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Novi Evropski vodič za prevenciju tromboembolizma kod A Fib

CHA₂DS₂-VASc skor za procjenu rizika od tromboembolizma kod A Fib!

Risk factor-based point-based scoring system - CHA₂DS₂ -VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	9

*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.



Major i non-major riziko faktori za procjenu tromboembolizma kod A Fib!

Risk factors for stroke and thrombo-embolism in non-valvular AF

Major risk factors	Clinically relevant non-major risk factors
Previous stroke	CHF or moderate to severe LV systolic dysfunction [e.g. LV EF \leq 40%]
TIA or systemic embolism	Hypertension
Age ≥ 75 years	Diabetes mellitus
	Age 65–74 years
	Female sex
	Vascular disease

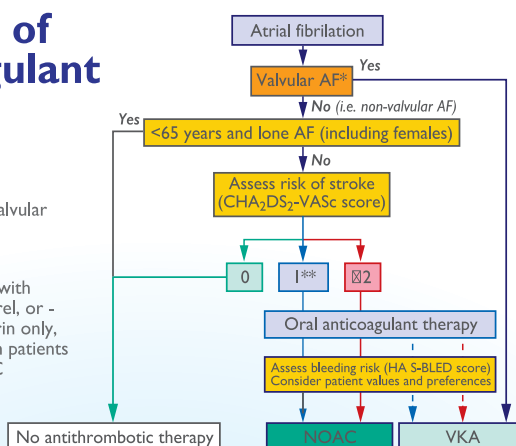
AF = atrial fibrillation; EF = ejection fraction (as documented by echocardiography, radio nucleide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left ventricular; TIA = transient ischaemic attack.



Algoritam antikoagulantne terapije nakon procjene CHA₂DS₂VASc i major risk faktora!

Choice of Anti-coagulant

- * Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.
- ** Antiplatelet therapy with aspirin plus clopidogrel, or - less effectively - aspirin only, may be considered in patients who refuse any OAC



NOAC - Novel Oral Anticoagulants, VKA - Vitamin K Antagonists

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Can the risk of the N diseases development be related to the degree of differentiation of tumor cells and the presence of peritumoral lymphocytic infiltration in the non-small cell lung cancer

Može li se rizik od razvoja N bolesti povezati sa stepenom diferencijacije tumorskih stanica i prisustvom peritumoralne limfocitne infiltracije u karcinomu pluća ne-malih stanica

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ABSTRACT

Introduction: the most important factor regarding the survival of patients with non-small cell lung cancer (NSCLC) is the mediastinal lymph node status. The influence of several factors on the occurrence of N1 and N2 metastases was investigated, the most common being lung cancer, tumor size, and the degree of differentiation of tumor cells. **Aim:** to determine the association between the degree of tumor cells (G stage) differentiation and the presence of peritumoral lymphatic infiltration (PTLI) with the occurrence of N1 and N2 metastases in NSCLC. **Materials and methods:** the study included a sample of 331 patients, of all ages, both genders, who underwent a complete resection of previously diagnosed lung cancer. Surgery was performed under general anesthesia technique employing a Carlens tube, with the prior zonal exploration of mediastinal lymph nodes and/or thoracoscopic exploration of the pleural cavity. The peritumoral compartment in which lymphocytic infiltration was investigated is an area around the intratumoral compartment that includes the edge of the tumor and a width of 1 mm beyond it. **Results:** the most common type of lung cancer among patients in this study was adenocarcinoma, with PTLI in more than 69% of cases. There is a 3,5 times higher risk of developing N disease when there is PTLI comparing with cases when there is none. PTLI was present in 86 (37,6%) patients with N0 disease, 128 (55,9%) patients with N1 disease, and 15 (6,6%) patients with N2 disease. **Conclusion:** the presence of PTLI is significantly associated with the occurrence of N1 and N2 metastases in patients with NSCLC.

Keywords: lung cancer, surgery, metastases, non-small cell lung cancer, prognostic factors

SAŽETAK

Uvod: najvažniji faktor preživljavanja pacijenata sa karcinomom pluća ne-malih stanica (NSCLC) je status medijastinalnih limfnih čvorova. Istražen je utjecaj nekoliko faktora na pojavu metastatske bolesti u limfinim čvorovima (N1 i N2), a najčešći su karcinom pluća, veličina tumora i stepen diferencijacije tumorskih ćelija. **Cilj:** Cilj ovog istraživanja je utvrditi povezanost između stepena diferencijacije tumorskih ćelija (G stadij) i prisustva peritumoralne limfocitne infiltracije (PTLI) sa pojavom N1 i N2 metastaza kod pacijenata sa dokazanim NSCLC. **Materijali i metode:** Istraživanjem je obuhvaćen uzorak od 331 pacijenta, svih dobni skupina, oba spola, koji su podvrgnuti kompletnoj resekciji prethodno dijagnosticiranog karcinoma pluća. Operativni zahvat je izveden u upštoj separisanoj anesteziji korištenjem Carlensovog tubusa, uz prethodno zonsko istraživanje medijastinalnih limfnih čvorova i/ili torakoskopsku eksploraciju pleuralne šupljine. Peritumoralni odjeljak u kojem je istraženo eventualno prisustvo PTLI definiran je kao područje oko intratumoralnog odjeljka koji uključuje rub tumora i širinu od 1 mm izvan njega. **Rezultati:** najčešći tip karcinoma pluća među pacijentima u ovom istraživanju bio je adenokarcinom, a PTLI je bila prisutna u više od 69% slučajeva. Rizik od razvoja N bolesti kada postoji PTLI je 3,6 puta veći u odnosu na slučajeve kada PTLI nije bila prisutna. PTLI je bila prisutna kod 86 (37,6%) pacijenata sa N0 bolešću, 128 (55,9%) pacijenata sa N1 bolešću i 15 (6,6%) pacijenata sa N2 bolešću. **Zaključak:** prisustvo PTLI značajno je povezano sa pojavom N1 i N2 metastaza kod pacijenata sa NSCLC.

Ključne riječi: karcinom pluća, operacija, metastaze, nemikrocelularni karcinom pluća, prognostički faktori

INTRODUCTION

Lung cancer is a significant health problem in more than 170,000 new cases diagnosed annually in the United States. Out of this number, about 45% of cancers are confined to the chest, with surgery still being the most effective method in controlling the disease (1). Therefore, only 25% of lung cancer patients are eligible for surgical treatment (stage I and II, selected IIIa, and only exceptionally IIIb and IV - eg, solid brain metastasis). The International Staging System for Lung Cancer (ISSLC) (TNM system)) is also used to evaluate the anatomical prevalence of cancer, which is also the best survival indicator. It serves as an international language for modifying clinician information and is a guide in the choice of therapy. N descriptor is of the interest to this paper. The most important factor in the survival of a patient with non-small cell lung cancer is the condition of the mediastinal lymph nodes. An analysis of the international IASLC database shows that the pre-existing N descriptor provides relevant survival stratification and is retained in the new 8th classification. The incidence of N1 and N2 metastases with respect to the presence of lymphovascular peritumoral infiltration and tumor grade in bronchial cancer are some of the under-researched data that can provide the clinician with valuable guidance on aggression, disease spread, prognosis, and treatment. The influence of a number of factors on the occurrence of N1 and N2 metastases have been investigated, the most common being lung cancer, tumor size and the degree of differentiation of malignancy.

Only 25% of patients with lung cancer are suitable for surgical treatment (stage I and II, selected IIIa, and only exceptionally IIIb). The TNM system is also used to evaluate the anatomical prevalence of cancer, which is also the best survival indicator. An analysis of the international IASLC database shows that the pre-existing N descriptor provides relevant survival stratification which is retained in the latest ISSLC classification (1). Assessment of lymph node status can be done by examining only those lymphonodes that are associated with the resection specimen, taking biopsy specimens from only those lymph nodes that appear pathologically altered, systematic biopsy of each lymph node, and complete dissection of mediastinal lymph nodes (2,3). The incidence of N1 and N2 metastases with respect to the presence of peritumoral lymphatic infiltration (4) and tumor grade in lung cancer are some of the under-researched data that can provide clinicians with valuable guidance on aggression, disease spread, prognosis, and treatment (5).

AIM

The aim of this study was to attempt to determine the association between the degree of differentiation of tumor cells (G stage) and the presence of peritumoral lymphatic infiltration (PTLI) with the occurrence of N1 and N2 metastases in non-microcellular lung cancer.

MATERIALS AND METHODS

The study included a sample of 331 patients, of all ages, both genders, with complete resection of proven lung cancer. Preoperative diagnostic protocol contained at least a CT scan of thoracic and upper abdominal organs in a contrast series with

determination of cTNM stage of the disease, bronchoscopy with biopsies, some of which were performed transthoracic, pathohistological, cytological and immunohistochemical analyzes, verification of lung status functionality for planned resection level, and cardiac evaluation of the possibility of introducing the patient to general anesthesia.

Surgery was performed under general anesthesia technique employing a Carlens tube, with the prior zonal exploration of mediastinal lymph nodes and/or thoracoscopic exploration of the pleural cavity. In addition to resection of the pulmonary parenchyma with the tumor, enlarged lymph nodes were dissected.

Within the histopathologic examination in HE (hematoxylin and eosin) staining, particular attention was paid to the presence of PTLI, the degree of tumor differentiation, and metastases in the hilar and mediastinal lymph nodes. The peritumoral compartment in which lymphocytic infiltration was sought was defined as the area around the intratumoral compartment that includes the edge of the tumor and a width of 1 mm beyond it (4). The inclusion criteria include patients of all ages, both genders, who underwent a complete surgical resection of previously diagnosed NSCLC. Patients who underwent exploratory thoracotomy and those who did not undergo an adequate surgical procedure to assess the N1 and N2 lymph node status were excluded from the study.

PTLI status data were marked as PTLI + (peritumor lymphatic infiltration found) and PTLVI - (peritumor lymphatic infiltration not found). The classification of tumor cell immaturity was indicated by the scale: well-differentiated tumor cells (G1 immaturity), medium differentiated (G2 immaturity), poorly differentiated (G3 immaturity).

Statistical analysis

The obtained data was processed by standard statistical methods, using the SPSS computer program for statistical analyzes (SPSS-Statistical Package for Social Sciences) version 21.0. The results were expressed as absolute numbers (N) and percentage values. Spearman's rank correlation coefficient was used to evaluate the association between the degree of differentiation of tumors and metastases into regional lymph nodes, as well as the relationship between PTLI and metastases to regional lymph nodes. Direct logistic regression was used to evaluate the impact of PTLI and the degree of tumor differentiation as independent variables on metastases to regional lymph nodes as a dependent variable (negative outcome). In the analysis of the dependence between the categorical variables, the value of $p < 0.05$ was taken as statistically significant.

RESULTS

As presented in Table I, in our sample the most common type of lung cancer was adenocarcinoma, with PTLI in more than 69% of cases. The sample was dominated by a medium degree of tumor cell immaturity (60.12%), with metastasis in the hilar lymph glands in about 40% of cases and mediastinal lymph glands in only 4.53% of cases.

Table I Main characteristics of the patients and lung cancer.

Characteristics		p - value
Gender		
Male	257 (77.64%)	< 0.005
Female	74 (22.36%)	
Age average (years)	62.69±7.46 (cover 21 – 86 years)	
Hystological type		
Adenocarcinoma	182 (55%)	< 0.001
Squamocellular carcinoma	140 (42.3%)	
Large cell carcinoma	9 (2.7%)	
Peritumoral lymphocytic infiltration (PTLI)		
Present	229 (69.18%)	< 0.001
Absent	102 (30.82%)	
Degree of differentiation		
G1	31(9.36%)	< 0.0015
G2	199(60.12%)	
G3	101(30.52%)	
N descriptor		
N0 (negative)	184 (55.59%)	< 0.154
N1 (positive)	132 (39.88%)	
N2 (positive)	15 (4.53%)	

PTLI was present in 86 (37.55%) patients with N0 descriptor, 128 (55.89%) patients with N1 descriptor and 15 (6.55%) patients with N2 descriptor.

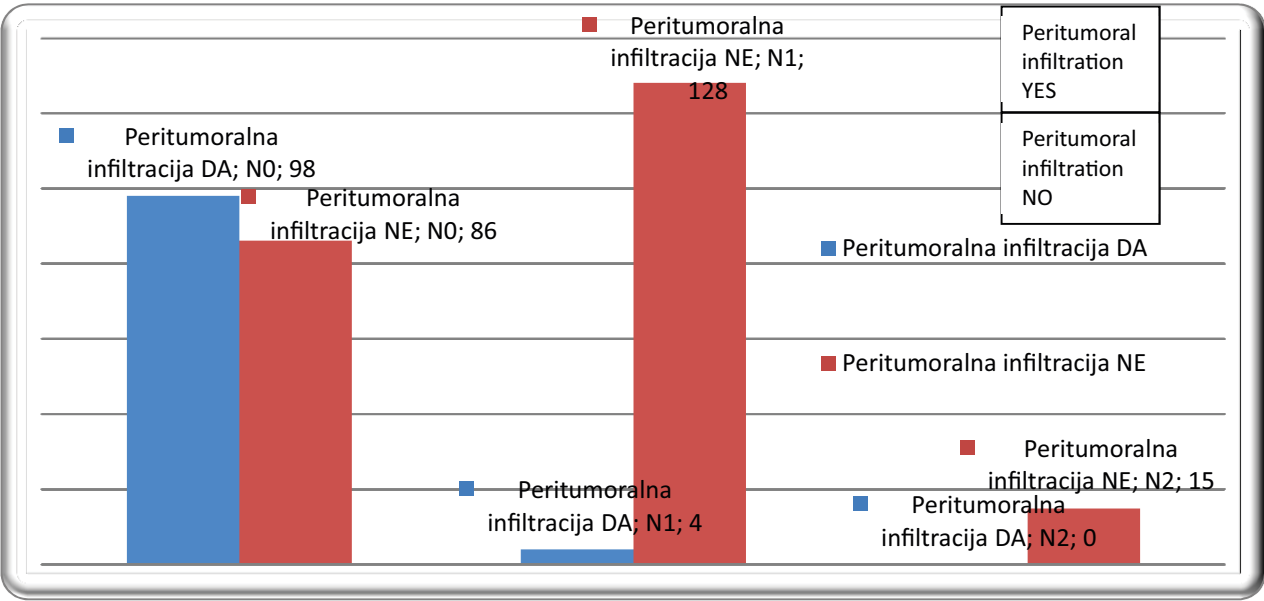


Figure I Ratio of PTLI and N stages of disease in observed resected sample of the lung cancer.

The Spearman rank correlation coefficient showed a significant association between PTLI and the occurrence of metastases to hilar and mediastinal lymph nodes ($p=0.544$, $n=331$, $p<0.001$). With regard to the relationship between the degree of

differentiation of tumor cells and the occurrence of metastases to hilar and mediastinal lymph nodes, Sperman's rank correlation coefficient showed a slight correlation between these variables ($p=0.225$, $n=331$, $p<0.001$).

Table 2 Prediction of the influence of two independent variables on the occurrence of metastases in regional lymph nodes by logistic regression model.

Logistic regression model	B	Std. error	Loose degree	p	Probability quotient	95% confidence interval for the probability quotient	
						Lower border	Higher border
Differentiation degree	1.065	0.719	I	0.1385	2.9014	0.7088	11.8764
PTLI	3.569	0.532	I	<0.001	35.4963	12.5204	100.6351
Constant	-5.1572						

Table 2 presents an assessment of the prediction of the impact of PTLI and the degree of differentiation of tumor cells, as independent variables, on the occurrence of metastases to regional lymph nodes. The logistic regression model also shows that PTLI, as an independent variable, has a statistically significant difference ($p < 0.001$) regarding the importance of findings for predicting metastasis to regional lymph nodes as opposed to the degree of tumor cell differentiation ($p = 0.1385$). Therefore, there is a 3,55 times higher risk of developing N disease when there is PTLI rather than when there is none.

DISCUSSION

PTLI was present in 86 (37.55%) patients with N0 descriptor, 128 (55.89%) patients with N1 descriptor, and 15 (6.55%) patients with N2 descriptor.

Wakabayashi, et al. (6) found PTLI in a sample of 178 patients resected for NSCLC in 64.9% of cases with N0 descriptor and 37.15% of cases with N1-2 descriptor, which was inversely different from the results of this study. The classification of tumor cell immaturity is indicated by the scale: well-differentiated tumor cells (G1 immaturity-31 (9.36%), medium differentiated (G2 immaturity-199 (60.12%), poorly differentiated (G3 immaturity-101 (30.52%). The sample was dominated by a medium degree of tumor cell immaturity (60.12%), with metastasis in the hilar lymph nodes in about 40% of cases and mediastinal lymph nodes in only 4.53% of cases.

The most represented were resectors without the presence of malignant cells in lymph nodes N0 (184=55.59%), N1 metastases were present in 132 (39.88%), and N2 metastases at 15 (4.53%). PTLI is a negative prognostic factor that significantly increases the risk of nodal and distant recurrence. Yoon Sung, et al. (7) investigated the relationship between the presence of PTLI, 5-year disease-free survival (DFS), the incidence of nodal recurrence, and distant metastasis. A total of 381 patients underwent complete resection and were diagnosed with pathologic T1-2N0 NSCLC. PTLI was present in 72 patients (18.9%). The DFS for all patients was 69.9%. Patients with PTLI showed a significant decrease in 5-year DFS (47.3 vs. 74.4%, $p < 0.001$). The patients with PTLI also showed a significantly increased 5-year cumulative incidence of nodal recurrence (22.5 vs. 8.7%, $p < 0.001$) and distant metastasis (30.4 vs. 14.9%, $p = 0.004$).

The presence of PTLI is unequivocally associated with a higher rate of local recurrence and worse overall survival in early lung cancer, as demonstrated in the study of Mimae, et al. The 5-year recurrence-free survival rates for patients without lymph node

involvement and PTLI was 91.2%, while in the group of patients with lymph node involvement and present PTLI the survival rates were significantly lower, i.e. 41.9%. Therefore, the presence/absence of PTLI stratifies the prognosis not only in patients with no nodal metastasis but also in those with metastasis.

According to our study, there is a 3,55 times higher risk of developing N disease when there is PTLI rather than in cases when there is none. It is undoubtedly a significant risk factor for regional lymph node involvement as well as a poor prognostic factor in NSCLC-patients. In these patients, it is necessary to evaluate oncologically adequate treatment strategies and recently several treatment options have been proposed, i.e. stereotactic ablative radiotherapy (SABR) and adjuvant chemotherapy are often discussed after the surgery (8).

CONCLUSION

The presence of PTLI is significantly associated with the occurrence of N1 and N2 metastases in patients with NSCLC.

