

Results: Twenty-nine (61.7%) men and 18 (38.3%) women with a mean age of 35.16 years (range = 0-84 years) were included in this retrospective study. Thirteen cases (27.7%) had bilateral, and 34 cases had unilateral ptosis(72.4%). Eight of the 13 patients with bilateral ptosis had bilateral and 5 of them had unilateral surgery. Blepharoptosis was due to congenital (60.0%), aponeurotic (19%), traumatic (1.8%), Horner's syndrome (1.8%) and myotonic dystrophy (1.8%). The preoperative mean MRD value was 0.56 ± 0.85 mm (0-3 mm). The levator function (LF) was poor in 18 eyes (32.7%), moderate in 9 eyes (16.4%) and good in 28 eyes (50.9%). Thirty-seven patients (67.3%) underwent levator aponeurosis, and 18 patients had frontal suspension with silicon tube surgery. In our postoperative controls, 33 patients were considered as successful. Three patients were considered as satisfactory, and one patient was considered unsuccessful.

Discussion: Levator aponeurosis and frontal suspension with silicone tube surgeries are both effective surgical methods to treat ptosis. Postoperative success is positively affected by determining the surgery method, according to LF. Our results showed that elevator aponeurosis surgery is more satisfying in good and moderate cases, and frontal suspension with silicone tube is best in poor cases.

Key words: ptosis, surgical, techniques.

INTRODUCTION

Blepharoptosis or ptosis is the lower than normal position of the upper eyelid, which vertically narrows the palpebral space. Treatment is usually surgical. Blepharoptosis is a cosmetic and functional disorder that causes even psychosocial problems. The cause, quantity and levator function are important in determining the surgical method to be selected. The correct diagnosis is decisive for the success of the treatment. The diagnostic categories of ptosis are scheduled as pseudoptosis, congenital, and acquired ptosis. Acquired causes include mechanical, myogenic, neuromuscular, neurogenic, and cerebral. Generally, two basic methods are applied: frontal muscle sling and levator surgery. Levator aponeurosis surgery is preferred in cases with good and moderate levator function, and frontal suspension surgery is preferred in cases with poor levator function.Müllerectomy and similar methods can be used in mild ptosis. The frontal suspension technique is a surgical method used in cases of blepharoptosis whe-

re the function of the levator palpebra muscle is insufficient. This surgery is preferred in congenital myogenic blepharoptosis, blepharophimosis syndrome, oculomotor nerve paralysis, Marcus-Gunn blepharoptosis, chronic progressive ophthalmoplegia (1-4).

We aimed was to classify the patients with blepharoptosis according to their LF and to apply frontal suspension with silicone tube or levator aponeurosis surgery methods to treat this problem and to compare our surgical results with the literature.

MATERIAL AND METHODS

Fifty-five eyes of 47 patients who underwent levator aponeurosis and frontal suspension with silicone tube surgery due to blepharoptosis were included in our study.Our study was conducted at the University of Health Sciences Kartal Training and Research Hospital Eye Clinic between January 2011 and June 2015. Classification of blepharoptosis type was made according to the findings obtained from anamnesis, examination, and operation.

Preoperative evaluation included visual acuity, anterior and posterior segment examinations, eye movements, and strabismus examination, Bell's phenomenon, jaw-winking phenomenon, eyelid line-height, LF and margin reflex distance (MRD) measurements. The degree of the blepharoptosis was determined according to the MRD and the LF. Additional ocular, systemic diseases were investigated. Patients were assessed with the MRD and asymmetry between the two eyelids in the post-operative period. Post-operative complications were also recorded. Patients with blepharoptosis were examined in three groups as good, moderate, and poor according to the LF. We used the LF as the main factor to decide the surgical method to be applied. If the LF was < 5 mm, it was evaluated as poor, 5-9 mm as moderate and > 10 mm as good. In patients with good and moderate LF, levator aponeurosis surgery and cases with poor LF had frontal suspension with silicon tube surgery. The effectiveness of the operation was evaluated in patients who were followed between 2 months and 36 months after surgery.

The efficacy of the surgery was evaluated in the post-surgical examination. Participants with MRD greater than 2 mm were considered successful, between 1 and 2 mm were considered satisfactory, and below 1 mm were considered unsuccessful. In addition, patients who required revision surgery were considered unsuccessful. The number of revision surgery, patient satisfaction, overcorrection, inadequate correction, and other complications were found for evaluating the surgical results.

The operation was performed under local anesthesia in adult patients with good cooperation. In patients who did not want to undergo a procedure with local anesthesia, pediatric patients were operated under general anesthesia.

RESULTS

Twenty-nine (61.7%) male and 18 (38.3%) female patients aged between 0 to 84 years (mean age 35.16 years). Ptosis was bilateral in 13 cases (27.7%) and unilateral in 34 cases (72.4%) including 17 right eyes and 17 left eyes. Eight of the 13 patients with bilateral ptosis were bilateral, and 5 had unilateral surgery (Table 1). Patients were followed between 2 months and 36 months (mean 15 months) after surgery.

Blepharoptosis causes of the 55 patients were congenital (%60.0), 19 aponeurotic (%34.5), traumatic (%1.8), Horner's syndrome (%1.8), and myotonic dystrophy (%1.8). Three patients had strabismus, and four patients had amblyopia. Three patients had previously undergone penetrant keratoplasty. One of the congenitally categorized patients had third cranial nerve palsy (Table 2).

Table 1. *The Gender of the Patients and the Affected Eye*

	n*	%
Gender		
Female	18	38.3
Male	29	61.7
Affected Eye		
Right	17	36.2
Left	17	36.2
Bilateral	13	27.1

n: Number of patients, %: percentage

Table 2. *Types of Ptosis*

	n*	%
Congenital	33	60
Aponeurotic	19	34.5
Traumatic	1	1.8
Horner syndrome	1	1.8
Myotonic dystrophy	1	1.8

n: Number of the patients, %: percentage

MRD values were found to be minimum 0 mm, maximum 3 mm (mean 0.56 ± 0.85 mm) on preoperative examination in the cases. Preoperative LF of the cases was 0 mm minimum, maximum 16 mm (mean 8.58 ± 4.45 mm). The LF in the eyes was evaluated as poor in 18 (32.7%), moderate in 9 (16.4%) and good in 28 (50.9%) cases (Table 3).

Table 3. *Preoperative Levator Function (LF)*

LF	n	%
Poor	18	32.7
Moderate	9	16.4
Good	28	50.9

n: Number of the patients, %: percentage

Thirty-seven patients (67.3%) underwent levator aponeurosis, and 18 patients had frontal suspension with silicon tube surgery. In postoperative controls 46 (83.6%) cases were successful, 7 (12.7%) were satisfactory, and 2 (3.6%) cases were unsuccessful. Revision surgery was performed on 2 cases that were accepted unsuccessful. Margin reflex distance (MRD) patients who undergone levator aponeurosis surgery was minimum 0 mm, maximum 3 mm, mean (0.78 0.94 mm) preoperatively. Preoperative LF of the cases was a minimum 7 mm, a maximum 16 mm (mean 11.29 2.47). The LF in patients with levator aponeurosis surgery was moderate in 9 eyes (16.4%) and good in 28 eyes (50.9%).

MRD values of the cases with frontal suspension with silicone tube surgery were minimum 0 mm, maximum 1 mm, average 0.11 ± 0.32 mm. The preoperative levator function of these cases was minimum 0 mm, maximum 4 mm, mean 3.00 ± 0.97. At the last follow-up after levator muscle surgery, 33 (89.2%) were successful, 3 (8.1%) were satisfactory, and 1 (2.7%) was unsuccessful.

In the last follow-up, frontal suspension surgery with silicone band 13 were (72.2%) successful, four patients were (22.2%) satisfactory, and one patient was (5.6%) unsuccessful (Table 4).

Two patients were accepted as unsuccessful in the evaluation after surgery. One of the unsuccessful patients underwent levator aponeurosis, and the other underwent frontal suspension with silicone tube surgery.

Table 4. *Results of the Surgeries*

Levator Aponeurosis Surgery	n	%
Successful*	33	89.2
Satisfactory**	3	8,1
Unsuccessful***	1	2,7
Frontal Suspension with Silicone Tube	**n**	**%**
Successful*	13	72.2
Sat2sfactory***	4	22,2
Unsuccessful***	1	5,6

n: Number of the patients, %: percentage, successful*; MRD ≥ 2 mm, satisfactory **; MRD 1–2 mm, unsuccessful ***; MRD ≤ 1 mm

These unsuccessful patients had revision surgery. No additional postoperative complications were observed.

DISCUSSION AND CONCLUSION

Blepharoptosis is a problem that often seen in ophthalmology clinics and treated with surgery. It is both a functional and aesthetic problem for the patient. When adults have more cosmetic problems in the preliminary plan, amblyopia, which can develop due to the prevention of visualization in the pediatric age group, is a special consideration. Variable factors in the formation of ptosis and anatomical differences between individuals may cause unexpected results at the end of the surgery. The success of the surgical procedure depends on the amount of ptosis, the etiology, and the good evaluation of levator muscle function before surgery. Although the clinical and anatomical characteristics of blepharoptosis are well assessed, the differences in the normal anatomy of the eyelids, the diversity of the etiopathogenesis of the disease, and the coexistence of different pathologies in some cases make the surgery relatively difficult and reduce the success rate (5-8).

Ptosis surgery success rates have increased with new methods developed in recent years. These methods include frontal suspension, transconjunctival resection, levator resection, levator aponeurosis surgery, aponeurosis repair, levator advancement, and aponeurosis (4).

Blepharoptosis may have different etiologies. It may be congenital or acquired according to the age of onset. At first evaluation, pseudoptosis and ptosis should be distinguished. Ptosis is the inadequate openness of the upper eyelid when there is no problem in the levator muscle. Bulbi, enophthalmos, hypotropia, dermatochalasis can cause fitizis. In these patients, it is more appropriate to consider surgical treatment of ptosis if necessary after the treatment of underlying scarring (such as orbital or strabismus surgeons) before deciding on ptosis surgery.

The application of ptosis surgery in adulthood allows the surgeon to perform local anesthesia. Thus, during operation, the patient can be brought to a sitting position, and the eyelid height can be adjusted during surgery. The fact that the visual acuity remains closed during infancy and early childhood is known to lead to amblyopia with sensory deprivation.

Congenital ptosis is associated with visual dysfunctions such as amblyopia, strabismus, and refractive errors.The highest prevalence was revealed for myopia with 30.2% (95%CI 3.0–69.8%), followed by 22.7% (95%CI 18.5–27.8%) for amblyopia, 22.2% (95%CI 7.8–63.1%) for astigmatism, 19.6% (95%CI 16.5–23.2%) for strabismus, 17.3% (95% CI 13.1–22.9%)

for anisometropia and 4.0% for hyperopia (95%CI 1.8–7.1%) (8). While population-based studies focused on the prevalence of amblyopia have reported a prevalence varying from 0.74% to 5.6% depending on ethnic group, in a study by Oral et al. on 83 eyes of 72 patients, they observed the frequency of amblyopia in congenital ptosis patients by 48% (10, 11).

Patients with ptosis are examined in three groups as good, moderate, and weak according to levator muscle function. The basal examinations of the eyelid, such as measurement of preoperative levator muscle function, MRD and palpebral opening, should be carefully evaluated. Traditionally, patients with poor levator function are treated with frontal suspension with sling surgery, while patients with good levator function are undergoing levator aponeurosis surgery. The results of levator aponeurosis resection in patients with moderate to good levator function are quite encouraging. Thus we preferred levator aponeurosis surgery in cases of good and moderate levator function.

Today, unlike classical levator resection, levator muscle surgery is intervened only in levator muscle aponeurosis, but Muller's muscle, which helps upturning of the lid and Whitnall ligament supporting the eyelid, is not performed. Thus, goblets, meibomian, and assisted lacrimal glands, which stabilize tears during surgery are not damaged. In this view, dry eye symptoms such as burning and stinging after surgery are less frequent.

Although there is a consensus on the use of the frontal suspension method in cases where the levator function is poor (less than 4 mm), there is no standard practice for the suspension materials. For the hanging, the autogenous fascia lata is considered as the best material with the least risk of infection, absorption, and rupture. Non-autogenous primary materials are; fascia, skin, muscle and sclera grafts, silicone strip, supra mid, silk, polyester sutures, expanded polytetrafluoroethylene (gore-tex) (12).

We used silicone strips as suspension material because we did not need to prepare the fascias for frontal suspension surgery, so it would reduce the case length and allow the cover height to be adjusted again. Levator aponeurosis surgery is a method applied to the levator muscle itself without interfering with Müller's muscle, tarsal ve conjunctiva.

Because of the easier recognition of anatomic structures, more resection of the tissues, and the possibility of advancing to the tars, the approach through the skin in levator aponeurosis surgery is more preferred than the conjunctival approach (13). Ünal et al. reported that 62 (83.7%) successful and 8 (10.8%) satisfactory 4 (5.4%) poor outcomes were found in this series of 74 eyes (7). Özay and colleagues also performed levator aponeurosis in 24 eyes of 21 patients and found that in cases with aponeurotic ptosis (93.4%) were successful, and 6.7% were satisfactory (14). Beden and colleagues achieved results in successful 17 (89.4%) cases and satisfactory in 2 (10.6%) cases in levator aponeurosis surgeries (6).

Older reported that they were successful in 95% of, 113 patients with aponeurotic ptosis (15). As seen in the above studies, levator surgery results are good in patients with good levator function. In our series, levator aponeurosis with good and intermediate levator muscle function is similarly good. According to our postoperative control, 89.2% of the patients who underwent levator muscle surgery were successful, and 8.1% were found to be satisfactory.

In our study, we preferred frontal suspension surgery in patients with poor levator muscle function.

Ali et al. reported that eyebrow strap with fascia lata is a safe and effective technique for correcting weak levator-function ptosis (16).

Many surgeons have searched for alternatives that can be used in place of the fascia lata because of taking the time frontal suspension technique with autogenic fascia lata, the difficulty of obtaining the autogenous fascia lata, the inadequate length of the material under three years of age and scarring of the leg. Tillett initially described the use of the silicone strip in the frontal suspension in 1966 (17).

Carter et al. using silicone strips, reported 0-31.8% recurrence of ptosis, and 4-5% uncovered (18). Unal et al. reported that 61.9% of the patients who applied silicone band with frontal hanging were successful, 14.3% had a satisfactory result, and 23.8% of cases had recurrent ptosis (19).

In the postoperative follow-up period of 72.2% of the patients we used silicone tape as frontal sling material, we found that the surgery was successful. We found satisfactory results in 22.2% of cases and poor in 5,6% of cases. With these results, the success rate of the silicone tube and frontal suspension surgeries are similar to the success rates in the literature. Common complications of levator muscle surgery are; lagophthalmic keratitis, infection, entropion, ectropion, scar formation, contour disturbance, conjunctival prolapse, hematoma, and loss of eyelashes.

In the frontal suspension surgery, the suspension material may come out, and infection, pyogenic granuloma development, and eyelash ptosis may occur. Also, recurrent ptosis may develop more frequently in these patients. Özdal et al. detected complications after levator surgery such as conjunctival prolapse in 5 cases, lagophthalmic keratitis in one case, valve hematoma in 5 cases, and minimal openness of the lid during sleep in 3 cases (5).Bayramlar et al. reported that slight

asymmetric cover line or irregular contour in 7 eyes of 27 eyes, and conjunctival prolapse in 1 eye when performing levator augmentation (20).

In studies with long follow-up periods, the repetition of ptosis is reported at higher rates. In a study conducted by Wilson et al., the success rate of the surgery with prolonged follow-up was reduced in the series of frontal suspension surgery with fascia lata. At the 2-3 years follow-up, the success rates were 90%, and this ratio decreased to 50% in 8th and 9th years (21).

Especially in childhood surgeries, patients and their relatives should be informed that additional surgery may be needed. In our cases, after levator aponeurosis surgery and frontal suspension surgeries, a total of two patients were evaluated as poor and revision surgery was performed. When all the patients were assessed, one patient had prolapsing in the lid skin and temporary lagophthalmos in one patient who had levator aponeurosis surgery. No further complications were observed in the controls. After the frontal suspension surgery.

When ptosis surgery is planned, it is very important to determine the correct surgical method to be applied to the patient. Levator muscle surgery for those who have good and moderate muscle function and frontal suspension surgery for those who have poor muscle function are most appropriate. As seen in our series, when surgery is planned according to muscle function, very successful results are obtained. Silicone tapes are safe materials for use in the frontal suspension surgery procedure applied to patients with poor levator muscle function.

Abbreviations

LF — levator function
MRD — margin reflex distance

Financial Disclosure and Conflict of Interest: We affirm that we have no financial affiliation (including research funding) or involvement with any commercial organization that has a direct financial interest in any matter included in this manuscript. There were no sources of grant support for this study.

Licensing

Sažetak

REZULTATI HIRURŠKIH TEHNIKA PRIMENJENIH U LEČENJU BLEFAROPTOZE

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Cilj: Naš cilj je bio da analiziramo stopu uspešnosti kod pacijenata koji su bili podvrgnuti operaciji aponeuroze levatora ili frontalnoj suspenziji sa silikonskim tračicama u odnosu na funkciju elevacije i da uporedimo naše rezultate sa literaturom.