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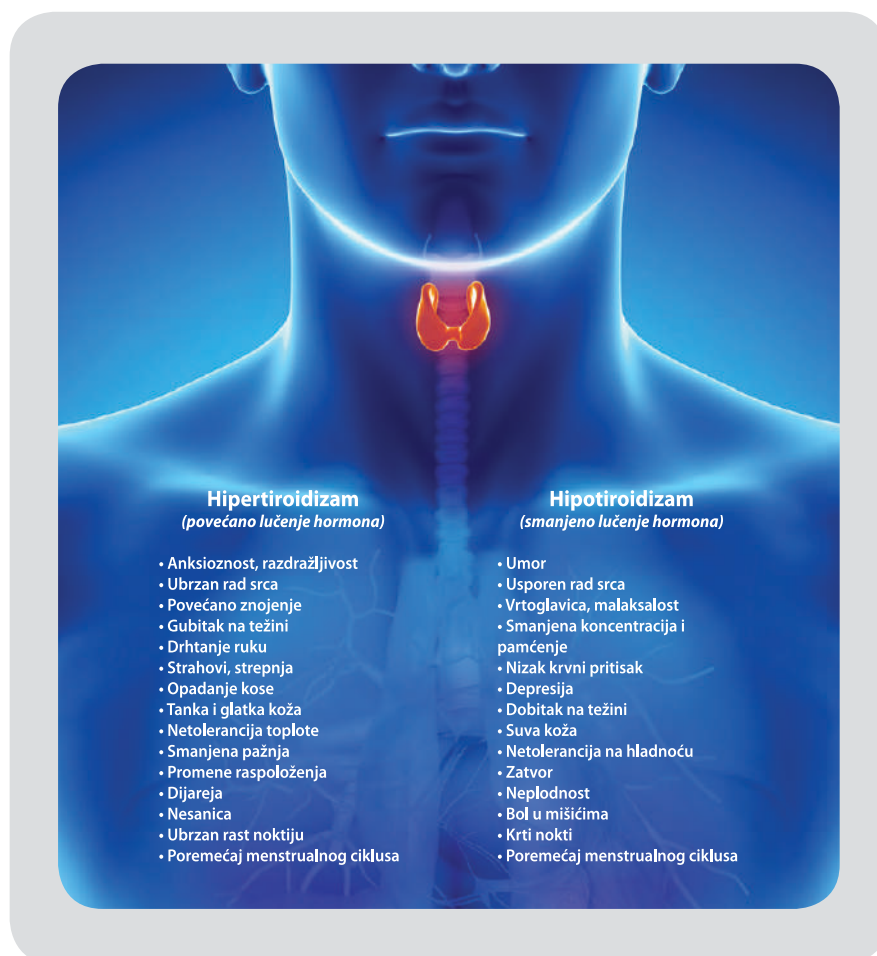
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Usage of RF generator in liver resection: our experience

Upotreba RF generatora u resekciji jetre: naše iskustvo

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ABSTRACT

Introduction: liver resection is a standard surgical procedure in which a portion of the liver is removed due to occurrence of primary and metastatic liver tumors. The RF generator is useful in terms of reducing the blood loss expressed in the first and repeated resection procedures, and selective or total vascular occlusion is less frequent with the use of this generator. **Aim:** to present our experience gathered through observation of patients who underwent liver resection using an RF resector (RF-LR), with special reference to the clinical significance of intraoperative blood loss and the course and outcome of the treatment in those patients. **Materials and methods:** this clinical study is of a retrospective-prospective nature. The patients were monitored for the occurrence of postoperative complications, postoperative deviations related to preoperative laboratory parameters taken the day before or after the operation were analyzed, and intrahospital blood loss and demographic data were also recorded. **Results:** the analysis of the surgical procedures showed a large number of non-anatomical resections: precisely in 15 (24.99%) patients. **Conclusion:** the results of the study statistically proved that the use of RF generator does not significantly reduce intraoperative and postoperative complications.

Keywords: RF generator; liver resection; metastases; complications; outcome

SAŽETAK

Uvod: resekcija jetre predstavlja standardni hirurški postupak u kojem se uklanja dio jetre zbog pojave primarnih i metastatskih tumora jetre. RF generator je koristan u pogledu smanjenja gubitka krvi koja je izražena kod prvih i ponovnih resekcionih zahvata, pojava selektivne ili totalne vaskularne okluzije je manja uz upotrebu ovog generatora. **Cilj istraživanja:** cilj studije je predstaviti naše iskustvo prikupljeno promatranjem pacijenata koji su podvrgnuti resekciji jetre pomoću RF resektora (RF-LR), uz poseban osvrt na klinički značaj intraoperativnog gubitka krvi i tok i ishod liječenja kod ovih pacijenata. **Materijal i metode:** ova klinička studija je retrospektivno-prospektivnog karaktera. Kod pacijenata se pratila pojava postoperativnih komplikacija, analizirali otkloni postoperativnih u odnosu na preoperativne laboratorijske parametre uzete dan prije odnosno poslije operacije, bilježio intrahospitalni gubitak krvi i demografski podaci. **Rezultati istraživanja:** analizom operativnih zahvata u studiji imali smo veliki broj neanatomskih resekcija i to: 15 (24,99 %) pacijenata. **Zaključak:** sve tehničke inovacije u modernoj hirurgiji jetre fokusirane su na smanjenju krvarenja tokom resekcije jetre. Rezultati našeg istraživanja su statistički dokazali da upotreba RF generatora ne utiče značajno na smanjenje intraoperativnih i postoperativnih komplikacija.

Ključne riječi: RF generator; resekcija jetre; metastaze; komplikacije; ishod

INTRODUCTION

Liver resection is a type of operative method carrying a significant risk of intraoperative bleeding, and as such is correlated with postoperative morbidity, mortality and long-term survival. Surgeon is often in a dilemma whether to use the classic method, "Crash-clamping" (CC-LR) during hepatic pedicle clamping (selective or total occlusion) while performing complex liver surgeries or to use new technical aids such as RF resector (1,2). Due to their characteristics, RF currents are suitable for application to parenchymal organs (3). RF currents can be used for tumor

ablation or for resection of a healthy liver parenchyma (3,4). Radiofrequency ablation (RFA) is used to resect unresectable liver tumors and produces coagulation necrosis of the liver parenchyma, thrombosis, and coagulation of small blood vessels.

Liver resection is a standard surgical procedure in which a portion of the liver is removed due to occurrence of primary and metastatic liver tumors. However, 60% of patients experience the tumor relapse after the procedure, with 40-60% of the occurrence in the rest of the liver. Almost half of recurrences (about 45%) occur within 6 months after the liver resection, and 88% of occurrences happen within two years (5). Only 10-25% of patients

with recurrence are considered suitable for a re-resection. Repeated resections present a major technical challenge with a higher morbidity rate, although mortality is the same as with primary resections. Numerous parameters determine the quality of liver resection procedures.

The most important of them are the duration of ischemia, blood loss, technical errors and complications, which, with adequate resection margin and exposure of anatomical landmarks, precisely determines the success rate of liver surgery (6,7,8). The RF generator is useful in terms of reducing the blood loss expressed in the first and repeated resection procedures, also the need for introduction into selective or total vascular occlusion is less frequent with the use of this generator. The RF resector uses RF energy via a standard generator to produce heat that is transferred via a metal probe and saline. RF energy overcoagulates the tissue and thus allows the closure of small blood vessels and bile ducts (3,4,6).

AIM

The aim of the study is to present the observations in patients with liver resection using the RF resectors (RF-LR), with special reference to the clinical significance of intraoperative blood loss, as well as the course and outcome of the treatment in these patients.

MATERIALS AND METHODS

This retrospective-prospective clinical study was conducted at Clinic of General and Abdominal Surgery of the Clinical Center of the University of Sarajevo on patients undergoing liver resection using an RF resector (RF-LR), regardless of the cause, during a four-year period. The study included thirty patients surgically treated by the same team of surgeons with practically the same experience. Patients were monitored for the occurrence of postoperative complications, deviations of postoperative in relation to preoperative laboratory parameters taken the day before or after the operation were analyzed, and intrahospital blood loss and demographic data were also recorded. The analysis used data from medical history, anesthesia chart and operative findings. Data was processed by descriptive statistics, and the Pearson's test was used to prove the correlation between the variables. The most significant obtained results are presented in the form of tables and figures.

RESULTS

The average age of the subjects using an RF generator (RF-LR) was 59.94 years. \pm 12.78. Fifteen (50%) of these patients were males and 15 (50%) were females. Based on the age group analysis, the following results were obtained: the study did not include a single patient under the age of 20. There were 3 (10%) patients in the 20-30 age group, 1 (3.33%) patient in the 31-40 age group, 3 (10.0%) patients in the 41-50 age group, 13 (43.33%) patients in the 51-60 age group and 10 (33.34%) patients in the age group > 60.

In the observed group there was no significant difference among the patients of individual age groups ($p=0.692$). The data are shown in Table 1.

Table 1 Age structure of patients ($p=0.962$).

AGE GROUP	NUMBER	PERCENTAGE
<20	0	0,00
20-30	3	10,0
31-40	1	3,33
41-50	3	10,0
51-60	13	43,33
>60	10	33,34
TOTAL	30	100

The analysis of the causes of the disease showed that there was a large number of colorectal adenocarcinoma metastases, specifically: 18 (30.0%). A slightly smaller number of cases occurred due to primary liver tumor (HCC), 5 (8.33%) cases and gallbladder tumor in 2 (3.33%) cases. Regarding benign diseases, there were 2 (3.33%) cases with hemangiomas, and 2 (3.33%) cases with echinococcus. Only 1 (1.66%) case was reported representing metastases of other tumors of the gastrointestinal tract.

The analysis of the surgical procedures showed that there was a large number of non-anatomical resections: in 15 (24.99%) patients precisely. There was 1 right hepatectomy (1.66%) and 2 (3.33%) left hepatectomies, 1 (1.66%) case of resection of 3 or more liver segments, 10 (16.66%) cases of segmentectomies and bisegmentectomies. No statistically significant differences were found among the examined groups, $p=0.893$.

Table 2 Types of resection procedures.

Liver resection	RF-LR	
	No.	%
Right hepatectomy	1	1,66
Left hepatectomy	2	3,33
Resection of 3 segm.	1	1,66
Extended left hepatectomy	1	1,66
Minor resection of 1 seg.	4	6,67
Minor resection (II, III)	2	3,33
Minor resection (VI,VII)	1	1,66
Minor resection (V,VI)	0	0,0
Minor resection (IV,V)	2	3,33
Resection of 2 segm.	1	1,66
Nonanatomical resection. Single	8	13,33
Nonanatomical resection. Multiple.	7	11,66
Total	30	100

Hemoglobin

Preoperative value of Hb was 135.03 ± 1.3 . Postoperative value of Hb was 116.80 ± 20.6 . There was a statistically significant difference within the T-test group = 4.101, $p < 0.0005$.

Hematocrit

Preoperative Hct value was 39.67 ± 3.7 . Postoperative Hct value was 33.17 ± 3.73 . Statistical analysis of preoperative and postoperative Hct values in the group showed that there was statistically significant difference within the group T-test = 6.649, $p < 0.0005$.

AST

Statistical analysis of preoperative and postoperative AST

values in the RF-LR group showed that there was no statistically significant difference within the group T-test = 1.003, $p = 0.32$.

ALT

Statistical analysis of preoperative and postoperative ALT values in the RF-LR group showed that there was statistically significant difference within the T-test group = 2.09, $p = 0.046$.

Bilirubin

Statistical analysis of preoperative and postoperative Bilirubin values in the RF-LR group showed that there was no statistically significant difference within the T-test group = 0.014, $p = 0.989$.

Blood loss in RF-LR group ranges from 200-1100ml with a mean $M = 03.33 \text{ ml} \pm \text{SD } 258.62$.

Table 3 Blood loss, $p = 0.029$.

Descriptive Statistics							
Operation type	No	Range	Minimum	Maximum	Sum	Mean	Std. Deviation
RF-LR	30	900	200	1100	15100	503,33	258,621

Hospitalization period in the RF-LR group ranged from 9 to 42 days with a mean bed rest of $M = 21.90 \pm \text{SD} = 10.23$ days.

Table 4 Hospitalization period, $p = 0.031$.

Descriptive Statistics						
Operation type	N	Minimum	Maximum	Sum	Mean	Std. Deviation
RF-LR	30	9	42	657	21,90	10,226

Statistical analysis of postoperative complications in the study group showed that 14 (46.7%) patients had complications, while 16 (53.4%) patients in the group did not have any complication.

In the study group, 6 patients (20%) had an intraabdominal collection which was resolved by intraabdominal postoperative drainage. There was one patient with pleural effusion (3.3%), 4 patients (13.4%) with biloma and biliary fistula, one patient (3.3%) with pneumonia and one patient (3.3%) developed pneumothorax. There was also one patient (3.3%) with wound infection.

Correlation between monitored variables in the RF-LR group

Using the Pearson's correlation test between the examined variables in the RF-LR group, it was found that postoperative Hemoglobin values were in a direct significant negative correlation with blood loss ($r = -.528$ $p = 0.003$ **) and length of hospitalization ($r = -.511$ $p = 0.004$ **). Hct values in the RF-LR group significantly negatively correlated with liver enzyme values AST ($r = -.368$ $p = 0.046$ *). AST was in a direct positive significant correlation with postoperative ALT values ($r = .954$ $p = 0.000$ **) Bilirubin ($r = .391$ $p = 0.033$ *) and blood loss ($r = .510$ $p = 0.004$ **).

Table 5 Correlation between monitored variables in the RF-LR group.

Correlations		Post. Hb	Post. Hct	Post. AST	Post. ALT	Post. Bilirub	Blood loss	Hospitalization	Complications	Age
Post. Hb	Correlation Pearson	1	-,042	-,247	-,352	-,206	-,528**	-,511**	-,101	-,127
	p		,827	,189	,057	,274	,003	,004	,732	,503
Post. Hct	Correlation Pearson	-,042	1	-,368*	-,308	-,140	-,185	,026	,108	,096
	p	,827		,046	,098	,460	,329	,890	,714	,613
Post. AST	Correlation Pearson	-,247	-,368*	1	,954**	,391*	,510**	,222	-,038	-,111
	p	,189	,046		,000	,033	,004	,237	,898	,560
Post. ALT	Correlation Pearson	-,352	-,308	,954**	1	,301	,585**	,290	-,046	-,074
	p	,057	,098	,000		,106	,001	,120	,876	,697
Post. Bilirub	Correlation Pearson	-,206	-,140	,391*	,301	1	,343	,083	-,158	-,193
	p	,274	,460	,033	,106		,064	,662	,590	,306
Blood loss	Correlation Pearson	-,528**	-,185	,510**	,585**	,343	1	,713**	-,288	,055
	p	,003	,329	,004	,001	,064		,000	,318	,772
Hospitalization	Correlation Pearson	-,511**	,026	,222	,290	,083	,713**	1	-,189	,206
	p	,004	,890	,237	,120	,662	,000		,518	,274
Complications	Correlation Pearson	-,101	,108	-,038	-,046	-,158	-,288	-,189	1	-,088
	p	,732	,714	,898	,876	,590	,318	,518		,764
Age	Correlation Pearson	-,127	,096	-,111	-,074	-,193	,055	,206	-,088	1
	p	,503	,613	,560	,697	,306	,772	,274	,764	

**Correlation is significant at the level of 0.01

* Correlation is significant at the level of 0.05

ALT was also found to be positively directly correlated with blood loss ($r=,585$ $p=0.001$)**, while blood loss was in a direct significant association (in addition to correlation with Hb, AST, ALT) and with the length of hospitalization ($r=,713$ $p=0.000$)**.

Pearson's correlation test found that there was a negative significant correlation ($r=-,527$ $p<0.01$) between the complication

variable and blood loss as well as the complication and hospitalization variables ($r=-,805$ $p<0.01$). Using the Pearson's correlation test it was found that there was a positive significant correlation between the variable blood loss and hospitalizations ($r=0.406$, $p<0.01$) (Figure 1).

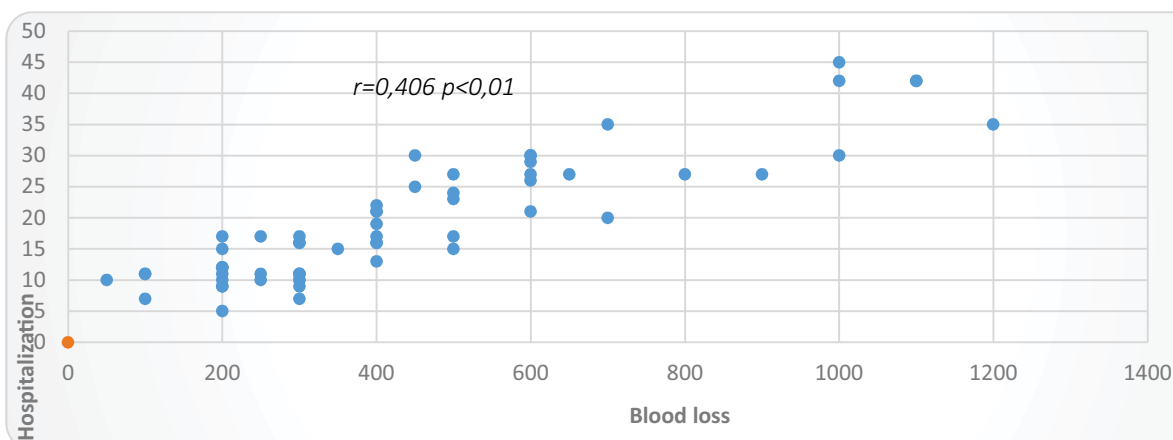


Figure 1 Blood loss - hospitalization.

DISCUSSION

Liver resection is a crucial part of primary liver cancer treatment, secondary tumor changes, and sometimes injuries, hemangiomas, and echinococcal minor cysts (9). The first operative techniques began with the digital separation of the liver parenchyma (fractur finger - digitoclasis), followed by the crash technique (Clamp-Crushing) using fine surgical instruments. These techniques were upgraded with the development of new technical aids (ultrasonic dissectors, ligatures, water-jet dissectors and RF generators). All technical innovations in modern liver surgery are focused on reducing bleeding during liver resection as it has been proven that massive bleeding and blood replacement by transfusion are associated with increased morbidity and mortality (9).

Most surgical procedures were performed due to colorectal cancer. According to the world literature, the incidence of colorectal cancer metastases is around 65% up to 72%, Miličević et al. (10) and Ayav et al. (4). Correlation analysis showed that the length of hospitalization was in significant negative correlation with postoperative Hb values ($r = -.511$ $p=0.004$) and in significant positive correlation with blood loss ($r = .713$ $p=0.000$). Other authors have come up with similar results where the average time of hospitalization ranges from 10.5 to 53.3 days. The average blood loss after liver resection, compared to the available literature, is similar and ranges from 140-750ml. Other authors have published similar results; Karamarković et al. (11) states blood loss of 330 ± 150 ml, Kin t, et al. (12) states (229.8 ± 76.8).

Bleeding is certainly the major intraoperative surgical complication and cause of death. Throughout history it has been one of the most important postoperative complication, along with bile leakage and liver failure (12,13). Pearson's correlation test showed that there is a negative significant correlation between postoperative values of Hemoglobin and blood loss ($r=-.528$, $p=0.003$). Same testing also shows a positive significant correlation between postoperative AST and ALT values ($r=.954$ $p=0.000$), and between AST and Bilirubin ($r = .391$ $p = 0.033$). Further results showed a negative significant correlation ($r = -.527$, $p<0.01$) between the variable "complication" and "blood loss" in the overall sample. There is also a negative significant correlation between the variable "complication" and the variable "hospitalization" in the overall sample ($r=-.805$ $p<0.01$), and a positive significant correlation between the variable "blood loss" and the variable "hospitalization" ($r=0.406$, $p<0.01$).

CONCLUSION

Nowadays, surgeons have a large number of operative techniques adaptable to resection of the liver and which of these techniques to choose depends mostly on the personal attitude and training of the surgeon. Despite all technical aids intraoperative blood loss was and remains a variable that undeniably influences treatment outcome. Obtained results in this study proved a significant correlation between blood loss and length of hospitalization which is consistent with the data in the available medical literature. RF liver ablation has an irreplaceable advantage in small lesions (up to 3 cm) located near large vascular structures as well as in changes that are diffusely distributed in large numbers. It also has its advantages and disadvantages and as such can be used equally in the liver resection surgery.

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Guillain-Barre syndrome in children: a single tertiary center study in Bosnia and Herzegovina

Guillain-Barre sindrom kod djece: studija tercijarnog centra u Bosni i Hercegovini

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ABSTRACT

Introduction: Guillain-Barre syndrome (GBS) is an acute, post infectious autoimmune disease of peripheral nervous system. **Aim:** to evaluate demographic and clinical features, treatment and clinical outcome of children with GBS. **Materials and methods:** the study was based on a cohort of 24 patients with GBS diagnosed, treated and followed up at Pediatric Clinic of the Clinical Center University of Sarajevo over the study period of 15 years. The patients met Brighton diagnostic criteria of diagnostic certainty and were scored by Guillain-Barre disability scale. **Results:** the mean value of the age of participants was 10.45 ± 4.87 years. The antecedent respiratory and gastrointestinal infection was present in 2/3 of patients. Cranial nerve involvement occurred in 41.7% of patients. The median time interval between onset of symptoms and lumbar puncture was 8 days (total range 2-30 days, interquartile range IQR 4.25-13.0). Elevated total protein concentration in cerebrospinal liquid (CSF TP) was found in 19/24 (79.1%) patients. Statistically significant positive correlation was found between CSF TP and interval in the period from the first symptoms of disease and lumbar puncture. ($R=0.507$; $p<0.05$) Treatment with intravenous immunoglobulins (IVIg) was administered in 21/24 (87.5%) patients, IVIg and plasmapheresis in one patient, and IVIg and methylprednisolone in one patients. **Conclusion:** CSF TP concentration is usually increased in the second week after the onset of GBS symptoms. Early diagnosis and adequate treatment of GBS are important for good clinical outcome.

Keywords: Guillain-Barre syndrome, children, cerebrospinal fluid, treatment

SAŽETAK

Uvod: Guillain-Barre syndrome (GBS) je akutno, post infektivno autoimuno oboljenje perifernog nervnog sistema. **Cilj:** evaluirati demografske i kliničke karakteristike, terapiju i klinički ishod kod djece sa GBS. **Materijali i metode:** studija je bazirana na kohorti od 24 pacijenta sa GBS, koji su dijagnosticirani, liječeni i praćeni na Pedijatrijskoj klinici Kliničkog centra Univerziteta u Sarajevu, tokom posljednjih 15 godina. Pacijenti su ispunjavali Brighton diagnostičke kriterije pouzdanosti, a za procjenu težine kliničke slike korištena je Guillain-Barre skala onesposobljenosti. **Rezultati:** srednja vrijednost dobi pacijenata sa GBS je bila 10.45 ± 4.87 godina. Predhodna respiratorna i gastrointestinalna infekcija je bila prisutna kod 2/3 pacijenata. Zahvaćenost kranijalnih nerava je bila prisutna kod 41,7% pacijenata. Mediana vremenskog interval između pojave prvih simptoma bolesti i lumbalne punkcije je bila 8 dana (totalni raspon 2-30 days, interkvartni raspon IQR 4.25-13.0). Povećane vrijednosti ukupnih proteina u cerebrospinalnom likvoru su ustanovljene kod 19/24 (79,1%) pacijenata. Ustanovljena je statistički signifikantna pozitivna korelacija između koncentracija ukupnih proteina u cerebrospinalnom likvoru i vremenskog intervala između pojave prvih simptoma bolesti i lumbalne punkcije ($R=0,507$; $p<0,05$). Terapija intravenoznim imunoglobulinima (IVIg) je ordinirana kod 21/24 (87,5%) pacijenata, IVIg u kombinaciji sa plazmaferezom kod jednog pacijenta, a IVIg u kombinaciji sa metilprednizolonom kod jednog pacijenta. **Zaključak:** koncentracija ukupnih proteina u cerebrospinalnom likvoru je obično povećana u drugoj sedmici nakon pojave simptoma GBS. Rana dijagnoza i adekvatna terapija kod GBS su značajni za dobar klinički ishod.

Ključne riječi: Guillain Barre syndrome, djeca, cerebrospinalni likvor, terapija

INTRODUCTION

Guillain-Barre syndrome (GBS) is an acute, post infectious, autoimmune disease of peripheral nervous system (1). It is important cause of acute flaccid paralysis (AFP) in children. The incidence of GBS in children is 0.6 per 100 000 per year. It is slightly

more frequent in males than in females (2-4). GBS is divided into the two major subtypes: acute motor axonal neuropathy (AMAN) and acute inflammatory demyelinating polyneuropathy (AIDP) (5). Brighton diagnostic criteria for GBS consist of four levels of diagnostic certainty, with Level 1 (the highest diagnostic certainty) and Level 4 (the lowest diagnostic certainty) (6) (Table 1).

Table 1 Brighton diagnostic criteria for GBS (6).

Diagnostic criteria	Level of diagnostic certainty			
	1	2	3	4
Bilateral and flaccid weakness of limbs	+	+	+	+/-
Decreased or absent deep tendon reflexes in weak limbs	+	+	+	+/-
Monophasic course and time between onset-nadir 12h to 28d	+	+	+	+/-
CSF cell count < 50/ μ l	+	+*	-	+/-
CSF protein concentration > normal value	+	+/-*	-	+/-
NCS findings consistent with one of the subtypes of GBS	+	+/-	-	+/-
Absence of alternative diagnosis for weakness	+	+	+	+

+ present; - absent; +/- present or absent

NCS nerve conduction studies

* if CSF is not collected or results not available, nerve electrophysiology results must be consistent with the diagnosis of Guillain-Barre syndrome

Clinical course of GBS was scored by Guillain-Barre disability scale, ranging from 0 to 6 (6) (Table 2).

Table 2 Guillain-Barré syndrome disability scale adapted (6).

Score	Description
0	A healthy state
1	Minor symptoms and capable of running
2	Able to walk 10m or more without assistance but unable to run
3	Able to walk 10m across an open space with help
4	Bedridden or chairbound
5	Requiring assisted ventilation for at least part of the day
6	Dead

GBS is the most common cause of nonpolio AFP worldwide (7). Preceding infection, vaccination or other immune stimulation, triggers the patient's autoimmune response targeting peripheral nerves and their spinal roots (4,5,8). Rapidly progressive bilateral weakness is ascending, associated with sensory and cranial nerve involvement and may progress to respiratory failure with need of ventilation at the intensive care unit (6). Normal concentration of cerebrospinal fluid total protein (CSF TP), especially when the sample was taken in the first week after the onset of disease, does not exclude GBS (8). Electrophysiological studies are helpful in supporting the diagnosis (8). Magnetic resonance imaging (MRI) of the brain and spine are not a part of the routine diagnostic evaluation of GBS, but can be helpful for excluding other diagnosis. Recently, gadolinium-enhanced magnetic resonance imaging of the nerve roots was reported to be equally accurate as nerve conduction studies and lumbar puncture (9). Ultrasound of the peripheral nerves is the new potential diagnostic method, by which the enlarged cervical nerve roots are found at the beginning of the disease (10).

MATERIALS AND METHODS

The study was based on a cohort of 24 patients who met diagnostic criteria of GBS treated and followed up at Pediatric Clinic of the Clinical Center University of Sarajevo, during the study period of 15 years. The follow up period ranged between 9 months and 15 years. Data were collected as follows: age, gender, preceding infection, neurological signs and symptoms at the admission to the hospital and at the nadir, CSF analysis, length of stay in hospital and intensive care unit, length of mechanical ventilation, treatment options and neurological outcome. All patients were classified according to Brighton diagnostic criteria for GBS into 4 levels and then into two groups: Level 1 GBS group and Level 2-4 GBS group. According to clinical course of disease, all patients in this study were scored by Guillain-Barre disability scale, ranging from 0 to six and then divided into two groups: mild/moderate GBS (GBS disability score 2 and 3) and severe GBS patients (GBS disability score 4 and 5). Nadir was defined as the highest Guillain-Barre syndrome disability score. Clinical onset of

GBS was defined as the first symptoms of paresthesia or symmetrical muscular weakness. CSF TP level of 0.40g/l was used as upper cutoff value of our laboratory. Other diagnoses than Guillain-Barre syndrome were excluded by the child neurologists according to routine diagnostic work-up.

Statistical analysis

The results were analyzed by standard statistical methods. SPSS (SPSS-Statistical Package for Social Sciences) computer program version 21.0. was used for statistical analysis. The results were presented as absolute numbers, percentage, and means (\bar{x}), standard deviations (SD), medians and interquartile ranges (IQR). The Shapiro-Wilk test was used to examine if variables are normally distributed. The Student t-test was used for comparative analysis of numerical variables with normal distribution. The Mann-

Whitney U test was used for variables without normal distribution. Differences in proportions were tested by the Chi-square or Fisher exact tests. The Spearman's rank correlation coefficient (Rho) was used as a measure of correlation between variables. P -value < 0.05 was considered to be statistically significant. Correlations between MRC sum scores were expressed by the Spearman rank correlation coefficient (r_s). Differences in proportions were tested by the Chi-square or Fisher exact tests and differences in continuous variables by the Mann-Whitney U test. P -value < 0.05 was considered to be statistically significant.

RESULTS

Demographical, clinical and biochemical data of GBS patients are summarized in Table 3.

Table 3 Demographic, clinical and biochemical data of GBS patients.

Demography		
Gender M/F ratio	16/8	2:1
Age (years)	range 1y7mo-16y8mo	10.45±4.87
Symptoms of antecedent infection		
Upper respiratory tract infections	8/24	33.3%
Gastrointestinal infection	8/24	33.3%
Other	8/24	33.3%
Diagnosis (Brighton criteria)		
Level 1	20/24	83.8%
Level 2	4/24	16.7%
Neurological symptoms at entry		
GBS disability score 2+3	12/24	50%
GBS disability score 4+5	12/24	50%
Cranial nerve involvement	11/24	41.7%
Ventilator dependent	1/24	4.2%
Neurological symptoms at nadir		
GBS disability score 2+3	11/24	41.7%
GBS disability score 4+5	13/24	58.3%
Cranial nerve involvement	11/24	41.7%
Ventilator dependent	3/24	12.5%
Cerebrospinal liquid examination		
Interval between the onset of symptoms and lumbar puncture (days)	8 days (median)	IQR 4.25-13.0
Protein concentration in CSF (g/L)	0.60 (median)	IQR 0.44-1.49
Cell count (no of cells <50μL)	2.0	0.0-3.0
Treatment		
IVIg	21/24	87.5%
IVIg+plasma exchange	1/24	4.16%
IVIg + methylprednisolone	1/24	4.16%
Plasma exchange only	0	0
Supportive treatment only	1/24	4.16%

There were no patients with GBS score 1 and GBS score 6. Mechanical ventilation was needed for only one patient (1/24, 4.2%) at the admission, but at the nadir three patients (3/24, 12.5%) were mechanically ventilated. Cranial nerve involvement occurred in 11/24 (41.7%) patients, equally in mild/moderate and severe GBS groups.

Lumbar puncture was performed in all 24 (100%) patients. The median time interval between the onset of symptoms and lumbar puncture was 8 days (total range 2-30 days, IQR 4.25-13.0). CSF TP

was elevated for 19/24 (79.1%) patients, with a median of 0.60 g/L, (total range 0.20-3.61, interquartile range IQR 0.44-1.49). CSF TP concentration has been compared with time interval between the first symptoms of disease and lumbar puncture for all participants. Significant positive correlation was found ($R_{ho}=0.507$; $p<0.05$). CSF TP concentration and time interval between the first symptoms of disease and lumbar puncture have been compared separately for mild/moderate and severe GBS group. Statistically significant correlation was present in mild/moderate GBS group

($Rho=0.776$, $p<0.01$), but in the severe GBS group there were no statistically significant correlation ($Rho=0.374$). CSF TP concentration was separately analyzed according to the certain days of disease duration when the lumbar puncture was performed: 0-

3, 4-7, 8-14 and >14 days after the onset of disease, with CSF TP concentration elevated in 75%, 57%, 100%, 80% of patients respectively (Figure 1).

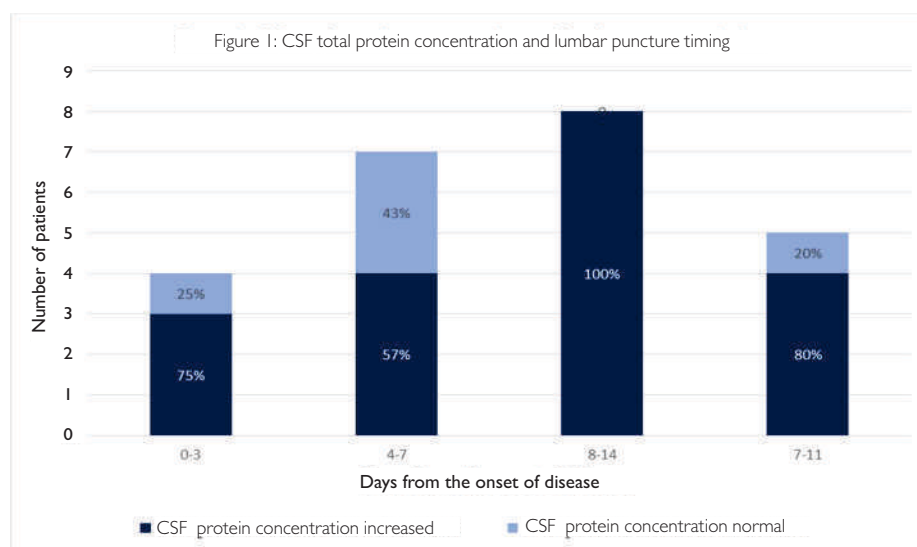


Figure 1 Total protein concentration and lumbar puncture timing.

One patient received supportive treatment only due to mild form of disease (GBS score 2) and late admission to the hospital (30 days after the onset of symptoms). The median time of stay in hospital was 20.0 days (total range 10-68, IQR 12.0-33.0). The clinical outcome for 23/24 patients was full recovery after 12-24 months follow up. One patient has been monitored for nine months and is still recovering. There were two cases of recurrence and no cases of lethal outcomes.

Comparison of variables between mild/moderate GBS group and severe GBS group is presented in Table 4. Length of stay in hospital for patients with severe form of GBS was 26.0 (16.0-43.5) days which was statistically significantly longer in comparison to the patients with mild/moderate form of disease, which was 14.0 (10.0-22.5) days ($p=0.028$). There was no statistically significant difference between GBS groups in respect of other variables.

Table 4 Comparison of variables between mild/moderate and severe GBS groups.

Variables	GBS score (2+3) (n=12)	GBS score (4+5) (n=12)	p
Age (years)	11.65±4.77	9.25±4.86	0.236
Cranial nerve involvement	4 (33.3%)	7 (58.3%)	0.207
Sensory deficits	4 (33.3%)	6 (50%)	0.340
Pain	4 (33.3%)	7 (58.3%)	0.207
Interval between onset of disease and lumbar puncture (days)	9.0 (4.0-15.5)	7.5 (5.25-9.75)	0.590
Protein concentration in CSF (g/L)	0.60 (0.48-1.18)	0.70 (0.40-3.01)	0.671
Cell count (No of cells $<50 \mu\text{L}$)	2.5 (0.0-3.75)	1.0 (0.0-2.75)	0.551
Length of stay in hospital (days)	14.0 (10.0-22.5)	26.0 (16.0-43.5)	0.028

CSF – cerebrospinal fluid, ICU – Intensive care unit

DISCUSSION

In this study, 24 children with GBS were evaluated during the study period of 15 years. The mean age of participants was 10.45 ± 4.87 years, similar to the study of Wu X, et al, where the mean age of participants was 9.4 ± 4.5 years (11). The boys were more affected (male/female ratio 2:1), similar to other studies (4,5,11-13). The antecedent infection, within 15 days before the onset of disease, was present in 2/3 of patients, with upper respiratory tract infection and gastrointestinal infection equally. It is

consistent with findings in other studies (5, 11). One child developed GBS after diphtheria-tetanus-pertussis-polio immunization that happened 7 days before the onset of first symptoms. Multiple studies found no evidence of an increased risk of GBS following any vaccination, as well as all vaccinations combined (14). In one case, 15 year old boy, GBS developed the second day after surgical intervention due to testicular torsion. The study of Lei Bao et al. confirmed that median duration between surgery and the onset of post-surgical GBS was 16 days (range 4-36 days) (15). There were also one case, 6 year old boy, with post-

infectious GBS followed by the development of myasthenia gravis within one month. Comorbidity of GBS and myasthenia gravis is extremely rare (16,17). Brighton diagnostic criteria for GBS in children have a high sensitivity, as children usually present with classic symptoms of GBS. In our study the Brighton criteria for level 1 fulfilled 20/24 patients (83.8%), while 4/24 patients (16.7%) fulfilled criteria for Level 2. In the study of Roodbol et al Brighton level 1 was present in 72% patients (9). Accurate diagnostic criteria for GBS are important for clinical practice in order to establish the diagnosis early and initiate specific treatment as soon as possible (6). Distribution of patients with mild/moderate and severe form of GBS was equal. There were no cases of lethal outcome, due to prompt diagnosis and treatment. The similar results were published by Roodbol et al (9). At the admission only one child (4.2%) was ventilated, but at the nadir there were 3 children (12.5%) who needed mechanical ventilation. In the the study of Roodbol et al at the admission 3% patients were mechanically ventilated, but at the nadir that result was 24%, which is much higher than in our study (9). In the Iranian study which enrolled 57 children with GBS, 8% of patients were mechanically ventilated (13). The cranial nerve involvement was present in 41.7% patients at the admission which is similar to Roodbol et al. study, with 53% of patients (9). In Indonesian study 29.6% of pediatric GBS patients presented with cranial nerve involvement (4).

The lumbar puncture was performed in all patients, while in the Dutch study of Roodbol et al. lumbar puncture was performed in 85% of patients (9). In our study the median time interval between the onset of symptoms and lumbar puncture was 8 days, while in the Dutch study the median time was 4 days (9). CSF TP baseline level was elevated in 19/24 (79%) patients. There was significant positive correlation between the CSF TP and timing of lumbar puncture ($Rho=0.507$; $p<0.05$). The same results are published by Bourque et al, (18). The CSF samples collected after the first week after the onset of symptoms showed increased CSF TP, with 100% for interval 8-14 days and 80% for interval above 14 days. Lumbar puncture performed in the first week after the onset of disease mostly help to rule out infectious or neoplastic disease (19). Timing of the CSF TP measurement is critical. There were no statistically significant correlation between CSF TP and time interval between the onset of symptoms and lumbar puncture, for severe GBS patients. CSF TP levels in GBS are elevated due to damage and increased permeability of the blood-CSF barrier and blood-nerve barrier and intrathecal synthesis of proteins. 80% of the proteins in CSF are blood derived, while the other 20% are brain derived (20). Albumins constitute 56-76% of CSF TP. Albumins are neither synthesized nor metabolized in CNS. They are exclusively synthesized in liver. A combination of elevated CSF TP level and normal cell count in CSF could be regarded as the CSF biomarker for GBS (10, 20). CSF TP is sensitive test for GBS in the second week after the onset of disease, but it may not predict the severity of disease reliably (6, 18, 21). Limited published studies on CSF TP in pediatric GBS are available.

IVIg have been used as the first line treatment for children with GBS, due to its safety and convenience (22). The majority of our patients (87.5%), were treated with IVIg only, while in the study of Gupta, et al. 96% of pediatric GBS patients were treated with IVIg (5). Treatment with IVIg should be started if patient is unable to walk independently for 10 m, within the first 2 weeks after the onset of weakness (8). IVIg was usually administered immediately after established diagnosis. It is more effective in the early stages of disease, before the serious damage to nerves develops, especially in patients with rapidly progressive weakness (8,10,11,23). Patients

with severe form of GBS have had statistically significant longer stay in hospital in comparison to mild/moderate form of GBS. Similar results were published by van Leeuwen et al, with median hospital stay of 17 days (IQR 11-26 days, total range 1-133days) (24).

CONCLUSION

This study evaluated the demographic and clinical characteristics of GBS in children. CSF TP is usually increased in the second week after the onset of symptoms. IVIg is the first line treatment for children with GBS, if diagnosed within 2 weeks of the first symptoms. Early diagnosis and adequate treatment of GBS are important for good clinical outcome.

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Naš prilog redukciji kardiovaskularnih bolesti u Bosni i Hercegovini!



Selection of osteosynthesis technique in the treatment of acute hand trauma

Odabir osteosintetske tehnike u tretmanu akutne traume šake

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ABSTRACT

Introduction: assessment of the fracture complexity and level, and selection of the most optimal osteosynthesis technique are important segments of postoperative recovery and functionality in acute hand trauma. **Aim:** To assess the gender and age distribution in the examined group, evaluate osteosynthesis techniques with concerning to the specificity of the fracture site, level, and complexity. **Materials and methods:** we assessed 120 cases of acute hand trauma with accompanying bone injury and indication for the osteosynthesis, treated at Clinic of Reconstructive and Plastic Surgery of the Clinical Center University of Sarajevo, in the period from 2014 to 2019, with the evaluation of gender and age distribution, etiological factors and various osteosynthesis techniques. **Results:** statistically significant difference was evaluated in gender distribution, with a higher male representation, (91.7%); χ^2 -test = 83.333; $p=0.0001$. The mean age was 41.65 ± 10.90 . Statistically significant difference found between the average age in relation to gender; $F=35.690$; $p=0.001$. The most common etiological factor was working machines (40.8%). Statistically significant correlation found between the osteosynthesis technique in relation to the fracture site, $\chi^2=69.813$; $p=0.001$, fracture level; $\chi^2=1.143$; $p=0.253$ and complexity; $\chi^2=14.904$; $p=0.001$. **Conclusion:** osteosynthesis with Kirschner wires is the preferred method with concerning to fracture localization, complexity, and level, due to the relative simplicity of the technique, and the ability to achieve the appropriate postoperative fracture position. The indication for use of the other available, as well as combined osteosynthetic techniques, depends on the degree of bone destruction, as well as the surgeon's preference.