Materijal i metode: U ovu studiju smo uključili dvadeset i pet očiju 47 pacijenata koji su imali operaciju aponeuroze levatora ili frontalnu suspenziju sa silikonskim tračicama. Pacijenti su grupisani kao dobri, umereni i loši shodno funkciji levatora. Dobrim i umerenim pacijentima je rađena operacija aponeuroze levatora, dok je kod loših rađena frontalna suspenzijia sa silikonskim tračicama. Period praćenja nakon operacije bio je od 2 do 36 meseci. Rezultati su evaluirani u odnosu na rub kapka-refleks distance (MRD) i smatrani su uspešnim ukoliko je MRD veća od 2 mm, zadovoljavajući ako je između 1 i 2 mm i neuspešnim ako je manja od 1 mm.

Rezultati: U ovu retrospektivnu studiju uključeno je 29 (61,7%) muškaraca i 18 (38,3%) žena, srednje životne dobi od 35,16 godina (0-84 godine). Trinaest slučajeva (27,7%) imalo je bilateralni oblik, a 34 slučaja jednostranu ptozu (72,4%). Osam od 13 pacijenata sa obostranom ptozom imalo je bilateralnu operaciju, a 5 njih je imalo jednostranu operaciju. Blefaroptoza je bila kongenitalna (60,0%), aponeurotska (19%), traumatska (1,8%), kod Hornerovog sindroma (1,8%) i miotone distrofije (1,8%). Srednja postoperativna vrednost MRD bila je 0.56 ± 0.85 mm (0-3 mm). Funkcija levatora bila je loša kod 18 očiju (32,7%), umerena kod 9 (16,4%), i dobra kod 28 očiju (50,9%). 37 pacijenata (67,3%) je podvrgnuto operaciji aponeuroze levatora, a 18 pacijenata imalo je frontalnu suspenziju sa silikonskim tračicama. U našim postoperativnim kontrolama, postignuti rezultati su bili uspešni kod 33 pacijenta, zadovoljavajući kod 3 i neuspešni kod 1 pacijenta.

Diskusija: Operacija aponeuroze levatora i frontalna suspenzija sa silikonskim tračicama su obe efikasne hirurške metode za lečenje ptoze. Na postoperativni uspeh pozitivno utiče izbor hirurške metode u odnosu na funkciju levatora. Naši rezultati su pokazali da operacija aponeuroze levatora je sa boljim rezultatima kod dobrih i umerenih slučajeva, a frontalna suspenzija sa silikonskim tračicama je najbolja kod loših slučajeva.

Ključne reči: ptoza, hirurške tehnike.

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SANAMED
2019; 14(3): 259–267
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.364
UDK: 616-002.828-053.31(497.6)"2016/2018"
616.94-053.31(497.6)"2016/2019"
ID: 281811468
Original article

CLINICAL AND LABORATORY CHARACTERISTICS OF NEONATAL CANDIDA SEPSIS

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Primljen/Received 05. 09. 2019. god.

Prihvaćen/Accepted 12. 10. 2019. god.

Abstract: **Introduction:** Steady progress in intensive treatment worldwide has increased the survival of immature neonates, but with multiple invasive procedures, which has increased the risk of infection and, consequently, fungal sepsis. Candida is the dominant cause, with the rise of resistant non-albicans species. The mortality rate is high and requires timely suspicion and adequate treatment to counteract fatal outcomes.

Objectives: To analyze the clinical and laboratory characteristics of Candida sepsis, compared to bacterial sepsis, in neonates treated in the neonatal intensive care unit. Methods: A retrospective cohort study conducted at the Intensive care unit of Pediatric Clinic Tuzla over a three-year period (2016-2018) analyzed the clinical and laboratory characteristics of neonates with Candida sepsis, evidenced by positive blood culture. The control group was neonates treated at the same time for proven bacterial sepsis. Statistical analysis applied standard methods, and the research was approved by the Ethics Committee of the institution.

Results: Out of the total 921 neonates treated over a three-year period, culture-confirmed Candida sepsis was found in 48 (5.2%). Prematurity and low birth weight were the most significant risk factors and affected neonates had a more difficult clinical presentation, more receiving parenteral nutrition, mechanical ventilation, intravenous gamma globulin, and longer intensive treatment. Candida sepsis manifested mainly as late-onset. Laboratory abnormalities mainly included CRP elevation, anemia, leukocyte count deviations, and thrombocytopenia. There was no difference in mortality, 44 neonates recovered (91.7%), while 4 (8.3%) died. Antifungal therapy lasted 20.6 ± 6 days, and intensive treatment 38.2 ± 23.2 days, and was significantly longer compared to the control. All isolates were Candida species without in vitro resistance. In 8 neonates (16.7%) treatment complications were recorded.

Conclusions: Neonatal Candida sepsis endangers life, complicates treatment, increases costs and mortality rate. Recovery depends on timely suspicion, adequate treatment, and supervision. Antifungal susceptibility is also important and requires monitoring of local epidemiological dynamics.

Key words: Candida sepsis, neonates, clinical and laboratory characteristics.

INTRODUCTION

Fungal sepsis is increasingly reported in neonates at tertiary neonatal care centers, and althought is less common compared to bacterial Gram-positive and Gram-negative sepsis, it has a higher mortality rate, especially in preterm infants with low birth weight, while infants who survive often have long-term neurological damage (1-5).

Candida is most commonly reported causative agents of neonatal fungal sepsis, but instead of the previously dominant (up to 80%) sensitive Candida albicans, today non-albicans Candida types are increasingly reported, including C. parapsilosis, C.tropicalisi C. glabrata that show varying degrees of resistance to fluconazole and other antifungal agents (6, 7, 8). It is very important to have current information on neonatal fungal isolates and their patterns of antimicrobial susceptibility, and thus be guided in the choice of empirical antifungal therapy (9, 10, 11).

The mortality rate is different and ranges from 20-75% (12, 13). The risk factors for neonatal fungal sepsis have been extensively studied and include prematurity, low birth weight, indwelling central venous catheter use, prolonged hospitalization, mechanical ventilation, endotracheal intubation, parenteral nutrition, prolonged broad-spectrum antibiotic use, exposure to H2- receptor antagonist, as well as previous Candida albicans colonization from mother (13-17).

Clinical presentations of fungal sepsis have also been investigated and were found usually as non-specific in neonates, including thrombocytopenia, lethargy, glucose instability, increased requirements for ventilation or apnea (16). The outcome depends mainly on early and in time identified cause, as well as the adequate causal therapy started in time. The definite diagnosis of fungal sepsis is not always easy to confirm because isolation and identification of the pathogen take time. Empirical antifungal therapy is based on local epidemiology monitoring of dominant agents in a particular unit (10, 11, 12). For rapid evaluation and decision, clinicians retaina combination of clinical and laboratory findings as a diagnostic tool for the evaluation of neonatal fungal sepsis.

The aim of this study was to determine the clinical and laboratory characteristics of neonatal confirmed candida sepsis in comparison with non-fungal neonatal sepsis.

PATIENTS AND METHODS

A retrospective cohort study, which included all consecutive neonates with positive blood culture, from those treated in the Neonatal intensive care unit (NICU) of Pediatric clinic Tuzla (capacity 20 beds, level III) over a three-year period (2016 to 2018). All neonates with Candida positive blood culture were designated as the test group. The control group consisted of neonates with a non-fungal positive blood culture. The study was approved by the Ethics Committee of the Institution.

Clinical and demographic data were obtained from medical records and electronic database of patients treated in the NICU, which included gender, gestational age, birth weight, perinatal risk factors, clinical presentation, laboratory findings, applied therapy, and the outcome. During admission, the clinical status of neonates was scored by SNAP-PE (Score for Neonatal Acute Physiology - Perinatal Extension) and CRIB II (Clinical Risk Index for Babies) score (18). Especially analyzed predisposing factors for fungal neonatal sepsis (presence of a central venous catheter, length of mechanical ventilation treatment, antibiotic therapy, parenteral nutrition and length of hospitalization).

Among laboratory findings we particularly analyzed potential markers of infection, including C-reactive protein (CRP), Complete blood cell (CBC) counts, the highest and lowest value for white blood cell (WBC) count, absolute neutrophil count (ANC), immature -tototal neutrophil ratio (I/T ratio), platelet count, and coagulation status.

The early onset of neonatal sepsis was defined as an infection that develops in the first 7 days of life, and late-onset of neonatal sepsis was defined as an infection that develops after the 7th day of life. The long-term antibiotics use was considered if it exceeded 14 days of continuous administration. Fluconazole was used as the first line of empirical antifungal therapy. There was no prophylactic administration of Fluconazole in NICU at the study time, and empiric antibiotic therapy for neonatal sepsis was Ceftazidime, Amikacin, which was corrected by Meropenem and/or Vancomycin, depending on further clinical course and findings in a particular patient.

All data were analyzed and compared in two groups of neonates, those with confirmed Candida sepsis were compared with a group of neonates with confirmed no fungal sepsis. For statistical analysis of data standard methods of descriptive statistics (central tendency measures, dispersion measures) were used. Parametric and non- parametric significance tests (X^2-test, Student's t- test), as well as linear correlation method, were used to test the significance of differences between the samples. Statistical hypotheses were tested at a significance level of $\alpha = 0.05$, i.e. the difference between the samples is considered significant if $P < 0.05$. We used Systat Software, SystatInc, Evanstan, IL, USA for statistical processing of data.

RESULTS

During the three- year period, 921 neonates were treated in NICU, and their basic clinical and demographic characteristics are shown in Table 1.

Out of a total of 921 treated neonates, Candida sepsis was found in 48 neonates (5.2%), evenly found in both genders. The basic clinical and demographic data of neonates treated for Candida sepsis are shown in the Table 2 compared to neonates with non-fungal

Table 1. *NICU admitted patients characteristics (n = 921)*

Characteristics	n	%
neonates	921	100.0
preterm	501	54.4
late preterm	328	35,6
very preterm	173	18.7
extremely preterm	58	6.2
low birth weight	278	30.1
very low birth weight	116	12.5
extremely low birth weight	38	4.1
Mechanical ventilation within NICU stay	330	35.8
Surgery within NICU stay	46	4.9
Clinically confirmed sepsis	396	42.9
Confirmed sepsis on blood cultures	235	25.5
Confirmed fungal sepsis on blood cultures	48	5.2
NICU: neonatal intensive care unit		

Table 2. *Baseline characteristics of fungal and non-fungal cases*

Variables	Fungal Sepsis (n = 48)	Non-fungal sepsis (n = 187)	p
Gestational age			
preterm	42 (87.5)	80 (42.8)	< 0.001
late preterm	11 (22.9)	41 (21.9)	0.8816
very preterm	31 (64.6)	39 (20.9)	< 0.001
extremely preterm	8 (16.7)	5 (2.7)	0.0002
Birth weight			
low birth weight	39 (81.25)	64 (34.2)	< 0.001
very low birth weight	20 (41.7)	11 (5.9)	< 0.001
extremely low birth weight	4 (8.3)	2 (1.1)	0.0049
Gender			
Male	25 (52.1)	116 (62.0)	0.2117
female	23 (47.9)	71 (38.0)	0.2117
Mode of delivery:			
cesarean section	18 (37.5)	67 (35.8)	0.8269
vaginal	30 (62.5)	120 (64.2)	0.8269
Maternal risk factors:			
No	8 (16.7)	104 (55.6)	< 0.001
EPH gestosis	7 (14.6)	23 (12.3)	0.6702
Diabetes mellitus	1 (2.1)	3 (1.6)	0.8112
Infection	8 (16.7)	32 (17.1)	0.9476
In vitro fertilization	2 (4.2)	8 (4.3)	0.9756
Premature rupture of membrane	4 (8.3)	40 (21.4)	0.038

Table 3. *Compared data of fungal and non-fungal cases*

Parameter	Fungal sepsis		Non-fungal sepsis		p
	Mean	SD	Mean	SD	
GA (weeks)	32.35417	3.789625	36.26738	3.279646	**< 0.001**
BW (grams)	1852.083	746.2700	2841.781	805.9642	**< 0.001**
AS 1st minute	5.904762	2.119074	6.989305	2.369132	**0.0042**
AS 5th minute	6.952381	1.321975	7.780749	1.675264	**0.0017**
PRM (hours)	4.095238	4.134063	5.189840	11.34193	0.5121
CRP (mg/*l*)	49.54792	70.13882	21.69626	40.06281	**0.0004**
Htc	0.506190	0.093353	0.515684	0.107224	0.5753
Leukocytes	9.190476	3.756182	14.12230	8.439908	**0.0001**
neutrophils	0.320952	0.148017	0.4096989	0.1862285	**0.0025**
ANC	3250.000	2240.187	6056.701	4551.286	**< 0.001**
ITR	0.074762	0.061937	0.081979	0.096580	0,7834
platelets	110.6667	97.57361	223.2781	116.6098	**< 0.001**
albumin	26.42857	4.632186	27.57219	4.219511	0.1021
Treatment (days)	38.19048	23.14653	12.40107	6.930112	**< 0.001**
CRIB II	5.952381	4.318289	3.941176	4.078763	**0.0029**
SNAPEPE II	36.80952	20.07889	23.51337	24.99298	**0.0008**

GA - gestational age; BW-birth weight; AS 1st min-Apgar score in the first minute; AS 5th minute-Apgar score in the fifth minute; PRM - premature rupture of membranes; CRP - C reactive protein; Htc - hematocrit; ANC - Absolute neutrophil count; CRIB II - Clinical Risk Index for Babies scoring system; SNAPEPE II - Score for Neonatal Acute Physiology-Perinatal Extension.

Table 4. *Clinical characteristics of fungal and non-fungal cases*

Variables	Fungal Sepsis (n = 48)	Non-fungal sepsis (n = 187)	p-value
CRIB II (mean ± SD)	5,95 ± 4,32	3,94 ± 4,08	**0.0029**
SNAPEPE II (mean ± SD)	36,81 ± 20,08	23,51 ± 24,99	**0.0008**
Early onset of sepsis (< 3 days)	0	76 (40.6%)	**< 0.0001**
Early onset of sepsis (< 7 days)	3 (6.2%)	112 (59.9)	**< 0 .0001**
Late onset of sepsis (> 7 days)	45 (93.8%)	75 (40.1%)	**< 0.0001**
Broad spectrum antibiotics > 3 n (%)	10 (20.8)	53 (28.3)	0.2951
Probiotics n (%)	12 (25.0)	42 (22.5)	0.7136
intravenous immunoglobulins n (%)	14 (29.2)	27 (14.4)	**0.0159**
ursodeoxycholic acid n (%)	8 (16.7)	11 (5.9)	**0.0145**
Mechanical ventilation n (%)	43 (89.6)	39 (20.8)	**< 0.001**
Parenteral nutrition n (%)	48 (100.0)	63 (33.7)	**< 0.001**
Inotropes n (%)	15 (31.25)	57 (30.48)	0.9178
NICU stay in days (mean ± SD)	38,19 ± 23,15	12,40 ± 6,93	**< 0.001**
Outcome			
Survivors n (%)	44 (91.7)	176 (94.1)	0.5442
Non-survivors n (%)	4 (8.3)	11 (5.9)	0.5442

CRIB II - Clinical Risk Index for Babies scoring system; SNAPEPE II - Score for Neonatal Acute Physiology-Perinatal Extension; SD - standard deviation; NICU - Neonatal intensive care unit

Table 5. *Laboratory characteristics of fungal and non-fungal because*

Variables	Fungal Sepsis (n = 48)	Non-fungal sepsis (n = 187)	p-value
CRP < 5 mg/*l*	15 (31.3)	100 (53.5)	**0.0061**
CRP > 5 mg/*l*	33 (68.8)	87 (46.5)	**0.0058**
Htc anemia	19 (39.6)	7 (3.7)	**< 0.001**
Htc normalž	21 (43.8)	138 (73.8)	**0.0001**
Htc polycythemia	8 (16.7)	42 (22.5)	0.3814
Leukocytes < 6	17 (35.4)	28 (15.0)	**0.0014**
Leukocytes > 13	31 (64.6)	75 (40.1)	**0.0023**
ANC < 1800	10 (20.8)	38 (20.3)	0.9389
ANC > 13000	4 (8.3)	24 (12.8)	0.39
Platelets < 150	38 (79.2)	50 (26.7)	**< 0.001**
Platelets > 450	1 (2.1)	7 (3.7)	0.5839
coagulation status normal	25 (52.1)	102 (54.5)	0.766
coagulation status disrupted	23 (47.9)	85 (45.5)	0.766

CRP - C reactive protein; Htc - hematocrit; ANC - Absolute neutrophil count

sepsis. Mostly, Candida sepsis was found in preterm infants with a low birth weight with an average gestational age of 32.3 ± 3.7 and a birth weight of 1852 ± 746 grams (Table 3). Neonates from the Candida sepsis group, compared to the non fungal sepsis group (Table 3), had slightly lower values of Apgar score in the first and fifth minutes.

Prematurity and low birth weight in our study were confirmed as the most significant perinatal risk factors for the onset of Candida sepsis in critically ill in-

fants (Table 4). More precisely, very preterm and extremely preterm neonates were significantly more frequent in the group of Candida sepsis compared to the non-fungal sepsis group. Low birth weight, very low birth weight, and extremely low birth weight neonates were significantly more frequent in the Candida sepsis group compared to the non-fungal sepsis group. Gender and mode of delivery did not seem to havea significant difference between groups. Maternal risk factors showed low significance, so "no-risk" and prolonged rupture of the membrane was slightly more common in the non-fungal sepsis group.

Neonatal disease severity scoring systems (CRIB II and SNAPE-PE II) were applied at admission for each neonate. Both scoring systems showed significantly higher values in neonates with Candida sepsis in relation to the non-fungal sepsis group. The severe clinical presentation of neonates with proven sepsis via positive blood culture was demonstrated by the necessarily applied supportive therapy shown in Table 3. Clinically, fungal sepsis manifested as late sepsis in almost all 48 patients, and the most common clinical presentation included respiratory deterioration, lethargy, feeding difficulties, and abdominal distension. Non-fungal sepsis had different onset times, with predominantly present early-onset sepsis, and the difference between the fungal and nonfungal groups was significant.

All neonates with fungal sepsis had an umbilical vein catheter, received parenteral nutrition and antibiotic therapy. Almost 90% of them required mechanical ventilation support, and the mean ventilation support length was 8 days. A quarter of neonates with Candida sepsis received H2- receptor blockers and had prolonged hospitalization.

Mechanical ventilation and parenteral nutrition have been used in the Candida sepsis group for a significantly longer period compared to the non-fungal sepsis group. Neonates with Candida sepsis received intravenous immunoglobulins more often compared to the non-fungal sepsis group and they were treated significantly longer in the NICU.

Laboratory findings in neonates with proven sepsis are shown in Tables 4 and 5. Differences between the two observed groups were found for the value of C reactive protein, leukocytes, neutrophils, absolute neutrophil count and platelet count. The most common deviation in neonates with Candida sepsis was presented as an increase in C- reactive protein and leukocytes with thrombocytopenia (Table 5). They also had a significant rate of anemia and leukopenia compared to the control group.

Fluconazole prophylaxis was not included at the time of the study, but Fluconazole therapy was included when there was a clinical suspicion of fungal sepsis before blood culture results were received. All blood culture isolates were Candida species group without in- vitro resistance. The duration of Fluconazole therapy averaged 20.6±6 days; 11 of them received supportive platelet concentrate; 14 patients received intravenous gammaglobulin. Despite its in-vitro sensitivity, Fluconazole was not effective in the treatment of two neonates and it was replaced by Amphotericin B.

There was no significant difference in mortality rates in the two observed groups. Out of 48 neonates with Candida sepsis, 44 of them survived (91.7%), and 4 neonates died (8.3%), while the non-fungal sepsis mortality rate was 5.9%. The length of intensive treatment was 38.2 ± 23.2 days. Mild toxic hepatitis was recorded as a complication of the total treatment in 8 neonates (16.7%) with Candida sepsis, while the same complication in the non-fungal sepsis group was recorded in 5.9% of cases. This difference between the observed groups had a slight significance.

DISCUSSION

Regardless of constant progress in the treatment of critically ill neonates globally, sepsis is still one of the major causes of morbidity and mortality in neonates (19). Existing published data have suggested that sepsis causes about 25% of all neonatal deaths, and mortality due to sepsis has increased by approximately 13.7% each year over the past 2 decades (19). The diversity of sepsis etiology varies from one region to another and changes over time even in the same place. This is attributed to the changing pattern of antibiotic use and changes in lifestyle and conditions that predispose neonates to infection (20). Fungal sepsis, mainly with Candida species, is an important cause of morbidity and mortality in critically ill neonates (21, 22, 23). A gradual decrease in susceptibility to routine antibiotic is more highlighted in lower birth weight and premature neonates. The outcomes may be improved by preventative strategies, earlier and accurate diagnosis, and adjunct therapies to combat infection and protect the vulnerable neonates during the infection (7). For these reasons, it is very important to know the local incidence, etiology, resistance and susceptibility of pathogens to antibiotics.

Suspected neonatal sepsis is a common indication for admission to the NICU. The incidence of confirmed neonatal sepsis in our NICU is currently 12 per 1000 live births, which is comparable to other reports and NICU results. Our study has found that candidemia is a common problem in critically ill neonates, with an overall incidence of 5.2%. This data is higher than those in the pieces of literature of European coun-

tries reporting an incidence of 1.1-1.3% neonates treated in NICU (10, 11, 12), and North and South America reporting an incidence of 0.5–1.6% (13, 14), but it is lower than published data in Asia, reporting an incidence of 4–7.7% (15, 16, 17). This variability may reflect differences in neonatal clinical practice among countries, as well as in the design of the study and patients involved in it. In our study, neonates with Candida sepsis were equally distributed by gender, which is generally consistent with the published literature, but sometimes reportedly preferred boys (3-6). Almost 90% were premature neonates, while over 80% were with low birth weights. That is the mostcommon result in other reports,with the predominance of very preterm neonates (below 32 gestational weeks) and very low birth weight (below 1500 g) (3, 4, 5). In our study very preterm and extremely preterm neonates were significantly more frequent in the group of Candida sepsis compared to the non-fungal sepsis group. All low birth weight categories were more frequently represented in neonates with Candida sepsis compared with the non-fungal sepsis group.

Neonatal disease severity scoring systems showed significantly higher values in neonates with Candida sepsis in relation to the non-fungal sepsis group. Severe clinical presentation of neonates with proven sepsis via positive blood culture was demonstrated by the necessarily applied supportive therapy. The risk for fungal sepsis in neonates is high due to aggressive and invasive treatment, such as central venous catheters, mechanical ventilation, parenteral nutrition and prolonged hospitalization (24). In our study, all patients with Candida sepsis had an umbilical vein catheter, received parenteral nutrition and antibiotic therapy. Almost 90% of them required mechanical ventilation, and the mean mechanical ventilation support length was 8 days. Central venous catheters and parenteral nutrition are reported to be a major risk factor for infection with non-albicans Candida species, both of which predispose to the formation of catheter biofilms. Amino acids from parenteral nutrition mediate cell differentiation, that could explain the high incidence of Candida sepsis in neonates with a central venous catheter receiving amino acid-rich parenteral nutrition (24). Mechanical ventilation has been described as a risk factor for neonatal fungal sepsis, although there are also very rare reports describing non- invasive support with continuous positive airway pressure as a risk factor (6). Most of our patients (89.6%) were on mechanical ventilation support.

Commonly, fungal sepsis is reported as the late-onset sepsis, as a study of Ozkan et al., 2014 (4), reported neonatal non-fungal sepsis more frequently than candidemia, with Candida sepsis manifesting as late-onset sepsis or very late-onset sepsis and without early-onset Candida sepsis. Mehara et al., 2013 (25) and Bizzarro et al., 2015 (20), also reported Candida sepsis more often as late-onset than early-onset neonatal sepsis. In our study, Candida sepsis manifested as late sepsis in almost all 48 patients, while non-fungal sepsis had different onset times, and it was predominantly (60%) early-onset.

Signs and symptoms of neonatal fungal sepsis are often subtle and non-specific (16), but enough to suspect, and as we wait for the results of blood culture, we need to use laboratory findings as a diagnostic tool in order not to be late with the right therapy. Laboratory studies used to evaluate neonatal sepsis include a complete blood cell count and differential, measurement of levels of C-reactive protein and other infection markers (26). Laboratory findings in our neonates with Candida sepsis showed differences in infection markers compared to the non-fungal group. The most common abnormalities in neonates with Candida sepsis were an increase in C- reactive protein and leukocytes with thrombocytopenia. They also had a significant rate of anemia and leukopenia compared to the control group. Reports of other mainly state thrombocytopenia (16).

All blood culture isolates in our study were from Candida spp. group without in vitro resistance, which is consistent with some published studies (3-6). There are regional differences in the incidence of the most common Candida species. Through a systematic literature review, we have found out that four Candida species (C. albicans, C. parapsilosis complex, C. tropicalisi C. glabrata complex) are associated with more than 95% cases of neonatal candidemia, but the distribution of these four species is different. In general, Candida albicans was dominantly isolated in Europe (4-7) and North and South America (13, 14), and Candida non-albicans were dominant in Asia (15, 16, 17).

However, more recent studies report the constant growth of non-albicans Candida species, with a frequency of over 50% in some NICU. This is partly associated with an increase in the clinical use of the azole antifungal therapy and prophylaxis (21, 22, 23), although this has also been reported in hospitals where Fluconazole has rarely been used for prophylaxis and therapy (4). Even some earlier reports, such as the Helsinki report (27), mention the Fluconazole resistance phenomenon in a C parapsilosis after more than 10 years of Fluconazole prophylaxis in NICU. Routine use of Fluconazole prophylaxis in this constellation is questionable.

The mortality rate in our neonates with Candida sepsis was 8.3%, while the non-fungal sepsis mortality rate was 5.9%, therefore without significant difference. The mortality rate due to neonatal fungal sepsis varied, and it was mostly high. It goes from 40% (4, 6) up to

75% (28), and is considered low if it was below 20% (29). Mortality rates in other studies are mainly related to known risk factors and their correlation. The length of intensive treatment was 38.2 ± 23.2 days. There was no consensus concerning the duration of therapy, and Fluconazole and Amphotericin B appear to be safe and effective for the treatment of systemic candidal infection in the neonates although more data are required regarding its use in very low birth weight neonates (3). In our study, mild toxic hepatitis was recorded as a complication of the total treatment in 8 neonates (16.7%) with Candida sepsis, while the same complication in the non-fungal sepsis group was recorded in 5.9% of cases. This difference between the observed groups had a slight significance. There are not many reports of treatment complications, mostly reporting mortality rates.

CONCLUSION

Neonatal Candida sepsis has a risky clinical course and outcome. It endangers life, complicates treatment, prolongs NICU stay, increases costs and mortality. Recovery of these neonates depends on timely clinical suspicion, adequate treatment, and supervision. Antifungal susceptibility is also important, which requires monitoring of local epidemiological data to improve treatment.

Candida sepsis is an important cause of morbidity and mortality in critically ill neonates. The incidence at our hospital is 5.2 per 100 admissions to the Neonatal Intensive Care Unit. Perinatal risk factors for fungal sepsis are prematurity and low birth weight. The umbilical vein catheter, parenteral nutrition, antibiotic therapy, and mechanical ventilation are also considered to be significant risk factors. We can conclude that Candida sepsis is an iatrogenic disease of modern neonatal intensive care and healthcare-associated infections that deserves urgent attention for its prevention as well as an effective treatment in order to minimize neonatal morbidity and mortality.

Abbreviations

NICU — Neonatal intensive care unit
SNAP-PE — Score for Neonatal Acute Physiology - Perinatal Extension score
CRIB II — Clinical Risk Index for Babies score
CRP — C-reactive protein
CBC — Complete blood cell
WBC — white blood cell
ANC — absolute neutrophil count
Htc — hematocrit
ITR (I/T ratio) — immature -to-total neutrophil ratio
SD — standard deviation
GA — Gestational age
BW — Birth weight
AS — Apgar score
PRM — premature rupture of membrane
MV — mechanical ventilation
EOS — early-onset sepsis;
LOS — late-onset sepsis

Acknowledgment: None

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

KLINIČKE I LABORATORIJSKE KARAKTERISTIKE NEONATALNE SEPSE IZAZVANE KANDIDOM

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Uvod: Neprestani napredak u neonatologiji povećava preživljavanje nedonoščadi uz primenu višestrukih invazivnih postupaka, što povećava rizik od infekcije, i shodno tome gljivične sepse. Candida je dominantan uzročnik uz porast rezistentnih ne-albicans vrsta. Smrtnost je visoka i zahteva pravovremenu kliničku sumnju i adekvatan tretman da bi se sprečio loš ishod.

Cilj studije bio je analiza kliničkih i laboratorijskih karakteristika Candida sepse u odnosu na bakterijske sepse kod novorođenčadi lečene na odeljenju intenzivne nege. Metode: Restrospektivna trogodišnja kohortna studija sprovedena na Odeljenju intenzivne nege Klinike za dečije bolesti Tuzla (2016-2018) analizirala je kliničke i laboratorijske karakteristike novorođenčad sa Candida sepsom, dokazanom pozitivnom hemokulturom. Kontrolnu grupu činila su novorođenčad koja su u istom periodu lečena zbog dokazane bakterijske sepse. U statističkoj obradi korištene su stan-

dardne metode, a istraživanje je odobrio Etički komitet ustanove.

Rezultati: Od 921 novorođenčeta koje je tretirano u trogodišnjem periodu, Candida sepsa potvrđena hemokulturom pronađena je u 48 (5,2%). Prematuritet i niska porođajna težina bili su najznačajniji faktori rizika, a pogođena novorođenčad imala su ozbiljniju kliničku sliku, češće su primala parenteralnu prehranu, mehaničku ventilaciju, intravenske gamaglobuline i duže su intenzivno lečena. Candida sepsa manifestovala se uglavnom kao kasna. Od laboratorijskih nalaza ova novorođenčad češće su imala porast CRP, anemiju, odstupanja u broju leukocita i trombocitopeniju. Nije bilo razlike u smrtnosti. Oporavilo se 44 novorođenčadi (91,7%), dok je 4 (8,3%) umrlo. Antifungalna terapija trajala je 20,6 ± 6 dana, a intenzivno lečenje 38,2 ± 23,2 dana i bilo je značajno duže u odnosu na kontrolnu skupinu. Svi izolati bili su vrste Candida bez in-vitro rezistencije. Kod 8 novorođenčadi (16,7%) prijavljene su komplikacije tretmana. Zaključak: Candida sepsa u novorođenčadi ugrožava život, otežava lečenje, povećava troškove i smrtnost. Povoljan ishod zavisi od pravovremene kliničke sumnje, adekvatnog lečenja i nadzora. Antifungalna osetljivost takođe je važna i zahteva praćenje lokalne epidemiološke dinamike.

Ključne reči: Candida sepsa, novorođenče, kliničke i laboratorijske karakteristike.

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SANAMED
2019; 14(3): 269–274
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.369
UDK: 616.831-001.31-074-053.2; 616.718.4-001.5-089.881
ID: 281758476
Original article

AN EVALUATION OF ENDOPROSTHESIS AND PERTROCHANTERIC EXTERNAL FIXATOR RESULTS IN ELDERLY INTERTROCHANTERIC FEMORAL FRACTURES

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Primljen/Received 06. 09. 2019. god.
Prihvaćen/Accepted 26. 11. 2019. god.

Abstract: **Objective:** In this study, 14-month clinical outcomes of the endoprosthesis and pertrochanteric external fixator application are retrospectively evaluated in elderly patients with pertrochanteric fractures.

Patients and Method: A total of 45 patients of 65 years old and older (25 females and 20 males) with a mean age of 78.1, who were treated due to intertrochanteric femur fracture between November 2013 and December 2014 and whose controls could be made were included in this study. The deaths that occurred within the postoperative 1 year were not included in the study. 28 patients with endoprosthesis as Group I, and 17 patients with pertrochanteric external fixator as Group II were evaluated.

Results: Table 2 shows the clinical evaluation results of the patients according to different criteria by the groups. The mean operation time was 45 min in Group I and 20 min in Group II. The external fixator application time is significantly shorter. The mean hospital stay was 14 days for Group I and 10 days for Group II. The hospital stay period of the external fixator group is 4 days shorter.

While 7 patients were taken into the intensive care unit in Group I postoperatively, only 1 patient was taken into the same unit in Group II. This difference was significantly in favor of the external fixator group.

While 14 patients in Group I needed a preoperative and postoperative blood transfusion, no patient needed blood transfusions in Group II. External fixator application is significantly more advantageous in terms of patient hemodynamics.

The mean time to postoperatively move the extremity independently in the bed was 24 hours in Group I and 36 hours in Group II.

All patients were exposed to the Harris hip scoring in the postoperative 12. month (the fixator was removed for the external fixator group).

Conclusion: In addition to internal fixation options and endoprosthesis applications in elderly intertrochanteric femoral fractures, an external fixator may also be a good treatment alternative with appropriate patient selection and proper application in accordance with the technique thanks to its short surgical time, less blood loss and easy applicability.

Key words: Elderly patient, proximal femoral fracture.

INTRODUCTION

Intertrochanteric femoral fractures are among the most important fractures that orthopedic surgery encounters frequently, especially in elderly patients (1). The choice of treatment method is challenging for the orthopedist since the bone quality of these patients is low, several elderly diseases that disrupt the general condition of the patient accompany the disease and there is the necessity of treating the fracture as soon as possible (2).

The main aim of the treatment of fractures in this region is to obtain a rigid bone fixation and a mobile hip joint (3). Intramedullary nails, plates, and screws of various types and features, hip prostheses and external fixators are among the treatment options. In these treatment methods, shortness, abductor-adductor, and flexor deficiencies, union, and stabilization problems are the conditions that make the choice of treatment difficult (2,4-11).

In this study, 14-month clinical outcomes of the endoprosthesis and pertrochanteric external fixator application are retrospectively evaluated in elderly patients with pertrochanteric fractures in two groups.

PATIENTS AND METHODS

A total of 45 patients of 65 years old and older (25 females and 20 males) with a mean age of 78.1, who

Table 1. *Distribution of Ewans fracture types according to the Groups*

Fracture Type (Modified Ewans)	Group I (Mean age: 79.6) n = 28	Group II (Mean age: 75.1) n = 17
Type I	13	7
Type II	10	3
Type III	3	3
Type IV	2	0
Type V	0	0
Type R	0	4

were treated due to intertrochanteric femur fracture between November 2013 and December 2014 and whose controls could be made were included in this study. The deaths that occurred within the postoperative 1 year were not included in the study.

Twenty-eight patients with endoprosthesis were evaluated as Group I, and 17 patients with pertrochanteric external fixator as Group II. The fracture types of the patients according to the Modified Ewans (Kyle) classification (12) are shown in Table 1.

Group I patients underwent calcar-assisted bipolar endoprosthesis with spinal anesthesia by three different orthopedic surgeons at the Orthopedics and Traumatology Clinic of Ministry of Health Evliya Celebi Training and Research Hospital affiliated to DPU. Group II patients underwent pertrochanteric external fixator with spinal anesthesia and scope control by the same orthopedic surgeons in the same clinic.