Keywords: fracture, Kirschner wires, osteosynthesis, hand trauma

SAŽETAK

Uvod: procjena kompleksnosti i nivoa frakture, kao i selekcija najoptimalnije postoperativne tehnike su važni segmenti postoperativnog oporavka i funkcionalnosti u akutnoj traumi šake. **Cilj:** procijeniti polnu i dobnu distribuciju u ispitivanoj grupi pacijenata, evaluirati vrste primjenjenih osteosintetskih tehnika u odnosu na specifičnost frakturnog mjesta, nivoa i kompleksnosti lezije. **Materijali i metode:** procijenili smo 120 slučajeva akutne traume šake sa pratećom lezijom koštanog sistema i indikacijom za osteosintezu, tretiranih na Klinici za rekonstruktivnu i plastičnu hirurgiju Kliničkog centra Univerziteta u Sarajevu, u periodu od 2014 do 2019 godine, sa evaluacijom polne i dobne distribucije, etioloških faktora, i primjenjenih tehnika osteosinteze. **Rezultati:** utvrđena statistički značajna razlika u polnoj distribuciji, sa većom zastupljenošću muškog pola, (91.7%); χ^2 -test= 83.333; $p=0.0001$. Srednja životna dob ispitanika je iznosila 41.65 ± 10.90 . Statistički značajna razlika utvrđena između prosječne starosne dobi pacijenta u odnosu na polnu zastupljenost, $F=35.690$; $p=0.001$. Najčešći etiološki faktor su bile radne mašine (40.8%). Statistički značajna korelacija utvrđena između primjenjene tehnike osteosinteze u odnosu na lokalizaciju, kompleksnost i nivo frakturne lezije zbog relativne jednostavnosti u primjeni i mogućnosti postizanja odgovarajuće postoperativne pozicije frakturnih segmenata. Indikacija za primjenu drugih dostupnih, kao i kombiniranih osteosintetskih tehnika je ovisna od stepena destrukcije, kao i preferencija hirurga.

Ključne riječi: fraktura, Kiršnerova igle, osteosinteza, trauma šake

INTRODUCTION

Bone injuries of the hand are very common in everyday practice, and therefore careful clinical assessment of each case is very important (1). Considering the complexity and the extent of the injury, fractures can be treated conservatively, or surgically, which refers mainly to dislocated extraarticular and most intraarticular fractures (2). All unstable fractures, with an unsatisfactory position of fracture segments and consequent dislocation, represent an indication for surgical correction, but the important fact is that most of these fractures were combined with the injury of the adjacent anatomical structures, which affects the complexity of surgical treatment and overall pre and intraoperative evaluation (3).

When setting the indication for surgical treatment and osteosynthesis, it is important to select the appropriate technique, which has to have a unique goal in terms of preserving bone length and ensuring postoperative hand functionality (4). The stability of fragments after surgical treatment is important for the proper formation of callus and the resistance of osteosynthetic material to the potential influence of external forces, especially in cases of early mobilization within the postoperative recovery program (5).

The use of minimally invasive techniques is preferred, the lower degree of tissue destruction is proportional to the smaller volume of scarring and potential contractures (6) so that minimal invasiveness in the surgical treatment of phalangeal and metacarpal fractures becomes the method of choice to optimize results and quality of surgery (7). Kirschner wire is the modality of choice in most bone injuries in hand trauma due to its relative simplicity in achieving good congruence of fractured fragments, its selection is often related to both surgeon's preferences and relative availability (8).

The combination of different osteosynthesis techniques represents the method of choice for more complex fractures when one technique cannot achieve satisfactory congruence of fractured fragments so that combining techniques optimizes the postoperative result (9). The proper diagnosis of phalangeal, metacarpal, and carpal fractures is crucial due to the possibility of their oversight in standard X-ray interpretations, so that other diagnostic modalities, such as Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) could be also used in evaluation (10), therefore carpal lesions have to be also carefully assessed from the point of potential combination with phalangeal and metacarpal fractures (11).

AIM

To assess the gender and age distribution in the examined group, evaluate osteosynthesis techniques to the specificity of the fracture site, level, and complexity, as well as the most commonly used osteosynthesis technique according to the estimated parameters.

MATERIALS AND METHODS

The study assessed 120 patients with acute hand trauma and accompanying bone injuries, with an indication for osteosynthesis, treated at Clinic of Reconstructive and Plastic Surgery of the Clinical Center University of Sarajevo, in the period from 2014 to 2019, with the evaluation of gender and age distribution, various etiological factors, osteosynthesis techniques concerning fracture sites and levels, and injury complexity. Statistical data processing was done through IBM SPSS Version 20.0 for Windows. Analysis of categorical variables was performed using Pearson's χ^2 -test or Fisher's exact probability test. A parametric test (Anova test) was used to compare the symmetric distribution of continuous variables. Mann-Whitney U test was used in the asymmetric distribution of continuous variables. The Pearson and Spearman rank correlation coefficients were used to examine the linear correlation. Statistical significance was set at the conventional level ($\alpha=0.05$). The results were shown in the graph and contingency tables (numbers with three decimal places). The level of significance was, $p<0.0$.

Study inclusion criteria: patients of all ages and genders with carpal, metacarpal, and phalangeal fractures; patients with indications for osteosynthesis and patients subjected to isolated or combined osteosynthesis techniques

Study exclusion criteria from the study: patients primarily treated in other hospital facilities, cases without the possibility of adequate postoperative evaluation

RESULTS

The study included 120 patients who met the inclusion criteria. Out of the total number of estimated cases in this study, 110 participants (91.7%) were male and 10 (8.3%) were female. We confirmed statistically significant difference in the frequency of gender representation, male subjects dominated, $\chi^2=83.333$; $p=0.001$. The average age of the estimated group was 41.65 ± 10.90 years. Statistically significant difference was found using the Anova test on the average age to the gender structure, $F=35.690$; $p=0.001$. The average age of the male subject was 43.22 ± 9.93 years, while female subjects were statistically significantly younger, 24.30 ± 3.36 years (Table 1).

Table 1 Correlation between average age and gender distribution.

	N	X	SD	SEM	95% CI		Minimum	Maximum
					Lower	Upper		
Male	110	43.22	9.93	0.94	41.35	45.10	18.00	70.00
Female	10	24.30	3.36	1.06	21.89	26.70	20.00	29.00
Total	120	41.65	10.90	0.99	39.67	43.62	18.00	70.00

$F=35.690$; $p=0.001$

Various etiological factors were evaluated with the resulting bone injuries (Table 2). Injuries with working machines were the most common 49 (40.8%), followed by sharp objects, 32 cases

(26.7%). Hand injuries in traffic accidents presented in the least number of cases in our study group, 3 cases (2.5%).

Table 2 Distribution of etiological factors.

		No	Percentage	Valid percentage	Cumulative percentage
Etiology	Working machines	49	40.8	40.8	40.8
	Sharp objects	32	26.7	26.7	67.5
	Heavy objects	14	11.7	11.7	79.2
	Explosive injuries	13	10.8	10.8	90.0
	Contusion injuries	9	7.5	7.5	97.5
	Traffic accidents	3	2.5	2.5	100.0
	Total	120	100.0	100.0	

Osteosynthesis with Kirschner needles was the most commonly used technique, 84 cases (70%), followed by cerclage, 20 cases

(16.7%), while other types of osteosynthesis were used in smaller percentages (Table 3).

Table 3 Representation of osteosynthesis techniques in the assessed group.

		No	%	Valid percentage	Cumulative percentage
Osteosynthesis techniques	Kirschner wire	84	70.0	70.0	70.0
	Cerclage	20	16.7	16.7	86.7
	External fixation	5	4.2	4.2	90.8
	Kirschner wire and cerclage	7	5.8	5.8	96.7
	Kirschner wire and external fixation	2	1.7	1.7	98.3
	Plate and screw fixation	2	1.7	1.7	100.0
	Total	120	100.0	100.0	

Osteosynthesis with Kirschner wire was the most common technique in phalangeal fractures, 50 cases (59.5%) and metacarpal fractures, 20 cases (23.8%). Cerclage techniques were also present in higher percentage in phalangeal fractures, 8 cases (40.0%) and metacarpal fractures, 6 cases (30.0%). Plate and screw osteosynthe-

sis represented only in cases of trapezoid fractures. Using χ^2 -test, a statistically significant difference was found in the correlation between osteosynthesis technique and fracture site, $\chi^2= 69.813$; $p=0.001$ (Table 4).

Table 4 Relation between osteosynthesis technique and fracture site.

		Fracture site						Total
		Phalangeal fractures	Metacarpal fractures	Trapezium fractures	Trapezoid fractures	Capitate fractures	Hamate fractures	
Kirschner wire	No	50	20	8	2	2	2	84
	%	59.5%	23.8%	9.5%	2.4%	2.4%	2.4%	100.0%
Cerclage	No	8	6	2	3	1	0	20
	%	40.0%	30.0%	10.0%	15.0%	5.0%	0.0%	100.0%
External fixation	No	0	4	1	0	0	0	5
	%	0.0%	80.0%	20.0%	0.0%	0.0%	0.0%	100.0%
Kirschner wire and cerclage	No	1	1	2	1	1	1	7
	%	14.3%	14.3%	28.6%	14.3%	14.3%	14.3%	100.0%
Kirschner wire and external fixation	No	0	0	1	0	1	0	2
	%	0.0%	0.0%	50.0%	0.0%	50.0%	0.0%	100.0%
Plate and screw fixation	No	0	0	0	2	0	0	2
	%	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	100.0%
Total	No	59	31	14	8	5	3	120
	%	49.2%	25.8%	11.7%	6.7%	4.2%	2.5%	100.0%

Osteosynthesis techniques were variably distributed to fracture levels. Kirschner wire was predominant in phalangeal fractures, 71 cases (84.5%), and metacarpal fractures, 8 cases (9.5%). The prevalence of other osteosynthesis techniques was significantly lower

compared with Kirschner wires (Table 7), χ^2 -test did not confirm a statistically significant difference between fracture level and osteosynthesis technique; $\chi^2=1.143$; $p=0.253$ (Table 5).

Table 5 Frequency of osteosynthesis technique to the fracture level.

			Fracture level				Total
			Phalanges	Metacarpal	Carpal	Phalanges/carpal	
Osteosynthesis technique	Kirschner wire	No	71	8	3	2	84
		%	84.5%	9.5%	3.6%	2.4%	100.0%
	Cerclage	No	14	2	2	2	20
		%	70.0%	10.0%	10.0%	10.0%	100.0%
	External fixation	No	3	2	0	0	5
		%	60.0%	40.0%	0.0%	0.0%	100.0%
	Kirschner wire and cerclage	No	5	2	0	0	7
		%	71.4%	28.6%	0.0%	0.0%	100.0%
	Kirschner wire and external fixation	No	1	1	0	0	2
		%	50.0%	50.0%	0.0%	0.0%	100.0%
	Plate and screw fixation	No	1	1	0	0	2
		%	50.0%	50.0%	0.0%	0.0%	100.0%
	Total	No	95	16	5	4	120
		%	79.2%	13.3%	4.2%	3.3%	100.0%

Statistically significant difference was found between lesion complexity and selection of osteosynthesis technique, $\chi^2=14.904$; $p=0.001$. Combined fractures, due to the presence of adjacent

anatomical structures injuries, represented the indication for various osteosynthesis techniques, Kirschner wire (85.2%), cerclage (85%), and a combination of these two techniques (71.4%) (Table 6).

Table 6 Representation of osteosynthesis techniques to fracture complexity.

			Lesion complexity		Total
			Combined fractures	Isolated fractures	
Osteosynthesis techniques	Kirschner wire	No	80	4	84
		%	95.2%	4.8%	100.0%
	Cerclage	No	17	3	20
		%	85.0%	15.0%	100.0%
	External fixation	No	3	2	5
		%	60.0%	40.0%	100.0%
	Kirschner wire and cerclage	No	5	2	7
		%	71.4%	28.6%	100.0%
	Kirschner wire and external fixation	No	1	1	2
		%	50.0%	50.0%	100.0%
	Plate and screw fixation	No	1	1	2
		%	50.0%	50.0%	100.0%
	Total	No	107	13	120
		%	89.2%	10.8%	100.0%

DISCUSSION

Acute hand trauma with bone injuries represent always a reconstructive challenge due to the possibility of associated injuries, the influence of multiple etiological factors, and resulting fractures of varying complexity, which need to be correctly clinically assessed and treated (12). During the evaluating of acute hand trauma, it is important to identify fractures, that could be successfully manually repositioned, as well as lesions with dislocation and with an indication for osteosynthesis, whose choice depends on surgeon preferences, material availability, and clinical experience and competencies (13). Preference of Kirschner wires as the most commonly used modality of osteosynthesis in bone lesions of the hand is the result of the relative simplicity of the method and the achievement of a satisfactory relation of fractured fragments (14). Although external fixation is used in more complex hand injuries, associated with more extensive tissue destruction, the use of Kirschner wires, isolated or combined with other modes of osteosynthesis, remains the method of choice for most surgeons (15). More complex bone lesions often require the use of cerclage techniques combined with other osteosynthesis techniques to achieve fracture site stability (16). The advantage of Kirschner wires over osteosynthesis with plates and screws is reflected in potential tendon adhesions and secondary procedures for metal implant extraction, although plate and screw osteosynthesis remains the method of choice for carpal lesions (17), with the respectable indication in metacarpal fractures (18), such as neck and oblique lesions (19). Kirschner wires represent a satisfactory alternative to plates and screws, with excellent postoperative results and reduction of the complication rate (20). Stability of all types of osteosynthesis and resistance to early mobilization and maintenance of an adequate position of fractured fragments is the most important factor in technique selection (21). Recent trends are towards finding more efficient ways of osteosynthesis in terms of preventing tendon irritation and increased peritendinous scarring, as well as preserving joint cartilage during surgical manipulation due to contracture prevention, as one of the unwanted postoperative complications, which are often uncorrectable in neglected cases (22). Specific osteosynthesis techniques are not directly related to potential irritation of surrounding soft tissue structures and scarring (23), so the use of Kirschner wires, as the dominant osteosynthesis modality in phalangeal and metacarpal lesions, mostly without combination with other techniques, resulted in stable fragments during surgical manipulation (24), thanks to the relatively simple and effective application (25), which made it a method of choice in our study.

CONCLUSION

Fracture lesions represent a significant segment of hand trauma. The degree of destruction and dislocation correlated directly with the type of etiological factor. The predominant presence of males in our study was the consequence of higher exposure to a potential etiological factors. The selection of osteosynthesis technique in our study was guided by the principle of simplicity with the most optimal result and minimal destruction of the surrounding tissue, which affected the quality of postoperative recovery and prevention of potential disability. The dominant application of Kirschner needles, isolated and combined, in fracture lesions of all levels and complexity, was the result of clinical experience, as well as the relatively easy achievement of a

satisfactory postoperative result. The use of other isolated or combined osteosynthesis techniques was conditioned in our study by the extent of destruction and the level of the lesion, depending on the clinical assessment of each case and the expected benefit.

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Significance of inflammatory parameters in obese pediatric population

Signifikantnost inflamatornih parametara kod gojazne pedijatrijske populacije

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ABSTRACT

Introduction: obesity is an excessive accumulation of fat in the body developed on a high sugar intake but other factors such as genetic predisposition also play an important role. **Aim:** to compare values of inflammatory parameters: (leukocyte count, platelet count, neutrophil, lymphocytes, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and Systemic Immunoinflammatory Index (SII) between obese children without comorbidities and their healthy peers in Bosnia and Herzegovina. Age and gender differences were tested. **Materials and methods:** the study included 75 obese children of prepubertal and pubertal age who came for the first time to the Pediatric Clinic for weight gain. The control group consisted of 75 healthy children of the same age whose body weight was within physiological range. After venipuncture, patients were tested for previously mentioned parameters analyzed on Cell-Dyn Ruby (Abbott, USA) hematology analyzer. **Results:** the analyzed parameters (neutrophil, lymphocytes, NLR, PLR, SII) showed significant difference ($p < 0.001$) between obese children and healthy peers except for number of leucocytes and platelets. Sex differences in all examined parameters were not seen in two examined populations. Age differences in obese children were evident in neutrophil count which was significantly lower in younger compared to older children ($p = 0.040$), while age differences in healthy children were evident in platelet count, which was significantly higher in younger than in older children ($p = 0.027$). **Conclusion:** a strong association between childhood obesity and inflammation was demonstrated in pediatric population of Bosnia and Herzegovina, and the new inflammation parameters (NLR, PLR, SII) can be used in the diagnosis of obesity.

Keywords: pediatric obesity, inflammation

SAŽETAK

Uvod: gojaznost je prekomjerno nakupljanje masnoće u tijelu razvijeno ishranom sa visokim unosom šećera, ali i drugi faktori poput genetske predispozicije također igraju važnu ulogu. **Cilj:** uporediti vrijednosti inflamatornih parametara: broj leukocita, trombocita, neutrofila i limfocita, odnosa neutrofila/limfociti (NLR), trombociti/limfociti (PLR) i Sistemske imunoinflamatornog indeksa (SII) između gojazne djece bez komorbiditeta i njihovih zdravih vršnjaka u Bosni i Hercegovini. Testirane su dobne i spolne razlike. **Materijali i metode:** istraživanje je uključivalo 75 gojazne djece prepubertetske i pubertetske dobi koji su se po prvi put javili na Pedijatrijsku kliniku zbog povećane tjelesne mase. Kontrolnu grupu sačinjavalo je 75 zdrave djece, tjelesne mase u fiziološkim granicama, iste starosne dobi kao ispitivana grupa. Nakon venepunkcije, pacijentima su određeni ranije pomenuti parametri, koji su analizirani na hematološkom analizatoru Cell-Dyn Ruby (Abbott, USA). **Rezultati:** svi analizirani parametri (neutrofili, limfociti, NLR, PLR, SII) su pokazali signifikantnu razliku ($p < 0,001$) između gojazne djece i zdravih vršnjaka osim broja leukocita i trombocita. Spolne razlike u broju neutrofila nisu pronađene kod gojazne djece. Dobne razlike kod gojazne djece su se pokazale u broju neutrofila koji su bili signifikantno niži kod mlađe u odnosu na stariju djecu ($p = 0,040$), dok su se razlike kod zdrave djece pokazale u broju trombocita koji su bili signifikantno viši kod mlađe u odnosu na stariju djecu ($p = 0,027$). **Zaključak:** u pedijatrijskoj populaciji Bosne i Hercegovine dokazana je snažna povezanost pretilosti i inflamacije, a novi parametri upale (NLR, PLR, SII) se mogu koristiti u dijagnozi gojaznosti.

Cljučne riječi: pedijatrijska gojaznost, inflamacija

INTRODUCTION

Obesity is an excessive accumulation of fat in the body. Main factor in development of obesity is a high sugar intake, but other factors such as genetic predisposition also play an important role. Obesity is highly associated with other diseases and syndromes such as hypothyroidism, Cushing's syndrome, insulinoma, polycystic ovary syndrome (1).

The prevalence of obesity increases with age, so that 340 million children and adolescents aged 5-19 are affected by this problem. 18% of children and adolescents aged 5-19 years are overweight or obese (2). Prevalence, in addition to being territorial, also varies between the genders: there is a significant difference in prevalence between girls and boys when it comes to obesity (3).

Obesity in the pediatric population is an increasingly present problem, something we face every day, both, in developed and underdeveloped countries. Childhood obesity is often associated with serious consequences such as dyslipidemia, hypertension, diabetes, proinflammatory conditions and non-alcoholic fatty liver, thyroid disorders (4). It is also associated with insulin resistance, development of type 2 diabetes and the development of cardiovascular disease (5). Furthermore, hypertension, high LDL cholesterol and high triglyceride concentrations, insulin resistance, inflammation, oxidative stress, and distribution of adipocytokines secreted in adolescence, are associated with endothelial dysfunction that induces the development of atherosclerosis in this population (5). Extensive research on childhood obesity and its risk factors is one of major public health priorities for the purpose of developing prevention programs, reporting predictors of comorbidities in order for obese children to improve their quality of life and increase their life expectancy (4).

Oxidative stress and inflammation easily explain the relationship between childhood obesity and metabolically unhealthy status observed in this population (6). Puberty could also affect this relationship, as it entails physiological cardiometabolic changes (6).

Commonly determined markers of inflammation include: C-reactive protein (CRP), fibrinogen, leukocyte count, neutrophil count in the differential blood count, and platelet count. Systemic Inflammatory Index (SII) (7), neutrophil/ lymphocyte ratio (NLR) (8) and the platelet/lymphocyte (PLR) ratio (9) are relatively new markers used in the diagnosis of inflammation, usually combined with other inflammation markers (CRP, fibrinogen).

They assist with diagnosis, progress and risk stratification of malignant, cardiovascular, autoimmune and other diseases (8,9).

Platelet/lymphocyte ratio is the only one of these indexes that has been used as a biomarker of obesity, especially in the pediatric population (10). Recent data suggest that the systemic immune-inflammation index, which is based on neutrophil, platelet, and lymphocyte counts, can better reflect the immune and inflammatory state of the body compared to their separate use (11). Nowadays, SII is often used in the diagnosis of malignancies, especially of the pancreas (8).