The mean follow-up period was 13.6 months for Group I patients and 14.3 months for Group II patients.

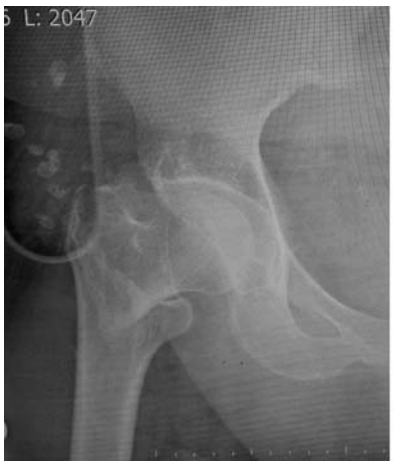

Figure 1: *76y*

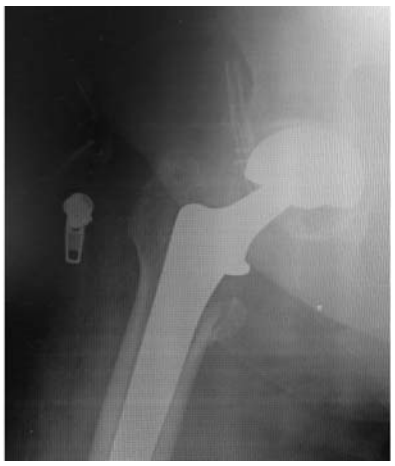

Figure 2. *Postop. 3rd day*

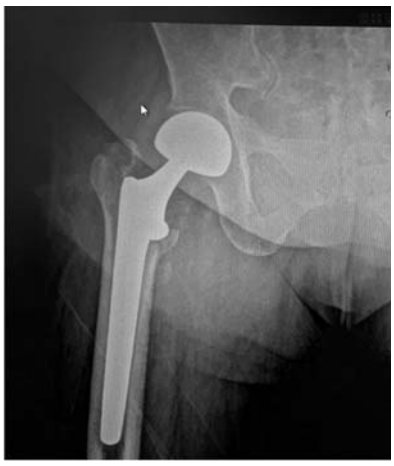

Figure 3*. Postop 3rd month*

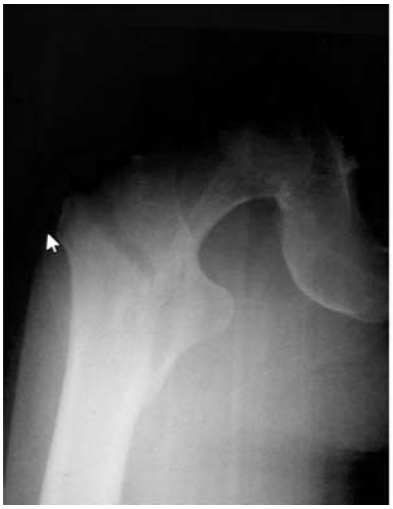

Figure 4. *70y m*

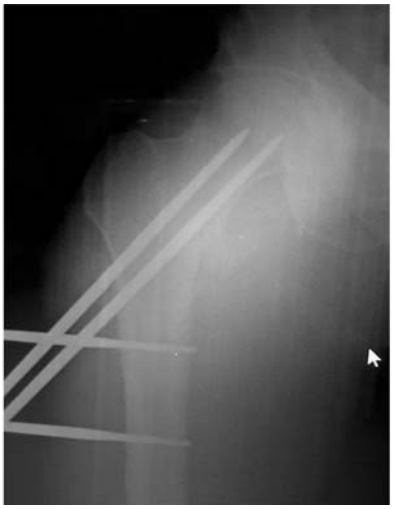

Figure 5. *Postop 3rd day*

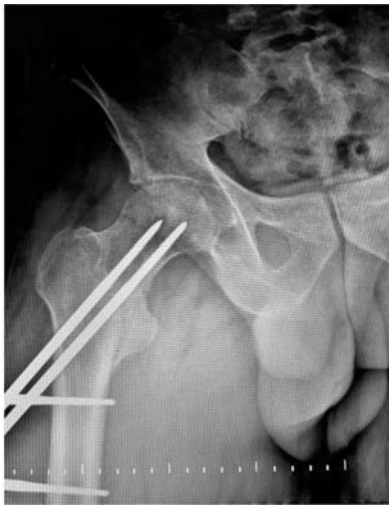

Figure 6. *Postop 4th month*

The fixators were removed in a mean of 7.3 months (4-10 months). The patients who died within the postoperative 1 year were not included in the study. Statistical analyses were performed by the U test at $P < 0.05$ significance level.

The two groups were compared in terms of the mean operation time, length of hospital stay, number of patients requiring intraoperative or postoperative blood transfusion, number of patients taken into postoperative intensive care unit, postoperative time to move the extremity independently in the bed, meantime of walking with walker assistance, mean full weight-bearing time, and number of patients who developed early complications in the first trimester postoperatively.

X-rays of exemplary cases are shown below (Figures 1-6).

RESULTS

Table 2 shows the clinical evaluation results of the patients according to different criteria by the groups.

The mean hospital stay was 14 days for Group I and 10 days for Group II. The hospital stay period of the external fixator group is 4 days shorter.

While 7 patients were taken into the intensive care unit in Group I postoperatively, only 1 patient was taken into the same unit in Group II. This difference was significantly in favor of the external fixator group.

While 14 patients in Group I needed a preoperative and postoperative blood transfusion, no patient needed blood transfusions in Group II. External fixator application is significantly more advantageous in terms of patient hemodynamics.

The mean time to postoperatively move the extremity independently in the bed was 24 hours in Group I and 36 hours in Group II. Although these values were not found to be statistically significant, our clinical observations suggest that patients with external fixators.

The mean time to stand up with postoperative help and support was found to be 48 hours in both groups, thus, no difference was observed between the groups in this respect.

The average time to postoperatively start to bear full weight to the extremity and walk in short distance without the assistance of others was 30 days for Group I and 45 days for Group II. This difference is significantly in favor of the endoprosthesis application.

In Group I, one or multiple of such complications as prosthesis dislocation, early loosening, protrusion, and infection were observed in 4 patients within the postoperative early trimester period, whereas in Group II, one or multiple of such early complications as nail protrusion, reduction loss, and infection were seen in 3 patients; therefore, no significant difference was found between the two groups in terms of early complications.

All patients were exposed to the Harris hip scoring in the postoperative 12. month (the fixator was removed for the external fixator group) and the results are shown in Table 3.

Table 2. *Clinical results*

Parameter	Group I	Group II	p
Average operation time	45 min	20 min	$P < 0.05$
Mean total length of hospital stay	14 days	10 days	$P < 0.05$
Number of patients requiring a blood transfusion	14 patients	–	$P < 0.05$
Number of patients taken in the postoperative intensive care unit	7 patients	2 patients	$P < 0.05$
Mean time to postop move the extremity independently	36 hours	24 hours	$0.05 < p < 0.10$
Meantime to walk with help and walker	48 hours	48 hours	$P < 0.05$
Mean full weight-bearing time	30 days	45 days	$P < 0.05$
Number of patients developing early postoperative complications(*) in the first trimester	4 patients	3 patients	$p > 0.05$

(*) For Group I; Loss of reduction, Nail protrusion, Nail bed infection
For Group II; Dislocation, infection, early prosthesis loosening

Table 3. *Harris Hip Score table in the postop 12th month*

	Group I	Group II	p
< 70 (Poor)	7	4	$p > 0.05$
70-79 (Fair)	15	7	$p > 0.05$
80-89 (Good)	6	4	$p > 0.05$
90-100 (Excellent)	–	2	–

No significant difference was found between the two groups in terms of poor, fair and good results. No good results were seen in the patients in group I, while 2 patients in group II demonstrated good results.

DISCUSSION

Hip fractures can cause many serious complications and even death as they make the patient bed-dependent. Therefore, it is of crucial importance to mobilize the elderly as soon as possible, in order to prevent probable complications arising from bed-dependence and to return the elderly to pre-fracture activity as much as possible. Fracture structure and type are as important as the general condition of the patient in choosing the treatment type (5, 6, 7, 8).

Although the endoprosthesis application seems to be advantageous in terms of early mobilization because it allows early weight-bearing, early mobilization and weight-bearing are also possible in external fixator applications when adequate reduction and stabilization is achieved (9, 12). In our study, there was not much difference in terms of stand up and weight-bearing performances of the two applications.

As in our study, postop mobilization may be delayed due to higher blood loss in endoprosthesis surgeries when compared to external fixator surgeries and to further deterioration of hemodynamic balance (13).

In cases where bone quality is thought to be insufficient, it is recommended to place three shank nails proximally and distally to prevent reduction insufficiency (14).

The incidence of nail bed infection in the treatment of pertrochanteric fractures with external fixator is variable, and rates up to 30% have been reported (9, 14, 15, 16). In our study, severe nail bed infection was seen in 2 cases (11.7%) but this was regressed through frequent dressing and nail bed care, and bone infection did not develop.

One of the most obvious causes of nail bed infection is tension in the tissues and skin and soft tissue damage due to improper placement of the Schanz nails and disruption of circulation in this region (17).

It is reported that the most common causes of infections seen in orthopedic surgery are prolonged operation times and tissue damage (18). Endoprosthesis operations are significantly longer and more traumatic than external fixator applications. The use of external fixators in hip fractures, which began to be used in the 1950s, is easy to apply and its duration is short. However, it is not recommended in extreme osteoporotic bones since insufficiencies may develop (9, 17, 18). Perprosthetic fractures are also frequently seen in excessive osteoporotic bones (19).

During the medullar cavity and insertion of the prosthesis in endoprosthesis surgery, coercion of the hip with excessive external rotation and adduction in lateral intervention and its coercion to excessive internal rotation in posterolateral procedure increases the risk of micro embolism (20).

In the application of external fixator, less microembolism and vascular system coercion occur due to the fact that the patient and the extremity is not given a coercive position and the medullary cavity is not performed.

Also in external fixator application, the fact that the patient's own bone tissue and hip joint are protected provides the opportunity to shift to endoprosthesis when necessary.

CONCLUSION

In addition to internal fixation options and endoprosthesis applications in elderly intertrochanteric femoral fractures, an external fixator may also be a good treatment alternative with appropriate patient selection and proper application in accordance with the technique thanks to its short surgical time, less blood loss and easy applicability.

Abbreviations

DPÜ: Dumlupınar University

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

EVALUACIJA REZULTATA UGRADNJE ENDOPROTEZE I PERTROHANTERNOG SPOLJAŠNJEG FIKSATORA KOD INTERTROHANTERNOG PRELOMA FEMURA KOD STARIJIH PACIJENATA

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Cilj: U ovoj studiji, retrospektivno je analiziran 14-mesečni klinički ishod primene endoproteze i pertrohanternog spoljašnjeg fiksatora, kod starijih pacijenata sa pertrohanternim prelomima.

Pacijenti i metode: U studiju je uključeno ukupno 45 pacijenata starosti preko 65 godina (25 žena i 20 muškaraca), prosečne starosti od 78,1 godinu, koji su mogli biti praćeni na redovnim postoperativnim kontrolama, a koji su lečeni zbog intertrohanternog preloma butne kosti, između novembra 2013. i decembra 2014. godine. Smrtni slučajevi koji su se dogodili u toku postoperativne godine nisu uključeni u studiju.

Evaluirani su pacijenti podeljeni u dve grupe i to: 28 pacijenata sa endoprotezom koji su predstavljali grupu I, a 17 pacijenata sa pertrohanternim spoljnim fiksatorom, grupu II.

Rezultati: Tabela 2 pokazuje rezultate kliničke evaluacije pacijenata prema različitim kriterijumima po grupama. Srednje vreme trajanja operacije bilo je 45 minuta u Grupi I i 20 minuta u Grupi II. Vreme aplikacije spoljnjeg fiksatora je znatno kraće. Prosečan boravak u bolnici za grupu I bio je 14 dana, a za Grupu II 10 dana. Period boravka u bolnici za grupu sa spoljnim fiksatorima je 4 dana kraći.

Dok je 7 pacijenata iz Grupe I postoperativno lečeno na odeljenju intenzivne nege, samo 1 pacijent iz Grupe II je lečen na ovom odeljenju. Ova razlika ide značajno u korist grupe sa spoljnim fiksatorima. Preoperativnu i postoperativnu transfuziju krvi je trebalo 14 pacijenata iz Grupe I, dok nikome iz Grupe II nije bila potrebna transfuzija. Primena spoljnog fiksatora je značajno povoljnija u pogledu hemodinamike pacijenta.

Srednje vreme za pomeranje ekstremiteta u krevetu bilo je 24 sata u Grupi I, a 36 sati u grupi II. Svi pacijenti su bili evaluirani prema Harisovom skoring sistemu u postoperativnom 12.mesecu (fiksator je uklonjen za grupu spoljnih fiksatora).

Zaključak: Pored opcija za unutrašnju fiksaciju i aplikacije endoproteze kod starijih pacijenata sa intertrohanteričnim frakturama femura, spoljni fiksator takođe može biti dobra alternativa lečenju uz odgovarajući odabir pacijenata i pravilnu primenu u skladu s tehnikom zahvaljujući kratkom vremenu operacije, manjem gubitku krvi i jednostavnoj primenjivosti.

Ključne reči: stariji pacijenti, fraktura proksimalnog femura.

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SANAMED
2019; 14(3): 275–278
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.330
UDK: 616.853-085.84
ID: 281838348
Case report

EPILEPTIC SEIZURES AS THE FIRST MANIFESTATION OF THE FRONTOPARIETAL ARTERIOVENOUS MALFORMATION OF THE BRAIN

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Primljen/Received 16. 04. 2019. god.

Prihvaćen/Accepted 19. 10. 2019. god.

Abstract: **Introduction:** Arteriovenous malformations of the brain include a group of congenital disorders in the early development of arterial-venous blood vessels of the brain. Their clinical presentation is most common in the form of a brain hemorrhage, epileptic seizures, and headaches.

Case report: We showed a man who at the age of 28 early in the morning after breakfast had the first generalized tonic-clonic seizure. After the second unprovoked epileptic seizure, antiepileptic therapy was introduced. The brain scanner showed the existence of arteriovenous malformations in the right frontoparietal region. As the size of the malformation was less than 30mm, it was decided that the patient should be treated with Gamma knife radiosurgery. After the successful radiosurgery together with the antiepileptic drugs treatment, the patient is in a stable 1.5 year- long remission of epileptic seizures without neurological failures.

Conclusion: Epileptic seizures can be the initial clinical manifestations of arteriovenous malformations of the brain. With an early diagnosis, adequate antiepileptic drugs therapy and neurosurgery, radiosurgery (Gamma Knife), which is often necessary, many symptomatic epilepsies enter a stable remission of epileptic seizures.

Key words: arteriovenous malformations, brain, epileptic seizures, radiosurgery, gamma knife.

INTRODUCTION

Symptomatic epilepsies constitute a significant percentage of epilepsies in both the early and adult stages of human development, with vascular diseases of the brain (arteriovenous malformations, cavernomas, and aneurysms) being particularly significant. Arteriovenous malformations (AVM) of the brain represent a congenital disorder in the early differentiation of the development of arterial and venous blood vessels of the brain by establishing direct contact between the arteries and veins without the presence of capillaries (1). An AVM structurally consists of the pathological vascular web, the "nest" - nidus, which is composed of one or more supply arteries that continue on the main drainage vein and its collector branches. Because of this, an AVM shows a pathological tendency of frequent hemorrhages with deposits of hemosiderin in the surrounding brain tissue, which creates potential conditions for epileptogenesis, or the occurrence of epileptic seizures (2). By localization, AVMs are classified into supratentorial and infratentorial, superficial (cortical) and deep (subcortical) malformations. The main predictor factors for the assessment of operational risk for each AVM are localization, size and type of venous drainage (3). The most common effects of an AVM on surrounding brain structures are circulatory disorders in terms of microhemorrhage, the "steal" phenomena, the "mass" effects caused by the AVM size and its compression on adjacent structures with possible obstruction of the flow of liquors and the development of hydrocephalus (4). In the pathophysiological sense, an AVM among other things, causes "blood steal" ("the steal phenomena") in the adjacent regions of the brain, because normal blood flow is diverted within the AVM, thus bypassing the surrounding brain structures. This type of "blood steal" from the surrounding brain, with consecutive hypoperfusion, carries a high risk of epileptic seizures (5, 6). The predominant clinical manifestation of an AVM is brain hemorrhage (subarachnoidal, intracerebral, and intraventricular, or any combination thereof) (7). It is thought that about 50-70% of patients with an AVM experience brain hemorrhage. An average of 8% of subarachnoid hemorrhage (SAH) is caused by an AVM. AVM hemorrhage carries a risk of death in 10-15% of cases. It is thought

that 15-20% of all sudden deaths are caused by an AVM (8, 9, 10). Crawford et al. 1986 (11), in their study of monitoring AVM patients for 20 years, found that the risk of hemorrhage was 42%, epilepsy 18%, neurological deficiency 27% and fatal outcome 29%. The mortality rate in the initial hemorrhage of people with an AVM ranges from about 10%-15%, and in aneurysm ruptures is about 50% (10). Epileptic seizures represent the second most common clinical manifestation of an AVM, more commonly seen in patients with severe malformations. Epileptic seizures are an initial symptom in 24-47% of patients with an AVM (11). The most common type of seizure is generalized motor seizures, ie focal seizure with generalization (55.8%), then focal seizures without secondary generalization (12, 13). A superficially localized AVM is mainly clinically manifested by epileptic seizures, while the deep ones have a greater tendency to bleed (14). The dominance of focal seizures with generalization is the consequence of chronic cerebral hypoxia around the AVM and hemosiderin deposits caused by micro-hemorrhages. Headache is also a common clinical manifestation, and it appears as an initial symptom in the range of 5-35% of cases and results in an increase in pressure in the venous sinuses (15). Neurological deficiency occurs in about 27% of cases (11). The natural history of an AVM is that the patient has an annual risk of bleeding of 3%, with a risk of developing an accompanying neurological deficiency of 35% and a fatal outcome of 10% (16).