Data on systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and their association with obesity, especially on the combined use of the above mentioned markers in the diagnostics of childhood obesity and inflammation in Bosnia and Herzegovina are scarce. Therefore, this article is aimed at exploring the role of the above mentioned parameters in development of childhood obesity in selected population from Bosnia and Herzegovina. Specific age and gender differences were tested.

AIM

This article is aimed at exploring the association between PLR, NLR, SII and development of childhood obesity in selected population from Bosnia and Herzegovina and diagnostic significance of these parameters. Specific age and gender differences were tested.

MATERIALS AND METHODS

In this study, a total of 150 children aged 3-18 years of both genders was recruited at Pediatric Clinic - Endocrinology Counseling of the Clinical Center University of Sarajevo. They were divided in two groups, group I being represented by 75 obese children with no comorbidities present and group II consisting of 75 healthy controls. Written informed consent was obtained from all participants recruited into this study (controls and obese children). Inclusion criteria for group I was the diagnosis of obesity on the basis of which parameter obesity was defined (BMI-age > 95th%) with no comorbidities present and no drug therapy applied. The control group consisted of 75 healthy children of both genders whose body weight is within physiological range, without diagnosed diabetes, liver, kidney and pancreas diseases, and endocrine changes in the thyroid gland. Children belonging both to experimental (obese group) and controls were also classified according to the value of nutrition. All obese children had BMI-age above the 95th percentile (95th%) while none of the children in the healthy group belonged to this category.

After obtaining detailed histories for all the children involved in the study, they were physically examined by a medical doctor (MD), and data were recorded on forms prepared for this study. Collected data included age (year), sex, height (cm), weight (kg), body mass index (BMI) (kg/m²), family history of chronic diseases, and the laboratory findings.

Blood samples collected from 21 November 2017 to 1 January 2019 were taken during the patients' hospitalization or during regular follow up. Complete blood count and differential blood count were determined on Cell-Dyn Ruby analyzer (Abbott, USA), for all study subjects.

Ethical Committee of the Clinical Centre University of Sarajevo approved this study which was carried out in compliance with the Helsinki declaration.

Statistical analysis

For statistical analysis of the data, we used the IBM SPSS Ver. 21 program. Parametric and nonparametric tests were used in the analysis, depending on the type of distribution of analyzed parameters. An assessment of the normality of data was tested by the Shapiro-Wilk and Kolmogorov-Smirnov tests. Using the student t-test, we compared the data that followed the normal distribution, and the Kruskal Wallis and Mann Whitney test for data that were not normally distributed. $p < 0.05$ for all tests was considered statistically significant.

RESULTS

In the total population, the number of male children was 75 (50%) while 75 (50%) were females. In the group of healthy controls, the ratio of male to female children was 1.03, and in the group of obese children 0.97. In the group of healthy controls, 51 (68%) children were of prepubertal age (3-11 years), and 24 (32%)

were of pubertal age (12-18 years). In the group of obese children, 26 (34.7%) children were of prepubertal age (3-11 years), and 49 (65.3%) were of pubertal age (12-18 years).

A statistically significant difference in the values of all examined parameters except leucocyte and platelet counts was observed

between healthy and obese children (table 1). Mean values of BMI, neutrophilic granulocytes, neutrophil / lymphocyte ratio, platelets / lymphocytes and SII were significantly higher in obese children compared to healthy controls ($p < 0.001$) while mean lymphocyte counts were lower in obese children.

Table 1 Differences in anthropometric measurements and the levels of different inflammatory parameters in obese and healthy children.

PARAMETER	Healthy children (N=75)	Obese children (N=75)	p
	Mean \pm SD	Mean \pm SD	
Platelets ($10^9/L$)	289.35 \pm 49.42	297.05 \pm 59.69	0.391
Neutrophils (%)	48.46 \pm 10.65	55.62 \pm 8.79	<0.001
Lymphocytes (%)	39.62 \pm 9.34	33.39 \pm 6.98	<0.001
	Median (25-75%)	Median (25-75%)	p
Age (year)	9.00 (7.00-13.00)	14.00 (11.00-16.00)	<0.001
BMI (kg/m^2)	17.10 (15.40-19.10)	30.00 (27.50-32.70)	<0.001
Leucocytes ($10^9/L$)	7.23 (5.77-8.53)	7.30 (5.77-9.36)	0.398
Neu/Lym	1.20 (0.90-1.60)	1.70 (1.30-2.10)	<0.001
Plt/Lym	7.10(6.00-9.30)	9.00 (7.40-10.60)	<0.001
SII	340.60 (238.00-536.40)	493.00 (378.90-659.60)	<0.001

Differences were tested using the student t test (results presented as mean and \pm SD- standard deviation) and Mann Whitney test (results presented as median with interquartile range, 25-75 percentile). p - significance between healthy controls and obese children, $p < 0.05$ was considered to be statistically significant. BMI, Body Mass Index; Neu/Lym, Neutrophils/ Lymphocytes ratio;

Plt/Lym, Platelets/ Lymphocytes ratio; SII, Systemic Immuno-Inflammatory Index.

Gender differences between tested populations are presented in Table 2. Gender differences in examined parameters were not observed between male and female children neither in the group of healthy controls neither in the group of obese children.

Table 2 Gender differences between anthropometric measurements and different inflammatory parameters in healthy and obese children.

PARAMETER	Healthy children (N=75)		p*	Obese children (N=75)		p**
	Male (N=38)	Female (N=37)		Male (N=37)	Female (N=38)	
	Mean \pm SD	Mean \pm SD		Mean \pm SD	Mean \pm SD	
Platelets ($10^9/L$)	289.34 \pm 48.23	289.35 \pm 51.28	0.999	296.70 \pm 62.87	297.39 \pm 57.27	0.960
Neutrophils (%)	47.09 \pm 10.58	49.86 \pm 10.69	0.262	54.62 \pm 8.66	56.59 \pm 8.93	0.334
Lymphocytes (%)	40.59 \pm 8.98	38.63 \pm 9.71	0.369	33.22 \pm 6.54	33.56 \pm 7.46	0.832
	Median (25-75%)	Median (25-75%)	p*	Median (25-75%)	Median (25-75%)	p**
Age (year)	9.50 (7.00-12.25)	9.00 (7.50-13.50)	0.757	13.00 (11.00-15.00)	14.00 (11.00-16.00)	0.169
BMI (kg/m^2)	17.40 (15.37-19.32)	17.00 (15.35-18.90)	0.783	30.00 (27.85-32.70)	30.25 (27.48-32.90)	0.824
Leucocytes ($10^9/L$)	7.28 (5.84-8.24)	6.70 (5.65-9.48)	0.954	56.60 (49.00-59.30)	56.60 (52.08-61.85)	0.585
Neu/Lym	1.10 (0.80-1.60)	1.20 (0.95-1.75)	0.336	1.70 (1.30-2.05)	1.75 (1.38-2.13)	0.607
Plt/Lym	7.15 (5.90-9.50)	6.90 (6.10-9.05)	0.865	9.00 (7.10-11.20)	9.00 (7.48-10.35)	0.920
SII	328.00 (219.13-537.80)	340.60 (240.45-526.40)	0.471	463.20 (374.90-701.20)	495.95 (415.03-640.85)	0.711

Differences were tested using the student t test (results presented as mean and \pm SD- standard deviation) and Mann Whitney test (results presented as median with interquartile range, 25-75 percentile). p^* - significance between male and female subjects in the group of healthy controls, p^{**} - significance between male and female subjects in the group of obese children, $p<0.05$ was considered to be statistically significant. BMI, Body Mass Index;

Neu/Lym, Neutrophils/ Lymphocytes ratio; Plt/Lym, Platelets/ Lymphocytes ratio; SII, Systemic Immuno-Inflammatory Index.

No significant age differences were found between tested populations as shown in Table 3, except for the values of BMI in both groups, as well as platelet count in healthy and neutrophil count in obese group.

Table 3 Age differences between anthropometric measurements and different inflammatory parameters in healthy and obese children.

PARAMETER	Healthy children (N=75)		p^*	Obese children (N=75)		p^{**}
	3-11 years (N=51)	12-18 years (N=24)		3-11 years (N=26)	12-18 years (N=49)	
	Mean \pm SD	Mean \pm SD		Mean \pm SD	Mean \pm SD	
Platelets ($10^9/L$)	298.18 \pm 47.52	270.58 \pm 49.07	0.027	311.19 \pm 58.70	289.55 \pm 59.44	0.136
Neutrophils (%)	48.09 \pm 11.07	49.22 \pm 9.88	0.662	52.63 \pm 9.29	57.21 \pm 8.18	0.040
Lymphocytes (%)	40.24 \pm 9.99	38.32 \pm 7.78	0.369	35.62 \pm 7.79	32.21 \pm 6.27	0.060
	Median (25-75%)	Median (25-75%)	p^*	Median (25-75%)	Median (25-75%)	p^{**}
Age (year)	8.00 (7.00-9.00)	14.00 (13.00-15.00)	<0.001	10.00 (9.00-11.00)	15.00 (14.00-16.50)	<0.001
BMI (kg/m^2)	16.10 (15.00-17.30)	20.00 (18.25-21.40)	<0.001	27.25 (25.80-28.98)	30.90 (29.55-33.20)	<0.001
Leucocytes ($10^9/L$)	6.55 (5.73-9.10)	7.42 (6.42-8.25)	0.481	53.90 (45.23-58.83)	57.00 (52.05-62.10)	0.563
Neu/Lym	1.10 (0.80-1.70)	1.30 (1.03-1.57)	0.292	1.60 (1.08-1.95)	1.70 (1.40-2.15)	0.090
Plt/Lym	7.20 (5.90-9.90)	6.90 (6.33-9.13)	0.633	9.00 (7.23-11.15)	9.00 (7.55-10.20)	0.960
SII	343.10 (223.40-542.00)	338.60 (268.98-480.85)	0.973	466.55 (343.78-662.45)	494.00 (411.40-660.25)	0.446

Differences were tested using the student t test (results presented as mean and \pm SD- standard deviation) and Mann Whitney test (results presented as median with interquartile range, 25-75 percentile). p^* - significance between age groups in healthy controls, p^{**} - significance between age groups in obese children, $p<0.05$ was considered to be statistically significant. BMI, Body Mass Index; Neu/Lym, Neutrophils/ Lymphocytes ratio; Plt/Lym,

Platelets/ Lymphocytes ratio; SII, Systemic Immuno-Inflammatory Index.

Pearson correlation analysis (Table 4) showed significant positive correlations between BMI and the following parameters: Neutrophils, Lymphocytes, Neutrophils/ Lymphocytes ratio ($p<0.001$ for all three), Platelets/ Lymphocytes ratio ($p=0.007$) and SII ($p=0.001$).

Table 4 BMI correlation to other analyzed parameters in the entire study group (N=150).

PARAMETER	BMI (kg/m^2)	
	Pearson r	p
Age (year)	.673**	<0.001
Leucocytes ($10^9/L$)	.092	0.264
Neutrophils (%)	.373**	<0.001
Lymphocytes (%)	-.393**	<0.001
Neu/Lym	.288**	<0.001
Plt/Lym	.218**	0.007
SII	.261**	0.001
Platelets ($10^9/L$)	-.032	0.695

All correlations were tested using Pearson test. Pearson r, value of Pearson's correlation coefficient, where »-« represents negative correlation, »**« correlation is significant at the 0.01 level, »*« correlation is significant at the 0.05 level. p- statistical significance of correlation between parameters. BMI, Body Mass Index; Neu/Lym,

Neutrophils/ Lymphocytes ratio; Plt/Lym, Platelets/ Lymphocytes ratio; SII, Systemic Immuno-Inflammatory Index.

Multiple linear regression analysis indicated that BMI values were an independent predictor of Neutrophil and Lymphocyte counts, Neutrophils/Lymphocytes and Platelets/Lymphocytes ratios; as well as Systemic Immuno-Inflammatory Index (Table 5).

Table 5 Multiple Linear Regression Analysis of the effect of BMI on other parameters.

PARAMETER	Unstandardized Coefficients		Standardized Coefficients	t	p	95,0% Confidence Interval for B	
	B*	Std. Error	Beta			Lower Bound	Upper Bound
Leucocytes (10 ⁹ /L)	0.028	0.025	0.92	1.120	0.264	-0.021	0.076
Neutrophils (%)	0.555	0.113	0.373	4.890	<0.001	0.331	0.779
Lymphocytes (%)	-0.496	0.095	-0.393	-5.205	<0.001	-0.684	-0.307
Neu/Lym	0.031	0.008	0.288	3.657	<0.001	0.014	0.047
Plt/Lym	0.093	0.034	0.218	2.724	0.007	0.026	0.161
SII	9.003	2.736	0.261	3.291	0.001	3.597	14.409
Platelets (10 ⁹ /L)	-0.253	0.645	-0.032	-0.392	0.695	-1.527	1.021

Multiple Linear Regression used Enter Method; p-value<0.05; Predictors: (Constant) BMI, Body Mass Index. Neu/Lym, Neutrophils/ Lymphocytes ratio; Plt/Lym, Platelets/ Lymphocytes ratio; SII, Systemic Immuno-Inflammatory Index.

DISCUSSION

Literature suggest that the background of obesity is chronic inflammation that may explain the interaction between obesity and metabolic complications (12), but obesity represents a complex multifactorial disease, also backed by genetic predisposition (13,14) and chronic inflammation. Adipose tissue has been shown to contribute to both initiation and maintenance of systemic inflammation (15).

Up to now, it has been proven that the peripheral blood of healthy overweight people shows the characteristics of a low degree of inflammation. Study of Keskin R, et al. (14) already confirmed the existence of a relationship between obesity and parameters of inflammation with wide range of biomarkers being associated with low-grade systemic inflammation, such as complete blood count (CBC) parameters, neutrophil / lymphocyte ratio, platelet / lymphocyte ratio and MPV (Mean Platelet Volume). A study done on 6,700 adult patients reported positive correlations between waist circumference and levels of leukocytes, lymphocytes, platelets, MPV, and also neutrophils.(16). However, similar studies reported no significant direct correlation between adiposity and platelet activation in obese individuals, namely, platelet function did not differ between obese and normally fed subjects. However, most of these obesity-related studies related to inflammatory parameters were conducted on adult participants, where a wide range of associated comorbidities interfered with elucidating the cause-and-effect relationship between inflammation and obesity (17).

The aim of this study was to determine diagnostic significance of classical inflammatory markers and specific newly described markers of inflammation such as systemic immune-inflammatory index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and specially their combined use in the diagnostics of childhood obesity and inflammation. Up to now, no such research on pediatric population has been done in Bosnia and Herzegovina.

Our tested population was chosen carefully (no comorbidities present). Therefore, the cause and effect relationship between inflammation and obesity could clearly be established.

Several authors including Marginean CO, et al (10) previously reported a significant association between overweight children and leukocyte, platelet, lymphocyte, and erythrocyte counts, without significant association with neutrophil count in a study done on 164

children, aged 5-18 years. It has also been shown that younger children have a higher percentage of lymphocytes and consequently a lower percentage of neutrophils (18) which corresponds to our results. In our study, the number of neutrophils was significantly higher in the group of obese children (p<0.001), while the number of lymphocytes was significantly lower in this group when compared to healthy children (p<0.001). At the same time, the number of platelets and leukocytes did not show significant differences between these two groups (p = 0.391, p=0.398, respectively). Our results can be explained by the fact that inflammatory status is reflected in neutrophil counts and seems to be directly related to degree of obesity as previously reported (19). At the same time, lymphocyte counts seem to be associated with nutritional status and general stress (18).

At the level of new inflammatory indicators (neutrophils/lymphocytes ratio, platelets/lymphocytes ratio and systemic immunoinflammatory index), interesting results were obtained in our study. Up to now, we are not aware of other published data related to their role in inflammation in obese pediatric population with no comorbidities. All of the above mentioned markers (NLR, PLR as well as SII indexes) were significantly higher in obese children compared to healthy controls, with p <0.001 for all three.

So far, NLR and PLR markers of the immune response have been associated with chronic inflammation (20) in cardiac and non-cardiac disorders, and also in autoimmune conditions and infections (21,22).

When obesity is concerned, several studies assessed the role of NLR and PLR in adult obese patients with related comorbidities. A study conducted with 155 obese, and obese patients with obstructive sleep apnea found significantly higher values of NLR in obese individuals (18). Obesity associated with metabolic syndrome and diabetes has also been associated with NLR (23,24). However, Oana MC, et al. (10) Bahadir, et al. failed to prove an association between NLR and obesity or metabolic syndrome (21). The same authors reported significantly higher number of lymphocytes and neutrophils and NLR in obese children while Vuong J, et al. (15) added to this white blood cells also. The study by Marginean CO, et al. (10) also showed a significant increase in lymphocyte counts in overweight children, but failed to show significant differences in neutrophil count and NLR between children with normal BMI and those with high BMI. Limitations of this study was related to a relatively small sample size and a lack of association with eating habits and an assessment of related complications. In the study of Li J, et al. (22), it was reported that younger people have a lower level of NLR compared to older

population and that its value correlates positively with blood pressure and BMI.

At PLR level, no significant differences between obese and normal-weight children were registered in Aydin M, et al study (16). Our results showing significant differences in PLR between two tested groups coincide with results of Oana C, et al. (10). We also detected statistically significant increase in systemic immune-inflammation index (SII) in obese population, comprehensively reflecting the balance between the host immune and the inflammatory condition.

In our study, no significant age or gender differences between tested groups at the level of NLR, PLR and SII were detected, although Wu L, et al. (23) in their study on adult obese subjects pointed out significant age and gender differences in NLR and PLR with no data on SII.

Correlation analysis between parameters further confirmed our findings. We found positive correlations between BMI and all other parameters: Neutrophils, NLR ($p < 0.001$ for both), PLR ($p = 0.007$) and SII ($p = 0.001$). Lymphocytes showed a negative correlation ($p < 0.001$) whilst Leukocyte and Platelet counts showed no significant correlation with BMI.

BMI correlation to inflammatory parameters was also found in the study of Furuncuoğlu Y, et al. (24). BMI was found to have a statistically significant positive linear correlation with lymphocyte number, PDW, SII and RDW ($p < 0.05$), and an extremely significant positive linear correlation ($p < 0.01$) was found between BMI and WBC, neutrophil count, PCT and platelet count.

Similar to the findings of the previously mentioned study, Märginean CO, et al. (10) showed a significant correlation between being overweight/obese and leukocyte, platelet and lymphocyte counts. However, it failed to show a significant association of these conditions with the neutrophil count. Also, despite the fact that NLR and PLR are immune response markers related to chronic inflammation, Märginean CO, et al. did not find significant correlations between these markers and obesity/overweight.

Apart from correlations, a multiple linear regression analysis in our research indicated that BMI values were an independent predictor of Neutrophils, Lymphocytes, NLR, PLR and SII.

Limitation of this study, as in all research about obesity, is the choice of a sample population. Another limitation may come from unstandardised definitions of obesity and overweight in childhood, as well as how describing obesity by BMI can result in inaccurate assessment of adiposity, because BMI does not distinguish lean muscle from fat mass.

CONCLUSION

In this study, a strong association between childhood obesity and inflammation was demonstrated in pediatric population of Bosnia and Herzegovina. In the future, new inflammation parameters, based on calculations from hemograms (NLR, PLR, SII - which are also very cheap), can be used in the diagnosis of obesity.

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Satisfaction of nurses with operation management and functions and reflections on satisfaction of health service beneficiaries

Zadovoljstvo medicinskih sestara-tehničara operativnim menadžerskim funkcijama i refleksije na zadovoljstvo korisnika zdravstvenih usluga

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ABSTRACT

Introduction: the health care system reform should meet the needs of the population for health care, which should be of high quality and accessible through the development of a financially sustainable system. The new health care system should be oriented at overall health of people and reducing the incidence rate. Graduate nurses should play a leading role in achieving health goals. Aim: to determine the satisfaction of nurses in the work process and connection with the satisfaction of end health service beneficiaries. Materials and methods: the study was quantitative, descriptive and analytic using methods of comparison, induction, deduction and compilation. It included 154 nurses employed in health institutions „Stari aerodrom“, „Blok V“ and „Konik“ in Podgorica, Montenegro. A survey questionnaire on assessing the satisfaction of health care beneficiaries in health institutions was completed by 162 health beneficiaries. The study was conducted in the period from June to September 2019. Results: the majority of nurses, 97 (63%) of them, stated that they were satisfied with interpersonal relations at work and that they had opportunity for continuous training. The largest number of respondents, 114 (74.1%) of them, stated that they were highly dissatisfied or dissatisfied with their wages. Half of the respondents were satisfied with the support of their superiors. Over two thirds of patients were satisfied with the attitude of nurses towards patients during the examination, their kindness, conscientiousness and explanations provided in the health institution. Over 60% of patients stated that they were satisfied with the waiting time for diagnostic and therapeutic procedures. Conclusion: nurses expressed a high degree of satisfaction with functions of operation management in everyday work processes, which correlates with the high degree of satisfaction with the provided health services expressed by the interviewed patients.