AVM diagnostics is most commonly performed via computerized brain tomography (CT, MSCT), magnetic resonance imaging (MRI, MRA), and cerebral angiography (17). Computerized brain tomography, magnetic resonance imaging, and transcranial doppler (TCD) are considered to be basic non-invasive diagnostic methods for AVMs. There is a tendency in modern neurosurgery towards using non-invasive methods in AVM diagnostics, although the use of angiography is still dominant. The treatment of a brain AVM with antiepileptic drugs (AED) gives good results in more than 68% of cases and the refractoriness of epileptic seizures to AED was present in about 32% of cases. Generalized motorseizures are dominant in 94.7% of cases and focal seizures occur in 5.3% of cases. Good medication control of epileptic seizures supports the view that there is no need for emergency surgical treatment of an AVM. Treatment of an AVM with palliative methods is often ineffective in terms of reducing morbidity and healing (18). The surgical procedure leading to complete healing is complete excision of the AVM with noremaining residue (19, 20). Other neurosurgical methods are embolization and radiosurgery (focused gamma radiation-Gamma Knife) (21, 22). Post-operatively, in an AVM there is a decrease in the frequency of seizures in 14-54% of cases, while in 7-22% of patients de novo epilepsy develops postoperatively (23). Patients who are deemed to carry a high risk of neurosurgical treatment of an AVM (resection, embolization or radiosurgery) are subject to drug treatment.

CASE REPORT

We showed a patient, aged 28, who reported to the neurologist due to the onset of the first epileptic generalized tonic-clonic (GTK) seizure. The seizure took place in the morning after breakfast and was not followed by prodromes or focal symptomatology. There was a sudden loss of consciousness with a fall and occurrence of GTK spasms and urination. After 2-3 minutes of the seizure, the patient regained his consciousness, felt heaviness in his body, exhaustion and nausea. He was healthy in the previous few days, he did not have headaches, and did not suffer from nervousness or insomnia. The vital signs upon admission were: blood pressure 120/80 mmHg, cardiac frequency 80/min, body temperature 36.7 °C. There were no abnormalities in the neurological findings. The values of routine biochemical and laboratory analyses of serum (glycemia, Er, Hgb, Le, ESR, urea, creatinine, bilirubin, transaminases, total proteins, albumin, Na, K, Mg, Ca) and urine were within reference limits. There was no evidence of previous epileptic seizures or hereditary epilepsy. Electroencephalography (EEG), which was performed on the day of the seizure, resulted in normal findings, ie epileptiform graft elements were not registered. Since it was the first unprovoked seizure with normal EEG findings, antiepileptic therapy was not included. A month after the onset of the first GTK seizure, a second epileptic seizure occurred, the same clinical manifestation lasting 3-5 minutes. An EEG recording was performed and did not register epileptic activity. The patient then had a CT, CTA of the brain that showed the presence of a 25 mm arteriovenous malformation in the right frontoparietal region (Clinic of neurosurgery in Belgrade, Serbia). The therapy includes AED valproate at an initial dose of 0 + 0 + 250 mg/day, with a gradual increase in the dose of 250 mg per week, to an effective dose of 500 + 0 + 500 mg/day. The patient was subjected to neurosurgical treatment and then, due to the size of the AVM (<30 mm), it was decided to carry out a Gamma Knife radiosurgery (Acibadem hospital in Istanbul, Turkey). On the first day after radiosurgery, another GTK seizure occurred during sleep, and the EEG recorded focal spikes and theta waves on the right frontoparietal without propagation to the homologous region of the opposite hemisphere. The dose of valproate was increased to 500 + 0 + 1000 mg/day after which there were no further seizures. The patient is in a stable 1.5-year remission of epileptic seizures,

without neurological failures and with regular neurosurgical and epileptologist examinations.

DISCUSSION

Arteriovenous malformations of the brain represent a congenital disorder in the early differentiation in the development of arterial and venous blood vessels of the brain. Due to their size, bleeding tendency and supratentorial localization often cause symptomatic epileptic seizures of the generalized or focal type. Epileptic seizures are treated with AED, but since they are symptomatic seizures associated with an AVM, they are usually drug-resistant (24). When an AVM is proven to cause epileptic seizures, neurosurgery, ie radiosurgery is indicated. Gamma Knife is stereotactic radiosurgery for the treatment of tumors and brain metastases (benign and malignant) which are smaller than 30mm and well limited. It is performed without general anesthesia, without opening the skull, lasting from 30 minutes to 2h, and after the treatment, the patient can go home the same day or the next day. Gamma Knife directs radiation to a focussed pathological spot in the brain that is computer-determined so that gamma rays destroy the tumor tissue with the maximum sparing of surrounding healthy tissue. Earlier, since there was no Gamma Knife, even in the case of a small tumor, the whole brain was radiated. Our case report shows that epileptic seizures can be the first symptom of a brain AVM and that Gamma knife treatment together with AED (before and after treatment) leads to a complete remission of epileptic seizures. Our case report confirms works from the literature that Gamma Knife neurosurgery may be a prominent alternative to the treatment of brain AVM (25, 26). Most neurosurgical studies indicate that the main predictor of post-radiation epileptic seizures is the existence of an AVM nidus residue after the treatment (27). Thus, the primary goal of stereotactic radiotherapy is the complete obliteration of the AVM nidus, which ensures the conditions for a complete remission of epileptic seizures and gradual elimination of anti-epileptic drugs (28).

CONCLUSION

Epileptic seizures can be the initial clinical manifestations of arteriovenous malformations of the brain. With an early diagnosis (CT, MRI, EEG), adequate antiepileptic drugs therapy and Gamma Knife radiosurgery, which is often necessary, a complete remission of epileptic seizures is established in most patients, and the use of antiepileptic drugs is stopped. Using this procedure and treatment, many symptomatic epilepsies enter a stable remission of epileptic seizures.

Abbreviations

AVM — arteriovenous malformations
SAH — subarachnoid hemorrhage
GTC — generalized tonic-clonic
AED — antiepileptic drug
EEG — electroencephalography
CT — computed tomography
MSCT — multi-slide computer tomography
MRI — magnetic resonance image
MRA — magnetic resonance angiography
TCD — transcranial doppler

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

EPILEPTIČKI NAPAD KAO PRVA MANIFESTACIJA FRONTOPARIJETALNE ARTERIOVENSKE MALFORMACIJE MOZGA

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Uvod: Arteriovenske malformacije mozga obuhvataju grupu kongenitalnih poremećaja ranog razvoja arterijsko-venskih krvnih sudova mozga. Njihova klinička prezentacija se najčešće javlja u vidu moždanog krvarenja, epileptičkih napada i glavobolje. **Prikaz bolesnika:** Prikazali smo muškarca koji je u 28 godinini starosti u jutarnjim satima, nakon doručka, imao prvi generalizovani toničko-klonički epileptički napad. Nakon drugog neprovociranog epileptičkog napada uvedena je antiepileptička terapija. Skener mozga je pokazao postojanje arteriovenske malformacije u desnom fronto-parijetalmom regionu. Kako je veličina malformacije bila manja od 30 mm odlučilo se za radiohiruško lečenje gama nožem (gamma knife). Nakon uspešno sprovedene stereotaksične radiohiruške terapije uz antiepileptičke lekove pacijent je u stabilnoj 1,5 g. re-

misiji epileptičkih napada i bez neuroloških ispada. **Zaključak:** Arteriovenske malformacije mozga mogu se manifestovati epileptičkim napadom kao inicijalnim kliničkim znakom. Ranom dijagnozom, adekvatnom antiepileptičkom medikamentoznom terapijom i često nephodnim neurohiruškim, odnosno, radiohiruškim tretmanom (gama nož), mnoge simptomatske epilepsije ulaze u stabilnu remisiju epileptičkih napada.

Ključne reči: arteriovenske malformacije, mozak, epilepsija, napadi, radioiohirurgija, gama nož.

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SANAMED
2019; 14(3): 279–281
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.354
UDK: 616.45-003.4
ID: 281830156
Case report

A CASE OF EPITHELIAL ADRENAL GLAND CYST

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Primljen/Received 28. 07. 2019. god.

Prihvaćen/Accepted 10. 10. 2019. god.

Abstract: **Introduction:** Adrenal gland cysts are relatively rare cystic lesions, which are usually discovered incidentally with the widespread use of radiological imaging techniques.

Case report: We reported a clinical case of a 36-year –old woman who presented with a 6 months history of right flank discomfort. The contrast-enhanced abdominal computed tomography revealed a well-circumscribed cystic lesion with a capsule in the Morrison's pouch measuring 57 x 51 mm. On abdominal magnetic resonance imagining (MRI), the cystic lesion exhibited a hypointensity on T-1 weighted images and hyperintensity on T-2 weighted images. Surgery was decided because of lesion size and doubts concerning its etiology. The final histopathological diagnosis was an epithelial cyst of the adrenal gland.

In summary, epithelial adrenal cysts are uncommon retroperitoneal lesions. In our case, open adrenalectomy was performed and the prognosis was excellent.

Key words: Adrenal, epithelial cyst, adrenal lesion, adrenal gland.

INTRODUCTION

Adrenal gland cysts are relatively rare cystic lesions, which are usually discovered incidentally with the widespread use of radiological imaging techniques. However, they may be presented with flank pain or gastrointestinal symptoms.

Cysts of the adrenal gland have been categorized into four subtypes by origin: pseudocysts, endothelial cysts, epithelial cysts and parasitic cysts (1). Epithelial cysts of the adrenal gland are uncommon accounting for only 9% of all adrenal cysts (2). Although adrenal cysts are benign in nature, some pieces of literature indicate that some cysts may be malignant with an incidence of 7% (3).

CASE REPORT

We reported a clinical case of a 36-year –old woman who presented with a 6 months history of right flank discomfort. Physical examination did not reveal any abnormalities. The contrast-enhanced abdominal computed tomography revealed a well-circumscribed cystic lesion with a capsule in the Morrison's pouch measuring 57 x 51 mm. On abdominal magnetic resonance imagining (MRI), the cystic lesion exhibited a hypointensity on T-1 weighted images and hyperintensity on T-2 weighted images (Figure 1). On admission, all laboratory examinations and adrenal-related hormones in the patient were in the reference range, so we ruled out any adrenal endocrine dysfunction. Surgery was decided because of lesion size and doubts concerning its etiology. An uncomplicated transabdominal right adrenalectomy was performed. She was discharged on the sixth postoperative day. The gross pathological examination revealed cystic lesion with dimensions 7 x 6 x 4 cm, weighting 116 g with the attached ad-

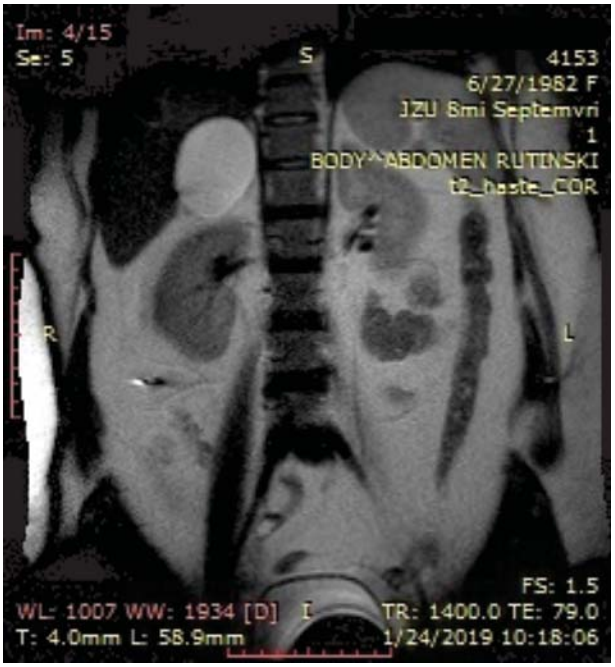

Figure 1. *MRI of the right adrenal cystic lesion*

renal gland. On microscopical examination, the cyst had a thin wall composed of collagenous tissue lined by cuboidal cells. Immunohystochemically, the cyst lining was positive for CKAE1/A3. The final histopathological diagnosis was an epithelial cyst of the adrenal gland.

DISCUSSION

Adrenal gland cysts are usually unilateral and commonly appear in the third and sixth decade of life (1). The male to female ratio is 1:3 (1). Most of them are asymptomatic lesions but when they have a large size, the symptoms include abdominal or flank pain and gastrointestinal symptoms. Rarely they can be presented with hypovolemic shock caused by bleeding inside the cyst (4) or sepsis caused by infection of a pseudocyst (5).

The majority of adrenal cystic lesions are asymptomatic and endocrine nonactive and may be incidentally detected by radiographic techniques (ultrasound, computed tomography, and magnetic resonance). An ultrasonographic finding of adrenal cysts includes well marginated, anechogenic lesions (6). CT scans demonstrate hypodense, non-enhancing masses (7). Abdominal MRI may show a hypointensity on T-1 weighted images and a hyperintensity on T-2 weighted images (7).

Adrenal gland cysts are classified in 1966 by Foster into four groups by histological type: endothelial, epithelial, pseudocysts and parasitic cysts. The epithelial cysts have been subdivided upon purpose into four groups: glandular or retention cysts, cystic adenomas and embryonal cysts (1). Microscopically, the epithelial cysts are lined by a single layer of cytokeratin positive cells.

Main indications for surgical excision of this adrenal cystic lesions are to relieve mass effect symptoms, to remove endocrine active adrenal cysts, to exclude malignancy and to treat complications. For adrenal cysts larger than 3.5 cm aspiration of adrenal cysts is recommended. Conservative management is indicated for small asymptomatic endocrine no active cysts smaller than 6 cm with aspiration only and follow up with interval CT scans (5).

In summary, epithelial adrenal cysts are uncommon retroperitoneal lesions. In our case, open adrenalectomy was performed and the prognosis was excellent.

Abbreviations

CT — computed tomography
MRI — magnetic resonance imaging

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

PRIKAZ SLUČAJ EPITELIJALNE NADBUBREŽNE CISTE

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Uvod: Ciste nadbubrežne žlezde su relativno retke cistične lezije, koje se obično otkrivaju slučajno zbog široke primene radioloških tehnika.

Prikaz slučaja: Prikazujemo slučaj žene, 36 godina starosti, koja je imala 6. mesečnu istoriju osećaja nelagodnosti u desnom lumbalnom predelu. Kontrasna tomografija abdomena otkrila je dobro ograničenu inkapsuliranu cističnu leziju u Morisonovom prostoru, dimenzija 57 x 51 mm. Na magnetnoj rezonanci abdomena cistična lezija se prikazala sa hiposignalom na T-1 slikama i hipersignalom na T-2 slikama. Urađena je hirurška ekscizija lezije zbog njene veličine i sumnjive etiologije. Konačna histopatološka dijagnoza bila je epitelna cista nadbubrežne žlezde.

Ukratko, epitelne ciste adrenalnih žlezda su retke retroperoperitonelne lezije. U našem slučaju, urađena je otvorena adrenalektomija sa odličnom prognozom.

Ključne reči: nadbubreg, epitelna cista, nadbubrežna lezija, nadbubrežna žlezda.

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SANAMED
2019; 14(3): 283–285
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.356
UDK: 616.831-009.7-085.846; 615.846
ID: 281805836
Case report

COMBINATION OF TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) AND OCCIPITAL NERVE BLOCK IN REFRACTORY CLUSTER HEADACHE

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Primljen/Received 08. 08. 2019. god. Prihvaćen/Accepted 02. 10. 2019. god.

Abstract: Cluster headache (CH) can be extremely resistant to medical treatment. There are no prognostic signs that can previously determent persistence and resistance to medical treatment. We report on medical treatment-resistant cluster headache that relieved with transcutaneous electric nerve stimulation treatment followed with occipital nerve block (ONB) method. A 39-year-old male patient that was diagnosed with a cluster headache that was resistant to a combination of the highest tolerated drug dose of verapamil, valproic acid, and oral methylprednisolone. Due to its resistance to medical treatment for one month, in addition, treatment with transcutaneous electric nerve stimulation and following (ONB) showed sudden and permanent control of headache.

Key words: cluster headache, nerve block, transcutaneous electric nerve stimulation, refractory cluster headache, occipital nerve.

INTRODUCTION

(CH) which is also known as trigeminal autonomic cephalgia represents the most common type of primary headache. (CH) earned clinical concern because it tops the list of severe headaches so early and accurate diagnosis will reduce the patient suffering, accurate diagnosis and treatment are vital. Cluster headaches are a unilateral headache with at least one autonomic symptom ipsilateral to the headache. These headaches occur between every other day up to eight times a day. They usually occur at approximately the same time of day, most often at night. Most patients are episodic, with daily attacks for weeks to months, followed by a remission for months to years.

CASE PRESENTATION

We report on a 39-year-old male patient that was diagnosed in July 2002 with (CH). Cluster headache diagnosis was made according to the International Classification of Headache Disorders (ICHD-III).

No previous history of head trauma or meningitis. His attacks were right-sided periorbital and 2-3 attacks per day lasted for a proximal 60 days. He is on anti-TNF –alpha as he was diagnosed with ankylosing spondylitis, then one year later he experienced the CH bouts, severe insomnia was the cardinal concomitant feature.

In 2004 and 2005 years he reported right-sided cluster headaches that lasted for one month. Brain magnetic resonance imaging (MRI) (Figure 1) and Brain Magnetic resonance angiography (MRI) were normal (Figure 2). Prophylactic medical treatments in most attacks where verapamil 120 mg/day, valproic acid 1000 mg/day and methylprednisolone 40 mg/day. On attacks using Sumatriptan 6 mg subcutaneous and Oxygen inhalation.

Remission period from the year 2005-2010 with no attack. In February 2010 after maxillary sinusitis

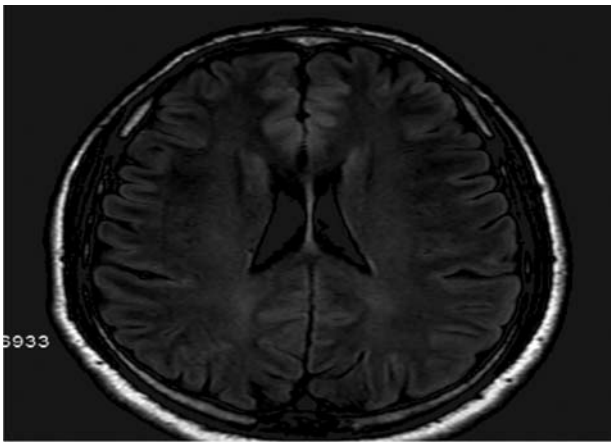

Figure 1. *Normal Brain MRI. Axial plane FLAIR sequence*

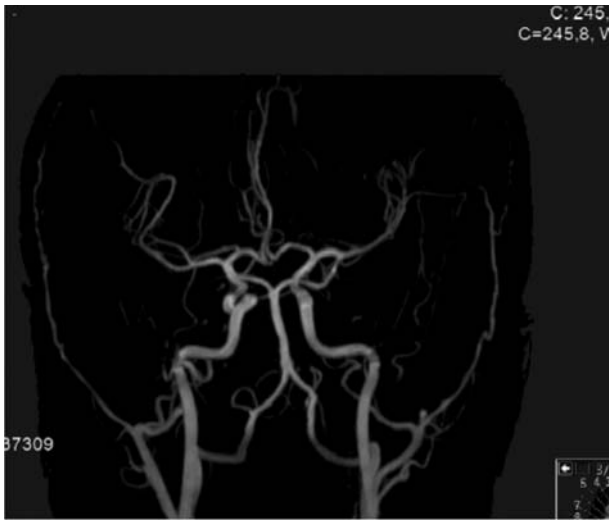

Figure 2. *Normal Brain MRA angiography. No stenosis or sign of vasculitis*

operation, headaches and effective sinusitis medical treatment reoccurred but with more severe duration and persistence. In the evaluation of the ear and nose diseases specialist, it was determined that there was no problem in terms of sinusitis. In 2010 attacks repeated for 92 days. Remission period was from the 2010-2014.

In July 2014 right-sided periorbital headache lasted for approximately 80 days. Lamotrigine 400 mg/day, verapamil 240 mg/day was used for prophylaxis and naproxen 750 mg for attacks.

In October 2018 right-sided CH attacks lasted more than 50 days. Verapamil and valproic acid combination and methylprednisolone oral treatment showed pour results. Medical treatment of all CH episodes lasted at least 60 days or longer and during these medical prophylaxes, CH bouts repeated frequently. We decided to switch to the TENS method in search of a more effective solution for these verity and frequency of CH attacks. Transcutaneous electrical nerve stimulation (TENS) is a non-invasive peripheral stimulation technique used to relieve pain. During TENS, pulsed electrical currents are delivered across the intact surface of the skin to activate underlying nerves.

After right-sided (TENS) ophthalmic brunch dermatome stimulation on the second day, he reported dramatic relive in pain that was more than 1/10 relieve on the pain scale. The patient was recommended to use the TENS device 30ìs pulse width, 12.000 Hz frequency and 4 mA current intensity for a fixed period of 20 minutes on the right periorbital area (1). TENS device dual-channel LT 3060 was used. In the initial phase, pain relief was 1-2/10 on the pain scale. After 16 days, CH reoccurs and after oral methylprednisolone 50 mg/day, right side occipital nerve block with local bupivacaine % 0.5 and 2 mg dexamethasone (2, 3), pain control was fully achieved. In this patient, this is the first time that complete control of CH pain was achieved in the second week. To date, the patient has not experienced pain.

DISCUSSION

CH may be resistant to medical treatment. In these patients, medical treatments are frequently changed during the treatment course. These patients have to receive multiple medical treatments and often face drug side effects. Due to multiple drug use and side effects our patient, was able to tolerate the above-mentioned doses. In this case, we have discussed the possibility of the reduction of refractory CH with TENS and occipital nerve block procedure as a treatment method in patients resistant to medical treatment. In the literature, we found that this method does not provide a clear frame work for head pain treatments (3, 4, 5). In our case probably underlying disease as may be the reason for refractory cluster headache. Because TENS was the short-lasting idea of adding occipital nerve blockade have provided full control of pain. The patient is still experiencing a painless life. With this combination treatment, we were surprised to see that the pain is completely controlled in very short time duration.

CONCLUSION

TENS has shown to be effective and safe in drug-resistant headache prophylactic treatment but most of the published clinical reports are limited to clinical case reports. ONB also has been shown to be effective in refractory CH. In our case, TENS and ONB achieved fast painkilling but it was a short time in the case of TENS compared to ONB. With this case, medical treatment-refractory CH patients suggest that two different methods of combination may work in pain control.

Abbreviations:

AS — ankylosing spondylitis
CH — cluster headache
Hz — hertz
ONB — occipital nerve block
TENS — transcutaneous electric stimulation
TNF-α — Tumor necrosis factor-alpha

Conflict of Interest: The author declare that there was no conflict of interest.

Source of support: None

Acknowledgement: This research did not receive any specific grant from funding agencies or non-profit sectors.

Licensing

Sažetak

KOMBINACIJA TRANSKUTANE ELEKTRIČNE STIMULACIJE NERAVA I BLOKA OKCIPITALNOG NERVA U LEČENJU REFRAKTORNIH KLASTER GLAVOBOLJA

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Klaster glavobolja može biti izuzetno otporna na lečenje. Ne postoje prognostički znaci koji mogu prethodno odrediti upornost i otpornost na medicinsko lečenje. Predstavljamo klaster glavobolju otpornu na lečenje koja je redukovana transkutanim tretmanom električne stimulacije nerva praćenim blokadom okcipitalnog nerva. Radi se o pacijentu, 39 godišnjem muškarcu, sa dijagnostikovanom klaster glavoboljom otpornom na kombinaciju najveće tolerisane doze verapamila, valproične kiseline i metilprednizolona. Zbog otpornosti na medicinski tretman u roku od jednog meseca, rađen je dodatni tretman transkutanom električnom stimulacijom nerava i blokadom okcipitalnog nerva, koji su pokazali iznenadnu i trajnu kontrolu glavobolje.

Ključne reči: klaster glavobolja, nervni blok, transkutana električna stimulacija nerava, refraktorna klaster glavobolja, okcipitalni nerv.

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SANAMED
2019; 14(3): 287–290
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.365
UDK: 616-002.52-06; 616.153-097
ID: 281854988
Case report

SECONDARY ANTIPHOSPHOLIPID SYNDROME REVEALED BY THE SUDDEN ONSET OF PNEUMONIA - CASE REPORT

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Primljen/Received 05. 09. 2019. god. Prihvaćen/Accepted 29. 11. 2019. god.

Abstract: **Introduction:** Secondary antiphospholipid syndrome (SAPS) is APS that occurs in the context of another medical condition. Although antiphospholipid antibodies (aPL) can occur in patients with viral, bacterial, or protozoal infections, they are rarely associated with thrombosis.

Aim: To present an uncommon case of pneumonia and pleural effusion complicated with pulmonary thromboembolism in a patient with systemic lupus erythematosus (SLE), due to non-diagnosed secondary antiphospholipid syndrome.

Case report: A 28 years old woman, never pregnant, with a family history of systemic lupus erythematosus, has been suffering from SLE from the age of 18. She had only articular and skin manifestations, without internal organ involvement. She has been taking Methotrexate (10 mg weekly) and Prednisone (5 mg daily) in the previous 10 years. She was presented at the Emergency department with the radiological finding of pleuropneumonia followed by temperature up to 39C, shortness of breath, cough, fatigue, and weakness.

Results: She was treated initially with three antibiotics and thoracocentesis. She developed pulmonary thrombosis without deep venous thrombosis. Laboratory findings were: ESR = 37 mm/h, CRP = 2+, ANA = 1/80 peripheral, RF negative, anti-dsDNA = 147 (positive > 40), anti-Sm negative, anticardiolipin IgG antibody 158 GPL (up to 12), anticardiolipin IgM antibody 5.5 MPL (up to 10), anti-beta2-glycoprotein IgG and IgM were negative and lupus anti-coagulant was 88" (18"-55"). The patient underwent Heparin and Warfarin treatment, by checking INR to be in a 2.6 to 3.5 range. Prednisolone and Hydroxychloroquine were also started.

Conclusion: All patients suspected with SLE should be evaluated for antiphospholipid antibodies (APL). However, APS diagnosis requires both clinical and laboratory features.

Key words: secondary antiphospholipid syndrome, antibodies, systemic lupus erythematosus, autoimmunity, thrombosis.

INTRODUCTION

Antiphospholipid syndrome (APS)or Hughes Syndrome is an autoimmune disordercaused by the blood clots forming increased risk accompanied by one of antiphospholipid antibodies (APL): anticardiolipin antibodies (aCLA), anti-beta2-glycoprotein (GP1) antibodies and/or lupus anticoagulant (LA), registered in two or more occasions 12 weeks apart, resulting inarterial/venous thrombosis and/or fetal loss (1, 2). APS can be primary-not accompanied by other autoimmune disorders and secondary-connected with mixed connective tissue disease, such as the systemic lupus erythematosus is (2, 3).

APS has a variety of manifestations: it can lead to metabolic syndrome X, it can affect cardiovascular system leading to valve disease, accelerated hypertension and acute coronary syndrome or neurological system causing tinnitus, Morbus Meniere, family headache, migraine, myelopathy and epilepsy, it can have orthopedic manifestations such as spontaneous fractures, avascular necrosis, and algoneurodistrophy and pul-

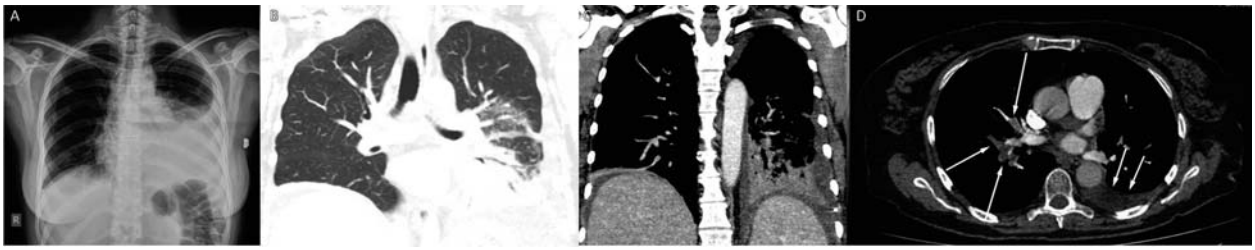

Figure 1. *Consolidation of posterobasal and laterobasal segment of the left lower lobe with positive air bronchogram phenomenon and with pleural effusion at the same side consistent with pleuropneumonia. Additionally, ground-glass opacification within an apical segment of the left lower lobe is visible as a sign of inflammatory changes (A, B, C); D) Pulmonary arteriography showing thrombosis of the right pulmonary artery*

monary manifestations as well like embolic, primary and secondary pulmonary hypertension and thrombosis of the pulmonary artery (2). Pulmonary embolism may be the first APS manifestation and recurrent pulmonary emboli may lead to pulmonary hypertension (4).The aim of this study was to present an uncommon case of pneumonia and pleural effusion complicated with pulmonary embolism in a patient with systemic lupus erythematosus (SLE), due to non-diagnosed secondary antiphospholipid syndrome.

CASE REPORT

A 28 years old woman has been suffering from SLE from the age of 18. She had only articular and skin manifestations, without internal organ involvement. She has not been regularly followed up, and her last evaluation at the Rheumatology Clinic was one year ago.She has been taking Methotrexate (10 mg weekly) and Prednisone (5 mg daily) in the previous 10 years. She was married, but never became pregnant. Her antiphospholipid antibodies were never checked up. She had a positive family history for SLE: her mother was diagnosed with it when she was 40. The patient was presented atthe Emergency department with high temperature up to 39C, shortness of breath, cough, fatigue, and weakness. On physical examination she was pale, but her hands were cyanotic. Auscultation has revealed decreased breath sounds, absent in the basal parts of the left lung. Her blood pressure was 120/80 mmHg and heart rate 80/bpm. Laboratory tests have shown leucocytosis of 15,9 x 1012/L(normal 4,4-11,5) withneutrophile (90%)-normal 50-70%, as predominant immune cell population, C reactive protein 180ng/ml (normal less than 5), Ddimer 1500 ng/ml (over 500 must be evaluated for pulmonary embolism) and cholesterol of 6,7 ng/ml (up to 5,5).Other biochemical parameters were in a normal range. The chest X-ray detected consolidation in the basal part of the left lung, accompanied by pleural effusion (Figure 1-A). Arterial blood gases were withinthe normal range. The patient was started with triple antibiotic therapy (Ceftriaxone, Ciprofloxacin, Metronidazole), along with low molecular weight (LMWH) heparin twice daily. The first thoracentesis was performed on the second day of admission followed by the second one, 3 days later. The pleural fluid has revealed the exudative type, yellow-coloredwith negative culture and smear. Sputum culture was negative as well. On thefourth day, the patient was afebrile. Thoracocentesis repeated three times more until regression (Figure 1- A, B, C).CT pulmonary angiogram (CTPA) has revealed thrombosis of the right pulmonary artery (Figure 1-D). Color Doppler sonography oflower extremities has excluded deep venous thrombosis.Laboratory findings were: ESR = 37 mm/h, CRP = 2+, ANA = 1/80 peripheral, RF = Negative, anti-dsDNA = 147 (positive > 40), anti Sm negative, anticardiolipin IgGantibody 158 GPL (up to 12), anticardiolipin IgM antibody 5.5 MPL (up to 10), anti-beta2-glycoprotein IgG and IgM were negative and lupus anti-coagulant was 88" (18"-55"). Anticardiolipin test and lupus anticoagulantwere repeated 6 weeks later showing similar results. ANCA was negative, protein C and S, antithrombin III and serum homocysteine were normal. The patient was diagnosed with antiphospholipid syndrome, secondary to systemic lupus erythematosus. According to guidelines,the patient underwent Heparin and Warfarin treatment, by checkingINR to be in a 2.6 to 3.5 range. Prednisolone and Hydroxychloroquine were also started. Dyspnea and cyanosis of the fingershaveimproved upon treatment.

DISCUSSION

All patients suspected with SLE should be evaluated for antiphospholipid antibodies (APL). However, APS diagnosis requires both clinical and laboratory features. If individuals are presented with APL only (without clinical manifestations) they are at less than 1% per year risk for the first time thrombotic event occurrence (5), and do not require specific treatment, but should be followed up. As compared to other APL, LA is the strongest predictor for both the arterial and veno-

us thrombosis future event (6), although alone not significantly associated with the elevatedrisk for thrombosis. In patients who tested positive for both LA and anti-â2GPI antibodies(or anti-prothrombin), the OR of a first time deep venous thrombus event increased to 10.1 (95 % CI 1.3–79.8) (7). Some authors have recently shown that the žtriple positivity' (defined as simultaneous LA, aCL and anti-â2GPI positivity) carriesa higher risk for thrombosis (and adverse pregnancy outcome), as compared to patients with only one APL positivity. In 10 years of follow-up, over 30% of those patients had a thromboembolic event (8).

The highest rates of diagnostic and therapeutic ambiguities are present for APS secondary to SLE cases, as it is difficult to find the relationship between clinical manifestations, antiphospholipid antibodies presence and SLE complications for most of them (9). According to literature, the anti-phospholipid antibodies (APL) frequency in SLE ranges between 6 and 80%. Some studies have indicated that 30-40% of SLE patients are presented with APL and third to half of them will develop APS (7).

CONCLUSION

For prevention of thrombosis, APS patients require long term Warfarin therapy withlow dose Aspirin and the INR range 2-3 for venous, or 3-4 for arterial and recurrent thrombosis. If APS associated with systemic lupus erythematosus, Hydroxychloroquine is effective for new thrombotic event prevention. Also, Hydroxychloroquine isrecommended for primary APS.

Abbreviation:

ANA — antinuclear antibody
aCL — anticardiolipin antibodies
APS — anti-phospholipid syndrome
APL — antiphospholipid antibodies
aCLA — anticardiolipin antibodies
anti-dsDNA — Double stranded DNA Antibody
anti Sm — anti Smit antibodies which confirm SLE
ESR — erythrocite sedimentation ratio
GP1 — anti-beta2-glycoprotein lupus anticoagulant
LA — lupus anticoagulant
INR — international ratio
LMWH — low molecular weight
CTPA — CT pulmonary angiogram
SLE — systemic lupus erithematodus
RF — rheuma factor
MPL — anticardiolipin IgM antibody

Acknowledgment: None

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

Funding: None

Licensing

Sažetak

SEKUNDARNI FOSFOLIPIDNI SINDROM OTKRIVEN KOD PACIJENTA SA PNEUMONIJOM - PRIKAZ SLUČAJA

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Uvod: Sekundarni antofosfolipidni sindrom je APS koji se javlja u sklopu nekog drugog zdravstvenog stanja. Iako se antifosfolipidna antitela (aPL) mogu javiti kod pacijenata sa virusnim, bakterijskim ili protozoalnim infekcijama, retko su povezana sa trombozom.