Keywords: nurses, patients, managerial functions, satisfaction

SAŽETAK

Uvod: reformom sistema zdravstva trebaju se zadovoljiti potrebe stanovništva za zdravstvenom zaštitom, koja bi trebala da bude kvalitetna i dostupna kroz razvoj finansijski održivog sistema. Novi zdravstveni sistem treba da bude orijentiran na cjelokupno zdravlje ljudi i smanjenje stope oboljevanja. U ostvarivanju ciljeva zdravlja za sve vodeću ulogu treba da imaju diplomirane medicinske sestre-tehničari. Cilj istraživanja: utvrditi zadovoljstvo kod medicinskih sestara-tehničara u procesu rada i povezanost sa zadovoljstvom krajnjih korisnika zdravstvenih usluga. Materijali i metode: istraživanje je kvantitativno, deskriptivno i analitičko. Korištena je metoda komparacije, indukcije, dedukcije i kompilacije. U istraživanju su učestvovali 154 medicinske sestre-tehničara, a zaposlena u Domu zdravlja „Stari aerodrom“, Domu zdravlja „Blok V“ i Domu zdravlja „Konik“ u Podgorici, Crna Gora. Anketni upitnik o procjenjivanju zadovoljstva korisnika zdravstvene zaštite u domovima zdravlja popunila su 162 korisnika zdravstvene zaštite. Istraživanje je provedeno od juna do septembra 2019 godine. Rezultati: većina medicinskih sestara-tehničara 97 (63%) je istakla da su zadovoljni međuljudskim odnosima u radnoj sredini, kao i da imaju priliku da se kontinuirano usavršavaju. Najveći broj ispitanika 114 (74,1%) istakao je da je veoma nezadovoljno ili nezadovoljno zaradom koju ostvaruju za posao koji obavljaju. Polovina ispitanika zadovoljna je podrškom pretpostavljenih. Više od dvije trećine pacijenata je zadovoljno odnosom medicinske sestre/tehničara prema pacijentu prilikom pregleda, ljubaznošću, savjesnošću, kao i objašnjenjima koja dobiju u zdravstvenoj ustanovi. Preko 60% pacijenata je izjavilo da je zadovoljno dužinom čekanja na dijagnostičke i terapijske procedure. Zaključak: medicinske sestre-tehničari su iskazali visok stepen zadovoljstva operativnim menadžerskim funkcijama u svakodnevnim radnim procesima, što korelira sa iskazanim visokim stepenom zadovoljstva pruženim zdravstvenim uslugama kod ispitanih pacijenata.

Ključne riječi: medicinske sestre-tehničari, pacijenti, menadžerske funkcije, zadovoljstvo

INTRODUCTION

A healthy population is potentially the most important resource of society in all segments of development, contributing to its overall social and economic progress. Thus, special attention has to be paid to health and conditions for preserving and improving health, which are achieved not only by the action of health sector but also by involvement of all social sectors. In that regard, the Constitution, as the most important state act, guarantees all citizens of Montenegro the right to health and health care in accordance with the law, the right to a healthy life and a healthy environment, as some of the fundamental human rights. Being one of the most complex social systems, the health system planning must take into account all aspects of its development, with special emphasis on sustainability, stability and rationality of the system, efficiency and effectiveness, quality and safety of health care at all levels, pursuing current social trends, demographic changes, health status and health needs of the population, especially in the part of chronic non-communicable diseases, as well as other factors that may affect its further development (1).

Within the health system transformation process, patients are placed in the center of attention with partnership being achieved with them, resulting in significant reducing of health workers paternalistic role. The success of a health system reform depends primarily on how much effort will be invested in reengineering and redesigning work processes in accordance with the competencies of health professionals, especially graduate nurses. Systematically planned and realized optimization and reorganization of staff in the health system directly affects the satisfaction of highly educated nurses by providing greater competencies in the field of health care and evaluation (2).

Health system reform should also bring changes in the leadership of healthcare managers who need to improve their managerial competencies and implement them in everyday practice and teamwork. Greater responsibility in the work of individuals, a healthy working environment, evaluation and motivation of employees is directly related to the quality of services and satisfaction of end users.

In Montenegro, the reform of primary health care (PHC) has been carried out, providing conditions for optimal necessary staff engagement with a satisfactory ratio between medical and non-medical staff (82%:18%) (3).

The reform of Primary Health Care also included a change in the method of payment by introducing a model of financing services as a combination of capitation and provided services (3).

The reform of the secondary and tertiary health care level involved the development of strategic and normative documents (human resources plan, strategy for improving hospital health care, strategy for improving the quality of health care and patients' safety, basic package of services for secondary and tertiary health care, national guidelines of good clinical practice, public-private partnership strategy, support for health network optimization in Montenegro) (4).

Priority issues related to the organization and functioning of the health care system depend on number of factors related to technical (staff, equipment, space) and technological performance of the system (skills and knowledge of health care providers, standardized procedures), continuous improvement of legislation, health care system management at different levels (management, leadership, health advocacy), cooperation of health and other sectors (social welfare, education, sustainable development,

tourism, economy, justice, etc.) and flexibility of the health system to changes (change management) (5).

Such health care restructuring can bring benefits to the entire system and enable people to be healthy in the long run. In this reform, the local community is expected to provide conditions for a healthy life of the population, and people are expected to contribute to their health (4,5).

AIM

To determine the satisfaction of nurses in the work process and the connection with the satisfaction of end health service beneficiaries.

MATERIALS AND METHODS

The study was quantitative, descriptive and analytic using methods of comparison, induction, deduction and compilation. This randomized controlled study was conducted in the period from June to September 2019 in health institutions "Stari aerodrom", „Blok V“ and „Konik“ in Podgorica, Montenegro. An anonymous questionnaire - a personal information sheet was used as the research instrument designed based on the existing literature and recommendations of the World Health Organization. The questionnaire related to the professional satisfaction of the employed nurses was completed by 154 nurses. The survey questionnaire related to the assessment of the health care beneficiaries satisfaction with health institutions was filled out by 162 health care beneficiaries.

RESULTS

Results of the survey related to the assessment of professional satisfaction of employees

A questionnaire related to professional satisfaction of the employed nurses was filled out by 154 nurses, of which 116 (75.3%) were with completed secondary education and 38 (24.7%) with advanced specialist's training. The sample comprised 34 (22.1%) males and 120 (77.9%) females. The youngest participant in the survey was 22 and the eldest was 60 years of age, whereas mean age was 44.4 (SD=9.059).

A total of 97 (63%) respondents stated that they were satisfied with interpersonal relations at workplace.

Majority of the respondents, 98 (63.6%) of them, stated that they had the opportunity for continuous professional development and that they were satisfied with the provided training. Half of the respondents stated that they were satisfied with the possibility of professional development.

Even 114 (74.1%) health workers stated that they were very dissatisfied or dissatisfied with their wages, whereas 26 (16.8%) of them stated that they were satisfied or very satisfied with their wages.

Around 50% of employees stated that they were satisfied or very satisfied with the support of superiors, while 33.8% stated they were neither satisfied nor dissatisfied.

Slightly more than 50% of employees in health care institutions answered that they were satisfied or very satisfied with the evaluation of their work by managers.

Slightly less than 60% of employees stated that they were either satisfied or very satisfied with their work.

Results of the survey related to the assessment of satisfaction of health care beneficiaries

A questionnaire related to the assessment of satisfaction of health care beneficiaries in health institutions was filled out by 162

respondents. The sample comprised 72 males and 90 females. The youngest participant was 18 and the eldest was 82, whereas mean age of the respondents was 46.42 (SD=12.771). The majority of respondents, 83 (51.2%) of them were with completed secondary education, 25 (15.4%) of them were with advanced specialist's training, whereas 34 (21%) of respondents had university degree. In addition, the sample also comprised 14 (8.6%) qualified and 6 (3.7%) unqualified respondents.

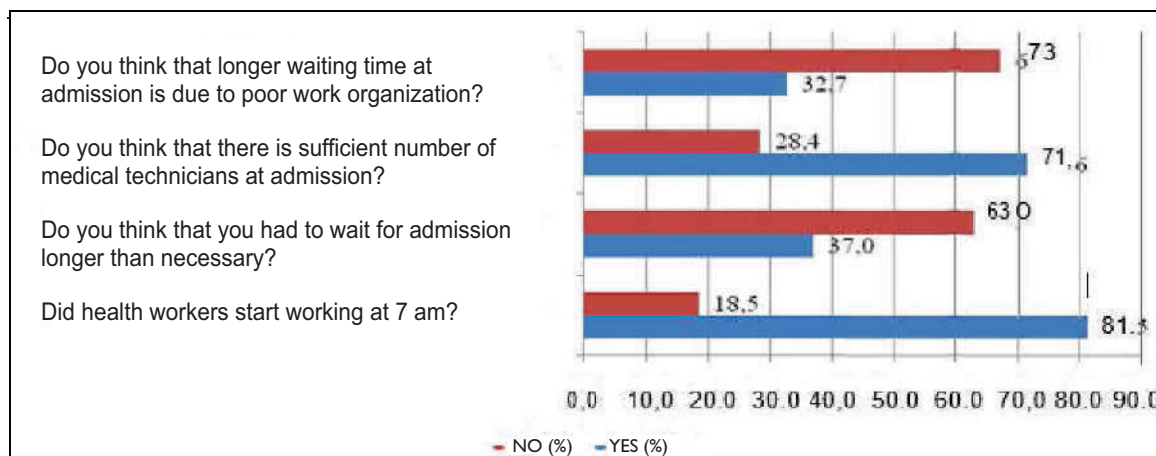


Figure 1 Satisfaction of respondents with healthcare services (admission, work organization).

Majority of patients was satisfied with waiting time at admission, good work organization and number of nurses at admission.

Almost all patients were satisfied with kindness of nurses at admission and provided information.

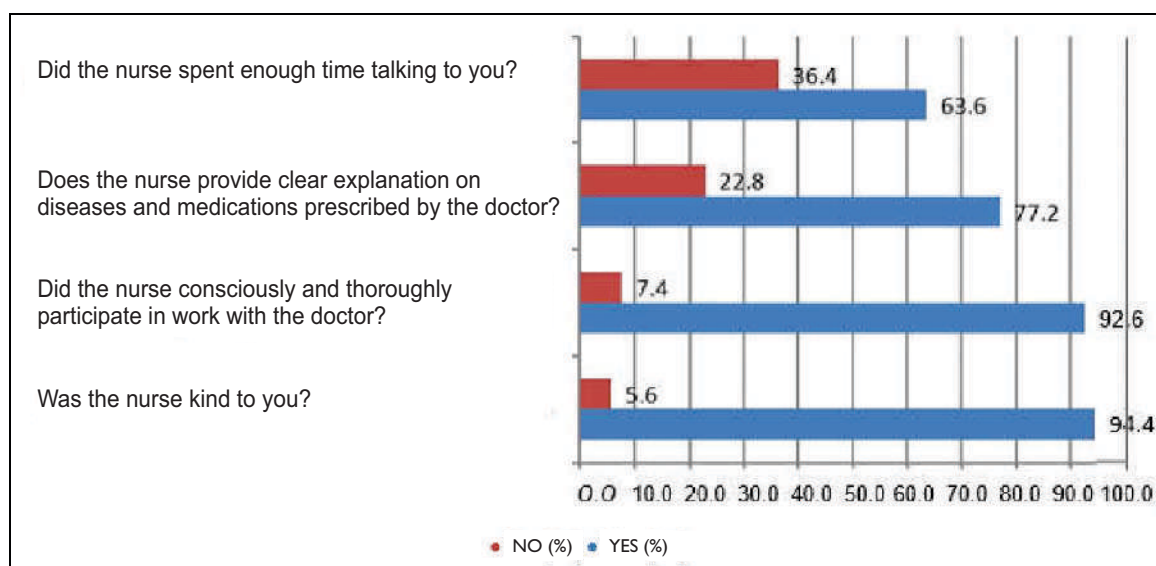


Figure 2 Satisfaction with professional attitude of nurses.

Majority of patients, 63.6% of them, expressed their satisfaction with time nurses spent in communicating with them. Large majority of patients, 77.2% of them, was satisfied with the way of getting

acquainted with the disease and the proposed therapy. Over 90% of the surveyed patients express great satisfaction with kindness and conscientiousness of nurses.

DISCUSSION

The studies of authors who examined the satisfaction of health service beneficiaries and health workers employed in the EU countries, confirmed the aforementioned statement that health service beneficiaries were generally satisfied with the quality of health services. This confirms that in the conditions of economic crisis and financial deficit, lack of health funds, reduced number of health staff, good work organization and application of principles and procedures of contemporary management result in satisfactory functioning of health system (6).

It is also important to emphasize that due to the saving attempts in the health system of Montenegro, the number of employed health workers is totally inappropriate with the number of inhabitants receiving such services, with respect to health system standards in Europe and in civilized countries (7).

It should be emphasized that the wages of health workers, considered to be inadequate and small based on the responsibilities and difficulty of the work they perform, not only stagnate but are also reduced by various taxes and regulations, resulting in considerable dissatisfaction of health care workers.

Studies conducted by number of authors show a potentially negative impact on quality of life and overall life satisfaction when it comes to the work and personal life of patients and health care workers (8).

Methods of improving the quality of health care involve external and internal control, continuous quality improvement, quality assessment by measuring patients' satisfaction and use of clinical guidelines. In many European countries, in the USA and in Australia, monitoring patients' satisfaction with health care and various levels of health care has become a common practice (9).

Accordingly, it can be concluded that it was necessary to make huge efforts and use organizational skills, knowledge and expertise of the respective health institutions management, in order to achieve the satisfaction of health care beneficiaries and employees of the respective institutions. This confirmed that the importance of health care reform, a new approach to community nursing and emphasizing the need for improving quality, developing and applying the methods and techniques of health services, should be implemented in other institutions of the health system of Montenegro.

Continuous medical education, and constant professional development and monitoring of research, development and medical achievements in early detection of a disease, successful diagnosis and treatment with the highest quality medical preparations are the only possible way to achieve quality in health, disease prevention, successful treatment and raising human health (10).

Lack of the most contemporary diagnostic devices and means can only be compensated by excellent professional and capable health staff, whose engagement leads to a positive outcome - healing (11).

The satisfaction of health service beneficiaries is significantly influenced by the kind attitude of health workers, as such attitude shows care and desire for a positive solution to the health problem, which has a positive effect on the disease of a compromised person (both mental and physical health) (12).

Only with a special emphasis on good communication that needs to be studied and dealt with, and raising it to the highest possible level in the organizational culture, can the quality of service be raised to a significant level, as proven in the study (13).

The study conducted among 124 employees working in intensive care units of Canton Sarajevo (Clinical Center University of Sarajevo and General Hospital „Prim. Dr Abdulah Nakaš“ in Sarajevo) in the period from 2010 to 2011, showed that respondents with longer work experience were less satisfied with the quality of work environment, teamwork, relationship between superiors and subordinates, etc. Work satisfaction in the intensive care unit is related to the level of education of employees, and additional training. Rewarding employees for successfully completed tasks is related to the work motivation with seriously ill patients (14).

Eminović E conducted a study at the Clinical Center University of Sarajevo on a sample of 301 nurses showed that the effects of nurses' work are directly (positively) correlated with material and non-material compensation of employers, which ultimately significantly design motivation for work and pleasure. The amount of monthly income or the subordinate-superior relationship correlates with work environment satisfaction. Non-material compensations are a key factor in motivating work productivity of nurses (15).

In 2019, Džananović S conducted a study at the Clinical Center University of Sarajevo and Dernbach Herz-Jesu Hospital (HJDK) on a total sample of 234 respondents, of which 169 (72%) respondents were from the Clinical Center University of Sarajevo (CCUS) and 65 (28%) was from the Dernbach Herz-Jesu Hospital (HJDK). As expected, there were significant differences in monetary compensation. Out of 166 respondents from the CCUS, who provided answers to this question, 18 (10.8%) had salary over BAM 2,000, whereas salary of majority of them was in the range from BAM 1,000 to 2,000. On the other hand, majority of the respondents from Germany had salary in the range from BAM 5,000 to 6,000 (46.0%), whereas 11 (17.5%) respondents had monthly salary over BAM 6,000. However, regardless of monetary compensation it was established that the CCUS employees were more satisfied with work conditions and work environment in respect to respondents from the Dernbach Herz-Jesu Hospital (HJDK) (16).

A study related to satisfaction of nurses working in operating theaters and surgical wards was conducted by Spevan M, et al. in the Clinical Hospital Center of Rijeka. The study conducted in 2016 included 126 nurses. The results of the study showed that there was statistically significant influence of the length of work experience and perception of interpersonal relationships on the level of employee satisfaction. Nurses working in operating theaters were statistically significantly more satisfied than nurses working in surgical wards. The study showed that nurses included in educational programs were statistically significantly more satisfied than nurses who were not included in educational programs (17).

In the study conducted among the patients of the Health Institute "Beli Manastir", in 2017, it was established that the patients were generally satisfied with the work of nurses in primary health care. 298 (50%) respondents were fully satisfied with the statement "I was satisfied with the visit to the nurse", and 250 (42%) respondents were satisfied (18).

Comparing this statement with the studies conducted worldwide, it can be noticed that the results are quite similar because patients are generally satisfied whenever their satisfaction with the work of nurses is investigated.

A study on the satisfaction of health care in outpatient clinics conducted in Spain in 2013 showed that the respondents were highly satisfied with the provided health care, which the authors compared with similar studies. They stated that their results

showed that the quality of nurses' work and patient satisfaction were closely linked and that nurses played a key role in high health care ratings (19).

A study related to satisfaction with health services was conducted in 2015 in General Hospital Zadar. Patients hospitalized in the General Hospital Zadar expressed high degree of satisfaction with the provided health services, which was in accordance with the results of studies conducted in health institutions of the Republic of Croatia (20).

A study related to the satisfaction of beneficiaries with health services conducted in 2017 in a special hospital for medical rehabilitation Daruvarske Toplice, as expected, showed a high degree of satisfaction, which obviously confirmed the quality of the Special Hospital for Medical Rehabilitation Daruvarske Toplice (21).

A study conducted in General Hospital Livno showed that over 84% of the respondents were satisfied with the attitude of doctors and nurses. There were no statistically significant differences in the level of satisfaction with provided health services in respect to respondents' age and gender. The respondents were mostly dissatisfied with providing information about the use of medications and their side effects - one fourth of the respondents never received an explanation about types of side effects regardless of gender. Majority of the respondents assessed their health as good or very good. In 85% of answers, the respondents assessed the Cantonal Hospital Livno with three top grades (22).

In a study conducted at the Clinical Center University of Sarajevo out of 5012 respondent included in the survey over 70% of them expressed their satisfaction with provided services, with an increase in 2018 to 88.6% (23).

Results of a similar study conducted in three hospitals in the Republic of Serbia showed satisfaction in the treatment services in the range from 93.3% to 97.2%. With regard to nursing services, satisfaction was always shown in 96.1% of the respondents (24).

A study related to the satisfaction of beneficiaries with the work of secondary and tertiary health care institutions was conducted in 2014 in internal medicine, surgical, and gynecological departments and in physical medicine and rehabilitation units and specialist services of 17 Belgrade hospitals. The study results showed that patients were least satisfied with nutrition and hospital accommodation (25).

In the EU countries, under the influence of various political, economic, social, demographic and cultural trends, there is a need for a serious reform of the health system in which health personnel with a degree in health care has a leading role.

Respecting the Directives of the European Council and the Parliament, which have precisely defined the processes and norms of health education, the member states have determined the competencies accordingly. Nowadays, reorganization in the field of health has been promoted and there is a tendency for higher education of non-medical staff and need for a clear definition of the field of work in accordance with competences (26).

In order for graduate nurses to achieve full satisfaction in their professional work, they must aim at building their own identity, self-perception of the profession, continuous education and lobbying through trade union and political activities. Managers of health care institutions should establish systems for evaluating the nursing profession and develop team cooperation, all of which reflects on the satisfaction of end users.