Cilj: Cilj je prikazati neuobičajen slučaj pneumonije i pleuralnog izliva komplikovanog plućnom tromboembolijom, kod pacijenata sa sistemskim lupusom eritematozusom (SLE), zbog nedijagnostikovanog sekundarnog antifosfolipidnog sindroma.

Prikaz slučaja: Žena starosti 28 godina, bez anamnestičkih podataka o trudnoći, sa sistemskim lupusom eritematozusom u porodičnoj anamnezi, a od kojeg se leči od svoje 18. godine. Imala je samo kožne i zglobne manifestacije bolesti, bez oštećenja unutrašnjih organa. Tokom prethodnih 10 godina lečena je Metotreksatom (10 mg nedeljno) i Prednizonom (5 mg dnevno). Službi hitne pomoći se javlja sa radiološkim nalazom pleuropnemonije praćene temperaturom do 39 stepeni, nedostatkom daha, kašljem, umorom i slabošću.

Rezultati: U početku je lečena sa tri antibiotika i torakocentezom. Razvila je plućnu trombozu bez duboke venske tromboze. Laboratorijski nalazi su bili ESR = 37 mm/h, CRP = 2+, ANA = 1/80 perifero, RF negativan, anti-dsDNA = 147 (pozitivan > 40), anti-Sm negativan, antikardiolipin IgG antitela 158 GPL (do 12), antikardiolipin IgM antitela 5.5 MPL (do 10), anti-beta2-glikoprotein IgG i IgM su bili negativni, a lupus anti-koagulant bio je 88" (18"-55"). Pacijentkinja je lečena heparinom i varfarinom, uz proveru INR-a da bude u opsegu od 2,6 do 3,5. Započeta je i terapija prednizonom i hidroksihlorohinom.

Zaključak: Svi pacijenti za koje se sumnja da imaju SLE treba da budu testirani na antifosfolipidna antitela. Međutim dijagnoza APS zahteva i kliničke i laboratorijske karakteristike.

Ključne reči: sekundarni antifisfolipidni sindrom, antitela, sistemski eritematozni lupus, autoimunost, tromboza.

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SANAMED
2019; 14(3): 291–296
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.329
UDK: 616.6-002.1:579.862
ID: 281775372
Review article

THE IMPORTANCE OF ENTEROCOCCUS BACTERIA IN ETHIOLOGY OF URINARY TRACT INFECTION

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Primljen/Received 02. 02. 2019. god.

Prihvaćen/Accepted 16. 04. 2019. god.

Abstract: Enterococci are classified as Streptococcus D group. Genetic studies in the 1980s have led to the conclusion that they have enough distinction to be classified into a particular genus.

Enterococci cause: urinary infections, especially in patients with catheter, in immunocompromised individuals, the infections of the biliary tract, soft tissue abscess, and wound infection. It is a relatively common cause of endocarditis, especially in people with damaged or artificial heart valve. Enterococci are the most common cause of urinary tract infections (IUT): about 10% of all and about 16% of intra-hospital IUT. In second place in frequency are intra-abdominal and pancreatic wounds, but these infections often cause multiple causes, so the assessment of the importance of enterococci in them is debatable. In third place is the bacteremia most commonly occurring in hospital conditions in immunocompromised patients who are lying long in hospitals and receiving antibiotics.

Key words: Enterococci, urinary tract, infection.

INTRODUCTION

Enterococcus bacteria represent a part of the normal microflora of the intestinal, biliary and female genital tract. They are natural components of soil, water, raw plants and animal products, where they increase the aromaticity (cheese and sausages). They are used as probiotics to improve the microbiological balance of the intestinal tract of both animals and humans.

In recent years, Enterococcus spp has become one of the leading causes of intra-hospital (nosocomial) infections in the urinary tract. What is an additional problem is increased resistance to antimicrobial drugs (1, 2, 3).

Enteroccuc species are gram positive cocci. The species consist more than 17 species, of which only a few cause disease in humans. More than 90% of human isolates are: Enteroccocus fecalis and Enterococcus feacium. Others that cause infection in humans are E.avium, E.gallinarum, E.Durans, E.raffinosis (Figure 1. and Figure 2).

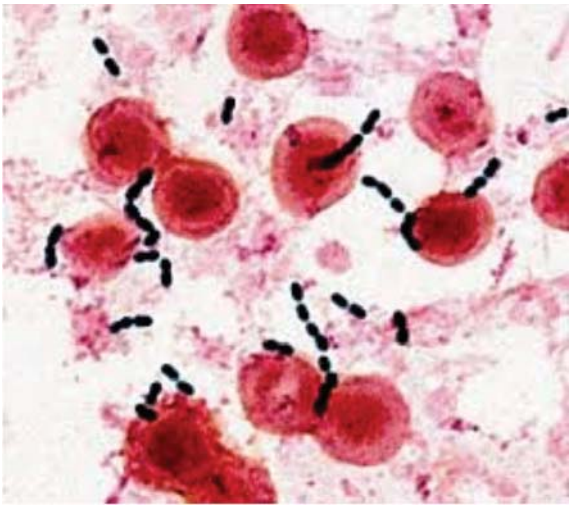

Figure 1. *Microscopic view of enterococci*

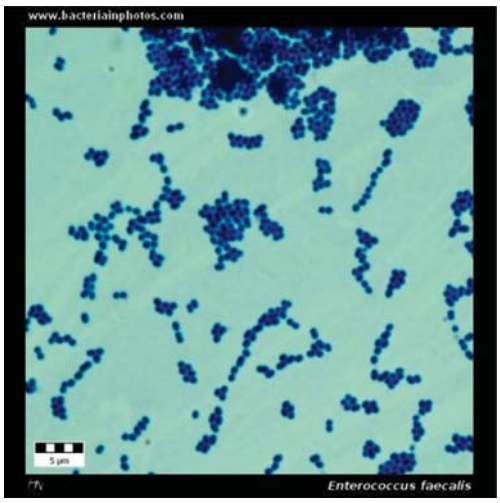

Figure 2. *Microscopic view of enterococci*

Initially, Enterococci are classified as Streptococcus D group. Genetic studies in the 1980s have led to the conclusion that they have enough distinction to be classified into a particular genus.

Enterococci cause: Urinary infections, especially in patients with catheter. In immunocompromised individuals, the infections of the biliary tract, soft tissue abscess, and wound infection. It is a relatively common cause of endocarditis, especially in people with damaged or artificial heart valve. Enterococci are the most common cause of urinary tract infections (IUT): about 10% of all and about 16% of intra-hospital IUT. In second place in frequency are intra-abdominal and pancreatic wounds, but these infections often cause multiple causes, so the assessment of the importance of enterococci in them is debatable. In third place is the bacteremia most commonly occurring in hospital conditions in immunocompromised patients who are lying long in hospitals and receiving antibiotics.

Pathogenicity of Enteroccocus

A model of the urinary tract of the mouse was used to study pathogenesis of E. faecalis in the urinary tract. It has been shown that E. faecalis has an advantage in developing compared to other bacteria from the genus of the renal kidney transmitted through blood by inoculation of pyelonephritis. They used another model to demonstrate that pyelonephritis, which causes Pseudomonas aeruginosa, is worser by E. fecalis, causing histological changes in the kidneys. The preoccupation of E. faecalis to kidneys in relation to the epithelium of the bladder is one of the possible explanations, but host factors involved in innate defense can also play an important role (4, 5, 6).

Urinary tract infections (IUT) whose E. faecalis mediator occur according to a strictly different mechanism from IUT mediated E. coli. In the typical case of IUT via E. coli, bacteria attack the surface umbilical cells and repeat it to higher levels, forming intracellular biofilms. The process is caused by a cytokine, a mediator of TLR4, which groups neutrophils to the site of infection.

In Enterococcus infections there is little or no inflammation in the fetus. Neutrophils represent only a small portion of the inflammatory cells at the site of the infections in the kidney. TLR2, which plays a role in the congenital response to gram positives, such as TLR4 plays a role in gram-negative, does not play a significant role in the congenital reaction to E.faecalis in the urinary tract. The recent discovery of the TLR11 receptor, which specifically recognizes uropathogens, indicates an additional innate mechanism that the host uses to respond to the enterococcus.

The ability of Enterococci to cause kidney disease is precisely established. The diagnosis of infection of the upper tract, or the lower, which causes Enterococcus, as well as gram-negative bacilli, is generally based on signs and symptoms. Therefore, the presence of fever and pain in slabs, with or without symptoms in the lower parts of the urinary tract, such as dysuria, frequency and urgency, indicate an infection of the upper part of the urinary tract. It is considered that symptoms in the lower part of the tract without symptoms in the upper part tracts represent infection of the bladder. Since Enterococcus has a strong kidney tropism, most of the episodic cystitis episodes are due to the transmission of infection from the upper urinary tract. Also, asymptomatic bacteriuria with Enterococcus is more often localized in the upper part than in the bladder. And as Enterococcal infections of the urinary tract bind to upper tract infections, it is possible to perform the implications of treatment. As infection of the upper urinary tract of the lens is longer than bladder infections (7, 8, 9).

Enterococcal infection occurs more frequently until the age of 10 and after the 60's, when genitourinary anomalies and obstructive abnormalities are more frequent. Enterococci are the third most common uropathogen-acquired urinary tract infection after E.coli and P.aeruginosa. Over 50% is in patients on stationary treatment, where there is a catheter. Also, neurological patients are targeted because of their specific condition when catheter is used.

These infections are not rare, but their diagnosis is not easy to establish. As it is usually associated with obstructive uropathy caused by urological and/or neurological disorders, their clinical manifestations may be mild or even absent. Pyuria is common, but it is non-specific manifestation in the absence of symptoms. It can be overwritten by catheterization and / or due to the presence of instruments in neurological symptoms or obstructive uropathy. In addition, the diagnosis of urinary tract infection caused by Enterococcus spp may indicate anomalies in the urinary tract that will only be diagnosed.

Enterococci have more genes that encode the factors responsible for the transmission of virulence.

Asa 1-plasmid gene. Codes the synthesis of the aggregation substance (AS). It is a protein that mediates binder binding to the host epithelium. It also mediates the plasmid exchange of information during bacterial conjugation.

Efa A-gene responsible for "avoiding" the immune response. It encodes the creation of a enterococcus surface protein (ESP), which participates in colonization, sustainability and the formation of biofilm on the surface of the urinary tract.

Esp-part of the great "pathogenic island", where other pathogenic genes are located.

Responsible for endocarditis and urinary infections and the creation of biofilm on cell epithelium by E.faecium.

ACE-encodes a protein mediating the adhesion of bacteria to collagen host cells.

HYL A-encodes hyaluronidase that plays an important role in the increase of bacterial invasion, especially the intestinal tract. The only isolated out-of-hospital community did not have a large plasmid containing this gene. The strains isolated from hospital patients are.

CYL A- gene for coding cytolysis of both eukaryotic and prokaryotic cells.

GEL E-gen responsible for synthesis of Zn metalloendopeptidase, which hydrolyzes gelatin, casein and hemoglobin.

IS16- encodes the enzymes necessary for bacterial transposition.

One of the main problems associated with the genus Enterococci is the tendency to gain resistance and the spread of antimicrobial determinants of resistance.

Hospital infections and Enteroccocus

Enterococci represent 16% of the causes of all nasocomial infections. Studies show that the urinary tract is the most common source of hospital infections. The main causes of this genus are E.faecium and E.faecalis. Enterococcus faecium has always had a higher degree of drug resistance, than E .faecalis.

But what's characteristic of the one-line is a high degree of resistance, such as the ability to survive under unfavorable conditions (temperature from 10 to 46, ph = 9.6), high resistance to antibiotics, etc.

Including non-selective use of antibiotics, prolonged hospitalization, seriousness of the disease and impaired immune response (already hospitalized patients), all of these factors are responsible for making Enterococci resistant to medication during hospital treatment. This eventually leads to environmental pollution and other infections.

Catheterization

It has been established that the presence of catheter plays a major role. It is necessary to pay attention to the duration of catheterization (preferably up to 30 days, no more) and that the catheter is always open.

The drainage bag should always be below the level of the bladder and tube.

In case of short-term catheterization, systemic antibiotics prophylaxis is not recommended. Also for patients who use catheterization with interruptions, prophylaxis by antibiotics is not effective. Cleaning the catheter with anibiotics and antiseptics is no progress. But catheters are introduced under antiseptic conditions. Medical staff respects the hygienic conditions in accordance with the protocol. Patients my for more than 10 years use catheters should be checked regularly for possible bladder cancer. Antibiotic therapy has proven effective only in cases of symptomatic infection. Treatment with antibiotics begins after the results of the urinary culture. Evacuate catheter before surgery. The silver and aluminum catheters have proven to be effective, i.e., causing asymptomatic bacteria, but only if used for up to 7 days. Preventing urinary infections caused by catheter or at least mitigating them is still a form of research.

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It should be noted that the resistance gene placed on plasmids can be easily and rapidly expanded horizontally, while the genes located on the chromosome are, as a rule, wider vertically and horizontally if it is a transposon that passes from the chromosome to a plasmid, and further propagates with a plasmid or a mechanism of transformation which in nature is probably not common (the transfer of a large part of the chromosomal DNA into a related bacterium).

Resistance to antibiotics

Resistance to antibiotics makes them ungrateful for treatment. There are two types of resistance:

1. Internal resistance

Characteristic of the species mediated by genomes located on chromosomes and is present in all members of the species. Enterococci show internal resistance to:beta lactams, cephalosporins, lincosamide, classical quinolones, aminoglycosides-show low levels of resistance, clindamycin.

Although most enterotoxic agents are sensitive to co-trimoxazole in vitro, this combination does not work when administered in vivo, as the Enterococcus is able to "skip" folic acid and bypass the inhibition of folate synthesis by co-trimoxazole. For his DNA, Enterococcus use exogenous folic acid.

2. Acquired resistance

Stems from mutations at DNA level DNA examples of acquired resistance:, ampicillin, HLAR-aminoglycosides, vancomycin, chloramphenicol, erythromycin, high levels of clindamycin, tetracyclon, fluoroquinolone.

The unpredictable sensitivity of Enterococcus to antibiotics requires testing of sensitivity, or resistance in vitro. When and on which antibiotics will the sensitivity of Enterococci be, depends on the site of infection and the estimated significance of a particular isolate.

Acquired resistance was found on all antibiotics that affect the enterotox (10-13). But they were also found on those antibiotics that are not used to treat enterococcal infection. The reason for this is the transfer of the resistance gene horizontally-to other types of bacteria, which are treated with other antibiotics, to which they now become resistant.

VRE (vancomicyn resistance Enterococci)

Colonization and infection

It is believed that a faecal transfer of VRE is often associated with a serious clinical infection and that it is very likely that colonization of the gastrointestinal tract occurs as a prelude to a clinical infection.

Risk factors for colonization and invasive diseases include the use of antibiotics (especially vancomycin, the third generation cephalosporins and antimicrobial agents against anaerobic activity, etc.) and various other factors, including the pre-mentioned colonization of the gastrointestinal tract (GI) with the VRE, the prolonged stay in the hospital, older age, proximity to the patient, care for patients with colonization of the gastrointestinal tract with VRE by the healthcare worker (14-18).

Furthermore, these colonized patients can contaminate themselves and the environment, and therefore have the potential to transfer VRE from the environment to patients. How VRE can survive on dry surfaces for a long time, it contaminates the environment by causing some diseases.

Screening method for determining VRE

Given the increasing rate of colonization with VRE and the increased concern over the possible impact of this organism on patients at high risk of infection, screening methods for the determination of VRE have been introduced. A reliable and recommended method of agar screening method involves the use of BHI (brain-heart infusion) agar with 6 ìg vancomycin per ml. The detected plates of inoculum 105-106 cfu (colony forming unit), were incubated at 35 E C for 24 hours. Their growth shows resistance, and absence of growth shows sensitivity.

Two enterotoxal solutions for the isolation of VRE from colonized patients are also available. These are enterotoxic mixtures with sodium azithromycin with sodium azide with 6 ìg vancomycin (EBVA) and M-enterotoxic mixture with sodium azide and trifenyltetrazolium with 6 ìg vancomycin.

Similarly, the antibiotic gradient (E test) method can also detect VRE. When suspicion of the results of the screening method is suspected, vancomycin should be confirmed using another method.

Daptomycin

Daptomocin is a cyclic lipopeptide antibiotic with a rapid bactericidal effect per gram of positive. It works by binding to the cell membrane, performing depolarization, inhibiting protein synthesis, DNA, RNA, and leading to cell death.

It is eliminated through the kidneys, and more than 50% in the unchanged state gets into the urine after iv. The above mentioned drugs have a lower percentage of renal excretion, which limits the effectiveness of VRE. Then, its MICs are similar for E.faecium and E.feacalis.

Respiratory response to daptomycin rarely occurs. According to previous studies, the VRE shows a high level of sensitivity to daptomocin. For linezolid, resistance is increasing. Quinopristin has a limited activity on E.faecalis. In addition, adverse effects (myalgia and athralgia) and the rapid increase in resistance have surpassed the benefit. Then, daptomycin has a wide therapeutic index.

A study conducted from January 2007 to December 2009 included hospitalized patients who have VRE and therefore need to stay longer in the hospital with a Foli catheter and this is not the first IUT. All treated patients achieved eradication with daptomycin. It was used in doses of 1.4 to 3.7 mg / kg per day. The determined doses were based on empirical knowledge of the practice, since there was no accurate dose in literature. An unusually high dose was given to a 30-year-old patient with quadriplegia who had I ST.aureus: 13 mg per kg. Daptomycin eradicated VRE regardless of the new kidney function. Daptomycin was well tolerated and there were no reports of kidney alteration, muscular weakness or pain, nor an increase in CPK enzymes.

The CPK level was measured at the start of the study and once every 7 to 10 days. Even with the patient who received the highest dose.

This is important for some subsequent studies that would determine the exact dose of daptomycin. The possible expected side effects are: degenerative changes in muscles, rhabdomyolysis and myopathy-the use of daptomycin only once a day reduces myotoxicity. More frequent is the occurrence of myotoxicity in patients with renal insufficiency, and therefore, a new CPC is monitored. If there is an increase, the therapy will be discontinued:gastrointestinal complaints, weakness, headache, screw.

Most VREs can be treated, except vancomycin antibiotics. Laboratory testing allows physicians to determine which antibiotic will work.

VRE is transmitted as well as Enterococcus. In healthy people it will not cause infection. VRE is transmitted by touch of the hand on your hands, when you touch an infected person or after contact with contaminated surfaces or equipment.

VRE infection can be without symptoms. Such people are called colonized and they most often do not even know that they are transmitters. VRE can be diagnosed with IUT, infections in the bloodstream or wounds associated with a catheter or surgical procedure.

We prevent the spread of VRE in hospitals by:

- The staff wash their hands with soap and water or rub their hands with alcohol before and after the care of each patient.

- In some cases, in the case of health services, clothing and gloves may be used to prevent the spread of doctors should take special measures (isolation measures) to prevent the spread of infection to others.

Isolation

Precautions serve patients with infected or colonized VRE. If a patient has a previous history of VRE isolation in clinical patterns from any source, the patient is sent to precautionary measures, and the Infection Control Department is informed of this. The infection control unit will monitor the patient during his stay in the hospital. Patients who carry vancomycin resistant E. gallinarum strains, E. casseli flavus, or E. flavescens can only be treated with standard precautions. Precautions require a private room and wearing clothing and gloves if it touches the patient or anything in the patient's room by hand or part of the clothing that is contaminated; since Enterococcus is an extremely durable organism and can survive for a longer period of time on objects, and because it spreads on surfaces in hospital rooms (especially in patients with incontinence of the chair), it is considered that all areas in the patient's room are contaminated.

Patients, who are in precautionary measures for isolation, are asked to stay in their rooms as much as possible. Patients may leave the department for treatment and / or therapy, if they observe isolation precautions. When the patient leaves the department, the secretary of the department should call the department to which the patient has started and to inform them of the patient coming from the isolation. Ideally, procedures and theraphies should be performed at the end of the day, away from other patients. When the patient leaves the room he / she should wear a protective suit and wash basins with soap and water. Staff in charge of transporting isolated patients should pay attention to avoid contaminating common areas in the hospital during transportation. The carrier should wear protective clothing and gloves. The carrier's gloves and gloves are considered contaminated and should not have any contact with anything except the patient and/or vehicle.

Conflict of Interest: The authors declare that they have no conflict of interest.

Source of support: None

Acknowledgement: This research did not receive any specific grant from funding agencies or non-profit sectors.

Licensing

Sažetak

VAŽNOST ENTEROKOKA U ETIOLOGIJI URINARNIH INFEKCIJA

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Enterokoke su klasifikovane kao Streptokok D grupe. Genetske studije 1980tih su došle do zaključka da se dovoljno razlikuju i da mogu da budu svrstane u posebnu grupu.

Enteroke izazivaju: urinarne infekcije, posebno kod pacijenata koji nose urinarni kateter i kod imunokompromitovanih pacijenata, infekcije bilijarnog trakta, abscese mekih tkiva i infekcije rana. Relativno če-

sto su uzrok endokarditisa, naročito kod osoba sa oštećenom i arteficijalnom srčanom valvulom. Enterokoke su najčešći uzročnici urinarnih infekcija: oko 10% od ukupnog broja i oko 16% intrahospitalnih infekcija urinarnog trakta. Na drugom mestu po učestalosti su intraabdominalne i infekcije pankreasa, ali pošto ove infekcije obično izaziva veći broj uzročnika, onda je važnost učešća enterokoka u njima diskutabilna. Na trećem mestu je bakterijemija koja se najčešće pojavljuje u bolničkim uslovima kod imunokomromitovanih pacijenata , koji su dugo hospitalizovani i dobijaju antibiotike.

Ključne reči: Enterokoke, urinarni trakt, infekcija.

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SANAMED
2019; 14(3): 297–298
ISSN-1452-662X

DOI: 10.24125/sanamed.v14i3.359
UDK: 616-099-083.9(497.11)
ID: 281865484
Letter to editor

LETTER TO EDITOR - THE TREATMENT OF ACUTE POISONING IN CLINICAL EMERGENCY CENTER OF KRAGUJEVAC

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Primljen/Received 22. 08. 2019. god.

Prihvaćen/Accepted 10. 10. 2019. god.

To the Editor,

All acute poisonings represent urgent conditions in medicine, no matter what clinical features are. Patients with acute poisoning make 3-5% of the total number of patients treated in emergency medical services „poisoning“, and can be accidental, suicidal and murderous. Making (providing) accurate diagnosis is often difficult because it implies the identification of poison; that is not always possible for auto and heteroanamnesis data, physical examination (checkup) of the patient, and clinical symptoms of poisoning are used for making the diagnosis (1).

A patient with symptoms of acute poisoning is immediately taken in emergency room where the doctor specialist of emergency medicine or the doctor specialist of internal medicine undertakes medical examination which implies: fast estimation of need for respiratory support and mechanical ventilation, or cardiorespiratory reanimation; monitoring of vital functions; measuring of arterial blood pressure, heart rate, arterial oxygen saturation by pulse-oximetry, electrocardiographic record of heart rate, x-ray lung recording; consultations with neurologist, surgeon, neurosurgeon, psychiatrist, or if it is necessary with doctors of other specialties; provision of venous line; applying of intravenous saline solution or intravenous sugar solution(dextrose solution); taking blood samples urgently; according to estimation testing blood on methyl-alcohol or ethyl-alcohol, or testing urine on psychoactive substances; estimation of consciousness; identification of signs of external physical injuries; nasogastric intubation in case of acute peroral poisoning except in case of poisoning by corrosive substances (acids, bases) when there are contraindications; this procedure is repeated until the stomach contents are clear and after that activated carbon is given to a patient (2).

If a patient is unconscious, the one needs to be intubated in order to protect the airways. After nasogastric intubation is being done, and after all activated carbon is given to a patient, if a patient is conscious and the collaboration can be established, the vomiting is caused by drinking hot water and after that activated carbon is given to a patient; after initial treatment in resuscitation room patients who are respiratory at risk (affected) of who have disturbances of consciousness are hospitalized in stationary rooms of Clinical Emergency Center, and those who have symptoms of light poisoning are taken in internist ambulance for observation and psychiatrist is consulted about the clinical conditions of them (3).

The poisoning time of observation is estimated on the stabilization of vital parameters, improving the state of consciousness, as well as the development of possible complications depending on the time of ingestion, the type of toxic substance, the time of reporting poisoning to doctors and present co-morbidity. Antidote therapy is used for poisoning in which it is indicated. Atropine® is used for poisoning by organo-phosphates, Naloxane® is used for poisoning by opiates, Aneksat® is used for poisoning by benzodiazepines, ethyl-alcohol is used for poisoning by methyl-alcohol and ethylene-glycol. Measures of extracorporeal detoxification like hemodialysis, hemoperfusion with activated carbon and plasma-pheresis are used in the stationary room of Clinical Emergency Center. Symptomatic and supportive therapy is also used. It is the base in the treatment of all acute poisoning because of a small number of antidotes. Toxic effects of organophosphate insecticides appear because of irreversible inhibition of enzymes of acetyl-cholinesterase which causes accumulating of acetylcholine in the central and peripheral nervous system, and in other tissues and organs. Clinical effects of accumulated acetylcholine are re-

flected in four clinical syndromes. Acute cholinergic crisis – the most important clinical syndrome that appears after a few minutes, but it also may appear twelve hours after consuming the poison. Effects are classified into three categories: muscarinic, nicotinic and central. Muscarinic effects are represented by intensified bronchial secretion, bronchial spasm, intensified perspiration, hypersalivation, lacrimation, incontinence of urine and feces, sickness and vomiting, bradycardia, hypotension, and myosis. Nicotinic effects are shown by muscular fasciculation, spasms, paralyzation of diaphragm, areflexia, respiratory insufficiency, hypertension, tachycardia and pupil dilation. Effects by CNS are anxiety, headache, tremor, confusion, convulsion, and depression of the respiratory system. The intermediate syndrome – neurology signs that are shown in the period of 24 to 96 hours after acute cholinergic crisis (muscular weakness of neck flexor; respiratory muscles, as well, as muscles of extremities dominant; delayed peripheral neuropathy, lesions of other organs). Every single patient who has been poisoned by chemical compounds of the group of organophosphate insecticides is attended by the aforementioned protocol for acute poisoning (4).

If the clinical status of the patient is specific, there is a possibility of taking the patient's blood and sending it for analyzes in the Toxicology Lab of Military Medical Academy in Belgrade. If it is possible, take biological material (urine, blood, lavage) for proving (substantiating) the poison and its metabolites (that could be important as a piece of evidence at the court). Specific therapy for these poisonings means giving of: Atropine® in the dosage of 1 to 2mg intravenously on every five minutes until the signs of hyper-atropinisation (dry lungs, dryness of skin and mouth, tachycardia, face(flushing) redness, mydriasis with decreasing dosage in correlation with the clinical features, so far signs of cholinergic crisis exist; reactivators (actifiers) of cholinesterase (compounds of the group of oximes–pralidoxime in the dosage of 1 g intravenously or intramuscularly in the salt solution on every 4 to 6 hours during the first 48 hours, and it is usually given to a patients for seven days); Diazepam® (anticonvulsants in dosage of 10 mg in every 8 hours intravenously whose purpose is preventing convulsion effect of accumulated acetylcholine); symptomatic and supportive therapy (correction of acid-base and electrolyte imbalance) (5).

The role of hemodialysis in acute poisoning has repented as an indispensable treatment for acute poisoning today (6).

Acknowledgments

No funding is used for the present work. All authors contributed equally and were involved in writing the paper and finally approved the submitted and published versions without any conflict of interest.

Conflict of Interests: The authors declare that there are no conflicts of interest related to this article.

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SANAMED
2018; 14(3): 299–299
ISSN-1452-662X

CORRECTION

Correction: Patterns of superior articular facet and morphometric study of Nepalese dry calcanei (Vol 13, No 1, p. 17-22, 2018)
Ispravka: Vrste gornje zglobne povrsine i morfometrijska analiza petne kosti kod Nepalaca (Vol 13, No 1, p. 17-22, 2018)

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The Editorial Board of "Sanamed" journal, in agreement with authors (Dhakal Arun, Adhikari Prashant, Khan G. Anwer, Gautam Aajeevan) of the paper "Patterns of superior articular facet and morphometric study of Nepalese dry calcanei (Vol 13, No 1, p. 17-22, 2018) who pointed out the technical errors that occurred after the paper was published, made the decision to do the necessary corrections in accordance with the prescribed procedure. According to that, the appropriate correction was made.

The following update was made:

In section Material and Methods, on page 17, the first sentence, instead of "A total of 142 dried calcanei (68 right, 74 left) without major defects and unidentified gender were assessed." shoud stand "A total of 142 dried calcanei (68 right, 74 left) without major defects and unidentified gender were assessed from March 2017 to November 2017."

SANAMED
2018; 14(3): 301–301
ISSN-1452-662X

CORRECTION

Correction: The influence of chronic stress on health and coping mechanisms (Vol 14, No 1, p. 97-101, 2019)
Ispravka: Uticaj hroničnog stresa na zdravlje i mehanizmi prevazilaženja stresa (Vol 14, No 1, p. 97-101, 2019)

Cvjetkovic Bosnjak Mina,[1, 2] Dubovski Poslon Milota,[1, 2] Bibic Zeljko,[3] Bosnjak Kristina[4]

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The Editorial Board of "Sanamed" journal, in agreement with authors (Cvjetkovic Bosnjak Mina, Dubovski Poslon Milota, Bibic Zeljko, Bosnjak Kristina) of the paper "The influence of chronic stress on health and coping mechanisms (Vol 14, No 1, p. 97-101, 2019) who pointed out the technical errors that occurred after the paper was published, made the decision to do the necessary corrections in accordance with the prescribed procedure. We apologize the authors for errors that occurred in published paper and thank them for assistance in detecting them. According to that, the appropriate correction was made.

The following updates were made:

a) Under the title of the paper on page 97, instead of Cvjetkovic Bosnjak Mina,[1,2] Dubovski Poslon Milota,[1, 2] Bibic Zeljko,[3] Bosnjak Kristina[4] shoud stand Cvjetkovic Bosnjak Mina,[1] Dubovski Poslon Milota,[1] Bibic Zeljko,[2] Bosnjak Kristina[3].

b) Under the authors names of the paper on page 97, instead [1] Clinic of psychiatry, Clinical centre of Vojvodina, Novi Sad, Serbia, [2] Faculty of medicine Novi Sad, University of Novi Sad, Serbia, [3] General hospital Vrbas, Psychiatry department, Vrbas, Serbia, [4] Faculty of sciences, Department of biology and ecology, Novi Sad, Serbia shoud stand [1] University of Novi Sad, Medical Faculty, Psychiatric Clinic, Clinical Centre of Vojvodina, Novi Sad, Serbia, [2] General hospital Vrbas, Psychiatry department, Vrbas, Serbia, [3] Faculty of sciences, Department of biology and ecology, Novi Sad, Serbia.

c) In the section "Saţetak" on page 101, under serbian translation of the title of the paper instead of Cvjetkovic Bosnjak Mina,[1, 2] Dubovski Poslon Milota,[1, 2] Bibic Zeljko,[3] Bosnjak Kristina[4] shoud stand Cvjetkovic Bosnjak Mina,[1] Dubovski Poslon Milota,[1] Bibic Zeljko,[2] Bosnjak Kristina[3].

d) In the section "Saţetak" on page 101, Under the authors names of the paper, instead [1] Clinic of psychiatry, Clinical centre of Vojvodina, Novi Sad, Serbia, [2] Faculty of medicine Novi Sad, University of Novi Sad, Serbia, [3] General hospital Vrbas, Psychiatry department, Vrbas, Serbia, [4] Faculty of sciences, Department of biology and ecology, Novi Sad, Serbia shoud stand [1] University of Novi Sad, Medical Faculty, Psychiatric Clinic, Clinical Centre of Vojvodina, Novi Sad, Serbia, [2] General hospital Vrbas, Psychiatry department, Vrbas, Serbia, [3] Faculty of sciences, Department of biology and ecology, Novi Sad, Serbia.

SANAMED
2018; 14(3): 303–303
ISSN-1452-662X

CORRECTION

Correction: Infection of urinary tract in menopausal women (Vol 14, No 2, p. 203-208, 2019)
Ispravka: Infekcije urinarnog trakta kod žena u menopauzi (Vol 14, No 2, p. 203-208, 2019)

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The Editorial Board of "Sanamed" journal, in agreement with author (Smjesko Gordana) of the paper "Infection of urinary tract in menopausal women (Vol 14, No 2, p. 203-208, 2019) who pointed out the technical errors that occurred after the paper was published, made the decision to do the necessary corrections in accordance with the prescribed procedure. We apologize the author for errors that occurred in published paper and thank her for assistance in detecting them. According to that, the appropriate correction was made.

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a) Under the title of the paper on page 203, instead of Smieško Gordana[12] shoud stand Smieško Gordana

b) Under the authors name on page 203, instead [1] Institute of Public Health of Vojvodina, Novi Sad, Serbia and [2] Department of Microbiology, Faculty of Medicine Novi Sad, University of Novi Sad, Serbia shoud stand University of Novi Sad, Medical Faculty, Institute of Public Health of Vojvodina, Novi Sad, Serbia.

c) In the section "Sažetak" on page 207, under serbian translation of the title of the paper instead of Smieško Gordana[12] shoud stand Smieško Gordana.

d) In the section "Sažetak" on page 207, under the name of the author, instead [1] Institute of Public Health of Vojvodina, Novi Sad, Serbia and [2] Department of Microbiology, Faculty of Medicine Novi Sad, University of Novi Sad, Serbia shoud stand University of Novi Sad, Medical Faculty, Institute of Public Health of Vojvodina, Novi Sad, Serbia

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SANAMED / glavni i odgovorni urednik Avdo Ćeranić. — God. 1, br. 1 (2006)– . — Novi Pazar : Udruženje lekara Sanamed, 2006– (Kraljevo : Ofset). — 30 cm

Tri puta godišnje. — Tekst na engl. jeziku. — Drugo izdanje na drugom medijumu: Sanamed (Online) = ISSN 2217-8171

ISSN 1452-662X = Sanamed

COBISS.SR-ID 135154444

ISSN 1452-662X