CONCLUSION

Nurses expressed a high degree of satisfaction with functions of operation management in everyday work processes, which correlates with the high degree of satisfaction with the provided health services expressed by the interviewed patients.

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A family outbreak of foodborne botulism following consumption of smoked meat in Sarajevo, Bosnia and Herzegovina

Porodična epidemija botulizma nakon konzumacije sušenog mesa u Sarajevu, Bosna i Hercegovina

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ABSTRACT

Introduction: botulism is a rare, neuroparalytic foodborne illness caused by consumption of a botulinum neurotoxin produced by the Gram positive anaerobic bacterium *Clostridium botulinum*. Clinical symptoms of botulism mostly appear after an incubation period of 12-36 hours, but incubation period up to 12 days is also reported. The disease usually presents with acute flaccid descending paralysis, double vision, ptosis, slurred speech, difficulty swallowing and gastrointestinal symptoms. Treatment should be started just after botulism is suspected. **Aim:** to report the first outbreak of botulism due to consumption of smoked meat in Bosnia and Herzegovina. **Materials and methods:** the study analyzed a family outbreak of botulism caused by eating smoked meat. All family members were admitted to Clinical of Infectious Diseases of the Clinical Center University of Sarajevo, in January 2014. **Results:** incubation period was from 1 to 4 days. All patients had neurological symptoms. They were treated with symptomatic therapy with favorable outcome of the disease. **Conclusion:** during the clinical course patients should be monitored for deterioration of neurological state, which can lead to respiratory insufficiency requiring mechanical ventilation. Specific antitoxin should be available at least in one or two largest clinical centers in Bosnia and Herzegovina.

Keywords: botulism, outbreak, foodborne illness

SAŽETAK

Uvod: botulizam je rijetka, neuroparalitička bolest koja se prenosi hranom, uzrokovana neurotoksinom koga proizvodi Gram pozitivna anaerobna bakterija *Clostridium botulinum*. Klinički simptomi se javljaju nakon inkubacije koja traje 12-36 sati, mada su opisani slučajevi inkubacije i do 12 dana. Bolest se obično prezentuje u vidu akutne descendente flakcidne paralize, dvoslika, ptoze, poremećenog govora, teškoća pri gutanju te gastrointestinalnih simptoma. Terapija bi se trebala ordinirati odmah nakon što se posumnja na botulizam. **Cilj rada:** prikazati porodičnu epidemiju botulizma nakon konzumacije sušenog mesa. **Materijal i metode:** analizirani su podaci o članovima porodice oboljelih od botulizma koji su konzumirali sušeno meso. Svi su hospitalizirani na Klinici za infektivne bolesti Kliničkog centra Univerziteta u Sarajevu u januaru 2014.godine. **Rezultati:** inkubacija bolesti je trajala 1 do 4 dana. Dominantni su bili neurološki simptomi. Pacijenti su tretirani simptomatskom terapijom uz povoljan ishod. **Zaključak:** za vrijeme tretmana pacijenata sa botulizmom neophodan je monitoring neurološkog stanja, koje može voditi respiratornoj insuficijenciji i potrebi za mehaničkom ventilacijom. Specifični antitoksin bi trebao biti dostupan barem u dva najveća medicinska Klinička centra u Bosni i Hercegovini.

Ključne riječi: botulizam, epidemija, bolest prenesena hranom

INTRODUCTION

Foodborne botulism is a rare, neuroparalytic illness caused by consumption of a botulinum neurotoxin produced by the Gram positive anaerobic bacterium *Clostridium botulinum*. The toxins predominantly affect peripheral neuromuscular junction and autonomic synapses, and are designated as types A to G based on antigenic differences. Types A, B, E and F produce human disease (1,2). Botulinum neurotoxin binds irreversibly to the presynaptic membranes of peripheral neuromuscular and autonomic nerve junctions, causing flaccid paralysis. *Clostridium botulinum* organisms

cause food poisoning because the heat-resistant spores survive food preservation methods that kill nonsporulating organisms and produce a potent neurotoxin under anaerobic, low-acid and low solute conditions (3). *C. botulinum* spores are found throughout the world in soil samples and can tolerate 100°C for several hours, while botulinum toxins are temperature sensitive, and all toxins are inactivated by heating to 85°C for five minutes (4). Foodborne botulism is most frequently recognized in outbreaks. Home-canned vegetables like beans, fruits and fish products, smoked meat are the most common sources of toxin, while commercial foods are rare cause of botulism (5,6). Clinical symptoms of botulism appear after

an incubation period which is 12-72 hours after ingestion, and vary of the toxin serotype (7,8). The disease usually presents with acute flaccid descending paralysis, double vision, ptosis, slurred speech, difficulty swallowing and gastrointestinal symptoms (9). Confirmation of the disease is primarily based on detection of the toxin in the serum, but also in the stool, or food sample. Treatment should be started just after we suspected botulism (7). Death cases occur from respiratory muscle paralysis, and rate among patients with botulism is 3-10% (2,3,9,10).

AIM

The aim of this study was to report the first outbreak of botulism due to consumption of smoked meat in Bosnia-Herzegovina.

MATERIALS AND METHODS

The study retrospectively analyzed medical records of four patients from the same family admitted to Clinic of Infectious Diseases of the Clinical Center University of Sarajevo, Bosnia and Herzegovina, in January 2014. The diagnosis of botulism was set based on the clinical picture and the epidemiological surveys due to

lack of appropriate test, not only in the Clinical Center University of Sarajevo, but also in all medical institutions of Bosnia and Herzegovina.

RESULTS

The first patient admitted to hospital was one of the twin brothers, 24 years of age. His symptoms started 12 days ago with muscle weakness, blurred vision, ptosis, dry mouth, dysphagia, dizziness, flatulence and constipation. Three days before the onset of the symptoms he consumed smoked sheep meat, bought in a local market. He initially approached a general practitioner, who suggested symptomatic therapy (laxative, vitamin B). He had no fever, diarrhea or sweating. Physician in general practice suspected possible botulism, and referred him to a Clinic of Infectious Diseases. On physical examination at admission, patient was afebrile, with blood pressure 90/60 mm Hg, pulse rate 80/min. Pupils were bilaterally dilated, with slow reaction on light. Tongue and mucose of the mouth were dry. Abdomen painful on palpation. Other family members had similar symptoms, excluding constipation. Their incubation period was from one to seven days. They were all treated with symptomatic therapy, with hospitalization from 8 to 14 days. All of them were discharged from hospital as fully recovered.

Table 1 Symptoms presented at admission to hospital with outcome of disease.

Patient	1	2	3	4
Age	45	51	24	24
Gender	F	M	M	M
Incubation Period (days)	4	1	3	3
Diplopia	-	-	-	-
Blurred vision	-	+	+	+
Dysphagia	+	+	+	+
Dry mouth	+	+	+	+
Dysarthria	-	-	-	-
Ptosis	-	-	+	-
Dizziness	+	-	+	+
Chest discomfort	-	-	-	-
Nistagmus	-	-	+	-
Dilated pupils	-	-	+	-
Nausea and vomiting	-	-	-	+
Constipation	-	-	+	-
Paralysis of extremities	-	-	-	-
Duration of hospitalization	10	9	14	8
Outcome	+	+	+	+

DISCUSSION

Botulism outbreak occurs rarely in the world, and this was the first described outbreak in Bosnia and Herzegovina. Botulism is also very rare illness in neighboring countries, with sporadic described

cases in last decades. It is usually caused by ingested bacteria from home-preserved products, rather than by commercially canned food (11). Symptoms usually appear within the next 36 hours after contaminated food consumption, but incubation can last up to 12

days (8,12). Nausea, vomiting abdominal pain and blurred vision with diplopia are the most common clinical manifestations.

Symptoms are sometimes nonspecific in the beginning, and can mislead to other diagnosis (13). Clinical diagnosis can be confirmed by finding toxin in the patient's serum and stool, and suspected food. Laboratory confirmation takes a considerable time, so clinical findings and response to treatment could be useful in diagnosis (14).

Diagnostic options are also very limited in Bosnia and Herzegovina, and it is very hard to reach the diagnosis if you lack all clinical symptoms, with positive epidemiology presented. In our small familiar outbreak, the first case was suspected due to dysphagia and blurred vision in the first patient referred by the general practice physician.

In a family outbreak in France, caused by ground green olive paste, a total of eight patients were infected. Their clinical presentation was severe at admission, with rapid development of all neurological symptoms including paralysis. Five of them were intubated and on controlled mechanical ventilation (15). In similar outbreak in China, 12 persons who after consuming smoked ribs in one of the restaurants got botulism. The first two cases, with neurological symptoms and progression to quadriplegia and respiratory insufficiency, required intubation and mechanical ventilation. Presentation of illness in other affected patients was mild to moderate, with typical presentation including dysarthria, dysphagia, diplopia, ptosis, and subjective muscle weakness. All patients received Botulism antitoxin A and fully recovered (16). Largest outbreak of Botulism in Turkey included 12 patients who consumed pasteurized yogurt. Clinical presentation was mild to moderate, all of them received Botulism antitoxin, with positive outcome. Diagnosis was confirmed with isolation of *Cl. Botulinum* from serum samples and the yoghurt (17). One of the largest outbreaks of Botulism was described in Iran with 27 patients affected. They all consumed homemade cheese, with different clinical presentation of illness. In this outbreak one lethal outcome was described (18).

In this outbreak we had patients with mild or moderate clinician presentation. There was no deterioration of clinical state during the hospitalization that could lead to paresis, paralysis or need for mechanical ventilation. It was impossible to take any sample for microbiology analysis, so the diagnosis was based only on clinical presentation with epidemiological data. Therapy options were also limited - only symptomatic therapy was given to all patients, since specific antitoxin at the time was not available anywhere in the country. Despite that, full recovery of all patients was noted, without any sequelae.

CONCLUSION

Botulism, even as a very rare disease in Bosnia and Herzegovina and in the rest of the world, should always be considered if patients with gastrointestinal and neurological symptoms were referred to hospital. Good epidemiological anamnesis can lead to proper diagnosis, even without appropriate microbiology support. During the clinical course patients should be monitored for deterioration of neurological state, which can lead to respiratory insufficiency requiring mechanical ventilation. Specific antitoxin should be available at least in one or two largest clinical centers in Bosnia and Herzegovina.

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Nebulized hypertonic saline in the treatment of acute bronchiolitis in infants and toddlers

Inhalatorni hipertoni rastvor natrijum hlorida u terapiji akutnog bronhiolitisa kod dojenčadi i male djece

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ABSTRACT

Introduction: bronchiolitis is the most common infection of early infancy and the most common reason of hospitalization in children up to six months of age. Therapeutic options of bronchiolitis treatment are limited. Nebulized hypertonic saline (NHS), as one of potential treatment, has been tested in number of clinical studies. American Academy of Pediatrics (AAP) published updated guideline for diagnosis and treatment of bronchiolitis suggesting usage of NHS in bronchiolitis. This article represents literature review aimed at analyzing the effectiveness of NHS in bronchiolitis therapy. Materials and methods: the article included the analysis of fourteen clinical studies: five of them related to usage of hypertonic saline in emergency departments (EDs) and nine of them in hospital environment. Each study was critically evaluated determining efficacy and security of NHS therapeutic usage. Results: the number of patients in EDs covered by the review was 1535 and there were 64.162 clinically treated patients and one multicenter study with 63.337 patients. Clinical studies were conducted by using different concentrations of NHS, in the period from 2010 to 2019 mainly assessing the clinical score of bronchiolitis and length of hospital stay. Conclusion: based on the analysis of all conducted studies and in accordance with AAP, NHS reduces clinical score of bronchiolitis and length of a hospital stay in patients hospitalized longer than 72 hours. Usage of NHS would be further evaluated through studies with larger samples and multicenter designed studies, incorporating standardized dosage and concentration of hypertonic saline for the final conclusion on clinically useful effects of NHS.

Keywords: bronchiolitis, nebulized hypertonic saline, infants

SAŽETAK

Uvod: bronhiolitis predstavlja najčešću respiratornu infekciju rane dojenačke dobi i najčešći razlog za hospitalizaciju djece do šest mjeseci. Terapijske opcije kod ove bolesti su limitirane. Inhalatorni hipertoni rastvor natrijum hlorida (NaCl), kao jedan od terapijskih modaliteta, ispitivan je u brojnim kliničkim studijama. Američka akademija za pedijatriju (AAP) je objavila ažurirani vodič za dijagnozu i tretman bronhiolitisa u kojem su date preporuke za upotrebu hipertone NaCl kod ove bolesti. Ovaj članak predstavlja pregled literature sa ciljem analize učinka nebuliziranog hipertonomog NaCl u terapiji bronhiolitisa. Materijali i metode: analizirano je četrnaest kliničkih studija, pet u kojima su evaluirale efikasnost upotrebe hipertonomog rastvora NaCl na urgentnim odjelima i devet u hospitalnim uslovima. Svaka studija je kritički evaluirana kako bi odredila efikasnost i bezbjednost terapijske upotrebe inhalatorne hipertone NaCl. Rezultati: istraživanjem je obuhvaćeno 1535 ispitanika koji su liječeni na urgentnim odjelima i 64162 ispitanika liječenih hospitalno, uključivši i jednu multicentričnu studiju sa 63337 ispitanika. Provedene kliničke studije su koristile različite koncentracije inhalatornog hipertonomog rastvora natrijum hlorida u periodu od 2010. do 2019. godine, procijenjujući klinički skor bronhiolitisa i dužinu hospitalnog boravka kao najčešće ishode. Zaključak: na osnovu analize svih provedenih studija, shodno preporukama AAP, nebulizirani hipertoni rastvor NaCl reducira klinički skor bronhiolitisa kao i dužinu hospitalnog boravka kod pacijenta koji su hospitalizirani duže od 72 sata. Upotreba hipertonomog rastvora bi se trebala dalje evaluirati kroz studije sa velikim uzorcima i multicentričnim dizajnom koje bi koristile standardizovano doziranje i koncentraciju hipertonomog rastvora NaCl, sa jasno definisanim ishodima, da bi se na kraju definitivno zaključilo da li hipertoni rastvor natrijum hlorida daje klinički značajne efekte ili ne.

Ključne riječi: bronhiolitis, hipertoni rastvor NaCl, dojenčad

INTRODUCTION

Definition, epidemiology and pathophysiology

Bronchiolitis represents the most common respiratory infection of early infancy and the most common reason of hospitalization of children up to six months of age. American Academy of Pediatrics defined bronchiolitis as prodromal viral infection of upper respiratory tract following respiratory exhaustion and wheezing in children up to two years of life (1). Around 90% of children would be infected with respiratory syncytial virus (RSV) up to second year of life while 40% of infected children would express infection of lower respiratory tract during primary infection (2). Around 3% of diseased children will require hospitalization and 2 - 5% of hospitalized patients will require mechanical ventilation and admission in intensive care unit (3,4). Majority of those children have RSV bronchiolitis and presence of risk factors such as chronic diseases and immunodeficiency. In the USA, around 100,000 children with bronchiolitis are hospitalized every year while annual costs have been estimated for around 1.73 billion US dollars (5). Mortality is less than 1% in children without risk factors while it is significant higher (3-10%) in children with chronic respiratory diseases and congenital heart disease. The most common cause of bronchiolitis is RSV, represented in 60-75% of all cases. In one study which included both hospitalized and outpatient treated patients with bronchiolitis, it was found that RSV was represented in 76 % of patients while other causes included: Rhinovirus (39%), Influenza (10%), Human metapneumovirus (3%), Coronavirus (2%), Parainfluenza (1%). Some patients also had coinfections (6). Clinical signs and symptoms of bronchiolitis include: rhinitis, cough, wheezing, tachypnea, expiratory dyspnea, nasal flaring and retractions. For diagnosis of bronchiolitis, it is sufficient to know epidemiological characteristics, age, risk factors and physical examination of the child. Pathophysiological processes are very important for defining clinical manifestation of bronchiolitis and purpose of certain therapeutics. It is manifested as inflammation of small airways - bronchioles developing necrosis of epithelium and peeling of affected cells, edema, increased secretion from submucosal glands and peribronchial cellular inflammation. These small airways, up to 300 microns in diameter, are being completely obstructed with cellular debris and viscous dense mucous and with epithelial cells fused with syncytium (7). Due to nonexistence of collateral ventilation, there is development of disseminated atelectasis and hyperinflation zone (8).

Therapy of Bronchiolitis

Therapeutical options for bronchiolitis are very limited. According to the AAP protocol, treatment includes measures for securing proper hydration and oxygen supplementation given that other measures have been declared as inefficient (9,10,11). Infants with bronchiolitis receive antibiotics because of fever, young age and physician concerns about secondary bacterial infection. Around 25% of hospitalized infants with bronchiolitis have radiological atelectasis which is hardly differentiated from bacterial infiltrate or consolidation. Antibiotic therapy is indicated in case of suspicious of bacterial infection and patients requiring mechanical ventilation due to respiratory failure. Oxygen therapy increases saturation of oxygen in blood acting as direct bronchodilator in lungs. According

to the AAP, oxygen therapy is indicated if saturation level is below 90%. A small partial arterial pressure increase of oxygen is combined with a significant saturation increase when saturation is less than 90%. When the saturation level is above 90%, partial arterial pressure should be increased enormously for further influence on the saturation increase. The most common controversies in therapeutic approach refer to the usage of Salbutamol and corticosteroids. Role of bronchodilators have been discussed in many meta-analysis and systematic review of literature (12,13,14,15,16,17). Results of these reviews have shown, despite temporary relief in clinical manifestation, that those drugs did not help in solving the disease and did not shorten duration of hospital stay. Potential side effects (tachycardia and tremors) combined with costs of those drugs, overcome any beneficial effects. Corticosteroids usage in treatment of bronchiolitis is controversial. Recent Cochrane systematic review showed that corticosteroids did not significantly reduce clinical score, hospitalization rate and hospital stay. This corresponds with the AAP recommendation for non-using of corticosteroids (18). Racemic epinephrine should be useful given its characteristics as agonist of alpha and beta receptors giving less edema and mucus plugs. However, action of epinephrine is transient. Studies have shown that it does not correspond with lessening of hospital stay. The AAP protocol partially recommends epinephrine in severe form of bronchiolitis (19,20,21,22,23). NHS has been tested as potential therapeutic. Due to pathophysiology of bronchiolitis including inflammation of airways and mucus plugs formation, improvement of mucociliary clearance could be useful in termination of this disease. Hypertonic saline using principle of osmosis, retracts water in mucus layer and in that way reduces viscosity of mucus but also lowers edema of mucosa and supports mucociliary clearance (24,25,26,27). The AAP supports usage of NHS in infants and children hospitalized due to bronchiolitis (28).

This article represents literature review aimed at analyzing the effectiveness of nebulized hypertonic saline in bronchiolitis therapy. Conclusions and outcomes of studies are presented in tables 1 and 2, with administered therapies, and exclusion and inclusion criteria of each study.

AIM

This article represents literature review with the aim of analyzing effectiveness, safety and the role of nebulized hypertonic saline in the treatment of bronchiolitis.

MATERIALS AND METHODS

Pubmed/Medline literature review, including clinical trials over the last five years, was performed using the search terms hypertonic saline, bronchiolitis and children. Languages other than English were excluded as well as indications for saline therapy other than bronchiolitis. The article included the analysis of fourteen clinical studies: five related to usage of hypertonic saline in emergency departments (EDs) and nine related to hospital environment. Each study was critically evaluated determining efficacy and security of NHS therapeutic usage. Tables 1 and 2 summarize the available literature on hypertonic saline for bronchiolitis in the outpatients and hospitalized patients, respectively.

RESULTS

Clinical Studies Evaluating Efficacy of Hypertonic NaCl use in Bronchiolitis Patients in EDs

In 2010, Al-Anasari, et al., conducted prospective randomized double-blind study covering in total 187 patients for comparison of efficacy of 5% NHS in combination with epinephrine and 3 % NHS with epinephrine. Primary outcome was a decrease in mean values of clinical bronchiolitis score - Clinical Severity Score (CSS) in both groups for 48 hours. Inclusion research criteria were: age \leq 18 months, middle and severe viral bronchiolitis, clinical score = 4. Exclusion research criteria were: wheezing or apnea in first 24 hours after viral contact, prematurity with \leq 34 GA, steroid usage during first 48 hours, progressive respiratory insufficiency requiring an admission in intensive care unit (ICU), patients having oxygen saturation \leq 85% on room air, chronic pulmonary disease, congenital heart disease or immunodeficiency. Conclusion of this study is that 5% NHS has more effective and safer application then 3% NHS in early started treatment of patients with bronchiolitis in non-hospitalized patients. But this study could not prove statistically significant difference between two tested groups (29).

In 2014, Florin, et al., conducted prospective randomized clinical study eliminating efficacy of 3% NHS comparing to NNS. Primary outcome was change in clinical score of bronchiolitis. Secondary outcome included vital signs, oxygen saturation, hospitalization need, side effects and improvement perception noticed by physicians and parents. Inclusion criteria were children between the ages of 2 - 23 months, first episode of moderate to severe bronchiolitis. Exclusion criteria were: previous episodes of wheezing, bronchodilators therapy, chronic pulmonary disease, cardiovascular disease, inability to receive nebulized therapeutics. Authors concluded that usage of hypertonic saline after standardized treatment in nonhospital conditions is less efficacious than usage of NS. So, administration of one dose of hypertonic saline is not recommended in acute diseases children due to only improved respiratory rate as part of clinical score of bronchiolitis. Despite no statistical significance, both patients' groups with severe clinical manifestations felt improvements (30).

In 2014, Jacobs, et al., conducted prospective double blind randomized study on 101 infants evaluating efficacy and security of 7 % NHS with racemic epinephrine comparing to combination of NS with racemic epinephrine. Primary outcome was clinical score of bronchiolitis (CSS). Secondary outcomes were hospitalization count, number of hospital discharge in 23 hours and a length of hospital stay. Inclusion criteria were: children between the ages of 6 to 18 months with first episode of wheezing and clinical score \geq 4. Exclusion criteria were: previously presented wheezing in

anamnesis, bronchodilators usage 2 hours before hospital arrival, children born with \leq 34GA, positive anamnesis of chronic pulmonary and kidney diseases as well as congenital heart disease, oxygen saturation 85 % in period examination and more serious diseases requiring hospitalization in ICU. Both groups experienced improvement regarding clinical score of bronchiolitis but without statistically significant differences in average score values. There was not a statistical significance difference between groups regarding a stay in EDs. Percentage of patients requiring hospitalization were similar between groups (31).

In 2014, Wu S, et al., covered 408 patients for conducting prospective double blind randomized clinical study for evaluation of albuterol efficacy with 3 % NHS comparing with combination of NS and albuterol regarding a length of treatment in EDs. Following outcomes were measured: hospital admission, recovery length of admitted patients and clinical score of bronchiolitis (RDAI). Inclusion criteria were children with age up to 24 months with primary diagnosis of viral bronchiolitis admitted from November to March. Exclusion criteria were: previously positive anamnesis for wheezing, bronchodilator usage, prematurity \leq 34 GA, congenital cyanotic heart disease, chronic pulmonary disease and tracheostoma. Study results showed that rate of hospital admission was significantly less in group of patients receiving NHS. This is a first study showing admission reduction to EDs. However, the length of hospital stay was not lowered. Clinical score was lower in both groups but without significant difference (32).

In 2017, Francois, et al., published results of multicentric, double blind randomized onto two parallel clinical studies conducted on 24 departments of emergency medicine in France during two seasons of bronchiolitis including 777 infants. This was the biggest study evaluating efficacy of NHS in EDs. They evaluated efficacy of 3 % NHS comparing to NS. Primary outcome was an arrival in hospital 24 hours after including into study. Secondary outcomes were an arrival in hospital in following 28 days, clinical score RDAI), symptoms duration, the length of hospital stay, accompanied signs and symptoms: bronchospasm, desaturation, cough, apnea and cyanosis. Inclusion criteria were: infants between the ages of 6 to 12 months with first episode of moderate and severe bronchiolitis. Exclusion criteria were: prematurity ($<$ 37 GA), immunological disease, heart disease, chronic pulmonary disease, malformation of musculoskeletal system, previous usage of NHS, inability to communicate with family (language barrier or missing telephone number of parents or relatives) as well as critically ill children hospitalized in ICU. Researchers concluded that NHS did not significantly lowered rate of admissions and mild side effects were more common in group receiving NHS. There was no difference in the length of hospital stay between groups (33).

Table 1 Clinical Studies Evaluating Efficacy of Usage Hypertonic NaCl in Bronchiolitis Patients in EDs (PO - Primary Outcome, SO - Secondary Outcome, RR - Respiratory Rate, CSS - Clinical Severity Score, HR - Heart Rate).

Authors Year	Outcomes	Inclusion criteria	Exclusion criteria	Therapies (Intervention vs. Control)	Conclusion
Al-Anasri, et al. 2010	PO: decrease in average value of CSS for 48 h	Age \leq 18 months, middle and severe viral bronchiolitis, CSS = 4	wheezing or apnea in first 24 h after viral contact, prematurity (\leq 34 GA), steroid usage during first 48 hours, respiratory insufficiency requiring an ICU admission, O ₂ saturation \leq 85%, cardiopulmonary disease, immunodeficiency	5 % NHS in combination with epinephrine vs. 3 % NHS with epinephrine	5 % NHS has more effective and safer application than 3 % NHS in early started treatment of patients with bronchiolitis in non-hospitalized patients; this study could not prove statistically significant difference between two tested groups
Florin, et al. 2014	PO: CSS SO: included vital signs, O ₂ saturation, hospitalization need, side effects, improvement in perception noticed by physicians and parents.	Children between the ages of 2 to 23 months, first episode of moderate to severe bronchiolitis	Previous episodes of wheezing, bronchodilators therapy, cardiopulmonary disease, inability to receive nebulized therapeutics.	3 % NHS vs. NS	Usage of 3% hypertonic saline after standardized treatment in nonhospital conditions is less efficacious than usage of NS; administration of one dose of hypertonic saline is not recommended in acute diseases children due to only improved respiratory rate as part of CSS; both patients' groups with severe clinical manifestations felt improvements without statistical significance
Jacobs, et al. 2014	PO: evaluation of CSS SO: hospitalization rate, rate of hospital discharge in 23 hours, a length of hospital stay.	children from 6 to 18 months with first episode of wheezing, clinical score \geq 4.	Previous wheezing, bronchodilators usage 2 hours before hospital, prematurity (\leq 34 GA), cardiopulmonary disease, O ₂ saturation \leq 85 %	7 % NHS with racemic epinephrine vs. combination of NS with racemic epinephrine	Both groups experienced improvement regarding CSS but without statistically significant difference in average score values; there was not a statistical significance difference between groups regarding a stay in EDs; percentage of patients requiring hospitalization were similar between groups
Wu S, et al. 2014	Hospital arrival, recovery length of arrived patients and clinical score of bronchiolitis (RDAI).	age up to 24 months with primary diagnosis of viral bronchiolitis admitted between November to March	previous wheezing, bronchodilator usage, prematurity (\leq 34 GA), cardiopulmonary disease tracheostoma.	3 % NHS with albuterol vs. combination of NS and albuterol	Rate of hospital arrival was significantly less in group of patients receiving hypertonic NaCl; the length of hospital stay was not lowered; clinical score was lower in both groups but without significant difference
Francois, et al. 2017	PO: an arrival in hospital 24 hours after including into study. SO: an arrival in hospital in following 28 days, clinical score RDAI, symptoms duration, the length of hospital stay, bronchospasm, desaturation, cough, apnea, cyanosis	infants between the ages of 6 to 12 months with first episode of moderate and severe bronchiolitis.	prematurity ($<$ 37 GA), immunological disease, cardiopulmonary disease, malformation of musculoskeletal system, previous usage of NHS, inability to communicate with family	3% NHS vs. NS	NHS did not significantly lowered rate of admissions and mild side effects were more common in group receiving nebulized hypertonic NaCl; there was no difference in the length of hospital stay between groups

Clinical Studies Evaluating Efficacy of Hypertonic NaCl Usage in Hospital Treated Bronchiolitis Patients

In 2012, Miraglia Del Giudice, et al., conducted double blind, prospective randomized controlled study including 109 patients examining effects of nebulized epinephrine in combination with NHS comparing with NS and epinephrine in hospitalized children

with bronchiolitis in Italy. The study analyzed two main outcomes: a) difference in the length of hospital stay between two groups; b) Changes in clinical score of disease. This study included children with age up to 2 years having clinical diagnosis of bronchiolitis. Exclusion criteria were: prematurity, existing cardiopulmonary disease, asthma, oxygen saturation less than 85 % or serious distress requiring reanimation. Authors concluded that usage of 3 % NHS is more effective compared to NS in hospitalized children with bronchiolitis regarding improvement of clinical manifestation as well as the length of hospital stay. However, there was not statistically significant difference between those groups (34).

In 2013, Sharma, et al., conducted randomized, control, double blind study involving 248 children with bronchiolitis in India evaluating efficacy of nebulized 2.5 % albuterol with 3 % NHS compared to albuterol in combination with NS. Primary outcome was the length of hospital stay defined as time needed for getting rate less than 3 of clinical bronchiolitis score. Inclusion criteria were: patients from one month to 2 years and moderate to severe clinical manifestations of bronchiolitis. Exclusion criteria were: previous usage of hypertonic saline inside 12 hours after arrival, altered mental status, heart and lung diseases, previous episodes of wheezing and serious respiratory distress. They concluded that NHS was not superior compared to NS in treatment of bronchiolitis and there was not any difference in the length of hospital stay between groups (35).

In 2014, Florens-Gonzales, et al., conducted prospective, randomized, double blind control study for evaluation of efficacy regarding usage of 7 ml 3% NHS with 3ml epinephrine compared to 7ml 3% NHS with 3ml aqueous solution in treatment of 64 hospitalized children with moderate to severe clinical manifestations of bronchiolitis. Primary outcome was the length of hospital stay. Secondary outcomes were: retraction, heart frequency, respiratory rate, cyanosis, vital signs, side effects, ICU hospitalization and mechanical ventilation. Inclusion criteria were: age up to 24 months, first episode of moderate to severe bronchiolitis with wheezing requiring hospitalization followed by upper respiratory tract infection. Exclusion criteria were: prematurity, chronic lung disease, heart disease, immunodeficiency, previous episodes of wheezing, asthma, previous usage of mechanical ventilation in home conditions or previous episode of bronchiolitis requiring mechanical ventilation. Regarding primary outcome, it was not found significant difference between groups. There was not statistically significant difference in term of clinical score of bronchiolitis, oxygen saturation, heart rate, respiratory rate. Third day of hospitalization in group receiving NHS and epinephrine, severity of clinical manifestations and heart rate were nonsignificantly improved (36). Authors concluded that usage of nebulized epinephrine with NHS was safe and there was significant trend of improved clinical relieve (36).

In 2014, Nenna, et al., conducted prospective, randomized, double blind control study including 39 children for evaluation of efficacy for usage of 2.5 ml 7% NHS with hyaluronic acid compared to 2.5 ml NS in infants up to 7 months old hospitalized because of mild and moderate bronchiolitis. Primary outcome was the length of hospital stay while secondary outcome was clinical severity score of bronchiolitis (CSS). Hyaluronic acid was used for prevention of cough side effects such as in case of hypertonic saline inhalation. Study covered infants having clinical score ≥ 4 . Exclusion criteria were: existence of infection of lower respiratory tract and wheezing episode, chronic lung disease, heart disease, immunodeficiency and prematurity (<34 GA). Authors concluded that therapy with hypertonic saline combined to hyaluronic acid

reduced average hospital stay for 0.7 days but without statistically significant difference. There was no difference in clinical score between groups during first three days of hospitalization. Many patients had a coughing as side effect in group receiving NHS and hyaluronic acid compared to group receiving NS. This is a first study including newborns as the most vulnerable population affected by bronchiolitis (37).

In 2014, Ojha, et al., conducted randomized, control, double blind study including 59 children for comparison between 3 % NHS with NS in hospital treatment of bronchiolitis. This study included children in age between 6 and 24 months with first episode of bronchiolitis. Exclusion criteria were: previous episode of wheezing, cardiopulmonary disease, immunodeficiency, respiratory insufficiency requiring mechanical ventilation, treatment with 3 % NHS and Albuterol 12 hours before involvement into study, prematurity (≤ 34 GA) and oxygen saturation less than 85% on fresh room air. This study showed that NHS was not superior compared to NS regarding improvement in clinical severity score of bronchiolitis and shortened hospital stay (38).

In 2014, Florin, et al., published results of multicentric retrospective cohort analysis examining the length of hospital stay for 63,337 hospitalized infants in USA treated with 3 % NHS. Authors collected data from 42 hospitals connected to Pediatric Information Health System in period of three years. Patients involved in this study were infants up to 12 months with diagnosis of bronchiolitis. Children with cystic fibrosis, spinal muscle dystrophy and bronchiectasis were excluded from this research. Observed outcome was the length of hospital stay. Authors concluded that usage of NHS could be useful in patients who were severely ill and for patients being hospitalized more than 4 days (39).

In 2016, Flores, et al., published results of randomized, double blind control study conducted on 68 infants examining effects of 3 % NHS to NS. Primary outcome was the length of hospital stay and clinical score of bronchiolitis. Secondary outcomes were oxygen supplementation, feeding through nasogastric tube, additional therapies. Safety of hypertonic saline application was evaluated. Inclusion criteria were infants less than 12 months old with acute bronchiolitis. Exclusion criteria were: previous episodes of wheezing, prematurity (< 34 GA), eczema, food allergy, chronic cardiopulmonary disease, neurological disorder, metabolic disorder, immunodeficiency, coma, heart rate > 80 /min, oxygen saturation < 88 % on fresh room air and assisted ventilation. Authors concluded that 3 % NHS, either safe for application, did not reduce the length of hospital stay, clinical score of bronchiolitis, oxygen supplementation, nasogastric tube feeding and additional therapies (40).

In 2019, Jaquet-Pilloud, et al., published results of multicentric, randomized clinical study involving 122 children. Study goal was an examination whether 3 % NHS shortened the length of hospital stay compared to standard supportive care. Standard care included suction of nasal mucus, hydration and oxygen supplementation. Secondary outcome was: the length of oxygen supplementation, needs for nebulized racemic epinephrine, ICU admission, readmission inside seven days after discharge and side effects such as bronchospasm, cough, apnea and cyanosis. Inclusion criteria were children from 6 to 24 months with moderate to severe bronchiolitis. Exclusion criteria were: previous wheezing episodes, heart disease, chronic lung disease, immunodeficiency, prematurity (< 34 GA), therapy with corticosteroids in last two weeks or bronchodilators in last 24 hours. Authors concluded that there was no significant difference in term of the length of hospital stay and

either in duration of oxygen therapy, needs for nebulized racemic epinephrine, ICU admission and readmission after hospital discharge in 7 days between groups (41).

In 2019, Beal, et al., published results of randomized, double blind control study covering 116 infants. They were examining application of 3 % NHS during three days or one day. Inclusion criteria were infants younger than 12 months with mild bronchiolitis (Wang CSS 4-19) requiring hospitalization. Exclusion criteria were: chronic cardiopulmonary disease, neurologic disease, prematurity (< 34 GA), asthma (at least third episode of wheezing), severe bronchiolitis, indications for ICU transfer in first 24 hours and corticosteroids or bronchodilators treatment.

Primary outcome was clinical score after 72 hours, including first 24 hours of opened treatment with 3 % NHS and 48 hours of blind treatment with NHS or NS. Secondary outcome was daily evaluation of clinical score between admission to following 72 hours, clinical remission defined as oxygen saturation above 92 % during wakefulness and more than 90 % during sleeping, spontaneous feeding for more than >2/3 of usual portion during last two meals, respiratory rate < 60/min and CSS < 4, oxygen supplementation and nasogastric tube feeding. Authors concluded that 3% NHS is more efficient during three days administration (42).

Table 2 Clinical Studies Evaluating Efficacy of Hypertonic NaCl Usage in Hospital Treated Bronchiolitis Patients (PO - Primary Outcome, SO - Secondary Outcome, RR - Respiratory Rate, CSS -Clinical Severity Score, HR - Heart Rate).

Authors Year	Outcomes	Inclusion criteria	Exclusion criteria	Therapies (Intervention vs. Control)	Conclusion
Miraglia Del Giudice, et al. 2012	Difference in the length of hospital stay between two groups; changes in CSS.	children with age up to 2 years having clinical diagnosis of bronchiolitis	Prematurity, existing cardiopulmonary disease, asthma, oxygen saturation less than 85 % or serious distress requiring reanimation.	nebulized epinephrine in combination with NHS vs NS and epinephrin	Usage of 3 % NHS is more effective compared to NS in hospitalized children with bronchiolitis regarding improvement of clinical manifestation as well as the length of hospital stay; there was not statistically significant difference between those groups
Sharma, et al. 2013	The length of hospital stay defined as time needed for ≤ 3 of CSS.	Age: a month - 2 years Moderate to severe clinical manifestations of bronchiolitis	Previous usage of hypertonic saline- inside 12 hours after arrival, altered mental status, heart and lung diseases, previous episodes of wheezing and serious respiratory distress.	nebulized 2.5 % albuterol with 3 % NHS vs. albuterol in combination with NS	NHS was not superior compared to NS in treatment of bronchiolitis and there was not any difference in the length of hospital stay between groups
Florens-Gonzales, et al. 2014	PO: the length of hospital stay; SO: retraction, HR, RR, cyanosis, vital signs, side effects, ICU hospitalization and mechanical ventilation.	age up to 24 months, first episode of moderate to severe bronchiolitis with wheezing requiring hospitalization followed by upper respiratory tract infection	Prematurity, cardiopulmonary disease immunodeficiency, previous wheezing, asthma, previous usage of mechanical ventilation in home conditions or previous episode of bronchiolitis requiring mechanical ventilation	7 ml 3% NHS with 3ml epinephrine vs. 7ml 3% NHS with 3ml aqueous solution	Usage of nebulized epinephrine with NHS was safe and there was significant trend of improved clinical relieve
Nenna, et al. 2014	PO: the length of hospital stay while SO: CSS	infants having clinical score ≥ 4	Infection of lower respiratory tract, wheezing, cardiopulmonary disease immunodeficiency and prematurity (< 34GA)	2.5 ml 7 % NHS with hyaluronic acid vs. 2.5 ml NS	Therapy with hypertonic saline combined to hyaluronic acid reduced average hospital stay for 0.7 days but without statistically significant difference; there was no difference in clinical score between groups during first 3 days of hospitalization
Ojha, et al. 2014	////	children in age between 6 and 24 months with first episode of bronchiolitis	Previous wheezing, cardiopulmonary disease, immunodeficiency, respiratory insufficiency requiring mechanical ventilation, treatment with 3 % NaCl and Albuterol 12 hours before involvement into study, prematurity (≤ 34 GA) and O ₂ saturation ≤ 85 %	3% NHS vs. NS	NHS was not superior compared to NNS regarding improvement in clinical score of bronchiolitis and shortened hospital stay
Florin, et al. 2014	The length of hospital stay	Infants up to 12 months, diagnosed with bronchiolitis	Children with cystic fibrosis, spinal muscle dystrophy and bronchiectasis	3% NHS	Usage of NHS could be useful in patients who were severely ill and for patients being hospitalized more than 4 days
Flores, et al 2016	PO: the length of hospital stay and CSS SO: oxygen supplementation, feeding through nasogastric tube, additional therapies.	Infants age less than 12 months with acute bronchiolitis	Previous wheezing, prematurity (< 34 GA), atopy, cardiopulmonary disease, neurological disorder, metabolic disorder, immunodeficiency, coma, HR > 80/min, O ₂ saturation < 88 %	3% NHS vs. NS	3% NHS, either safe for application, did not reduce the length of hospital stay, clinical score of bronchiolitis, oxygen supplementation, nasogastric tube feeding and additional therapies
Jaquet-Pilloud et al 2019	The length of oxygen supplementation, needs for nebulized racemic epinephrine, ICU admission, readmission inside seven days after discharge and side effects such as bronchospasm, cough, apnea and cyanosis	Children from 6 to 24 months with moderate to severe bronchiolitis	Previous wheezing, cardiopulmonary disease, immunodeficiency, prematurity (< 34 GA), therapy with corticosteroids in last 2 weeks or bronchodilators in last 24 hours.	3%NHS vs. standard supportive care (succussion of nasal mucus, hydration and oxygen supplementation)	There was no significant difference in term of the length of hospital stay and either in duration of oxygen therapy, needs for nebulized racemic epinephrine, ICU admission and readmission after hospital discharge in 7 days between groups
Beal et al 2019	PO: CSS after 72 hours(including first 24 hours of opened treatment with 3 % NHS and 48 hours of blind treatment with 3 % NHS or NNS) SO: daily evaluation of CSS between admission to following 72 hours, clinical remission defined as O ₂ above 92 % during wakefulness and more than 90 % during sleeping, spontaneous feeding for more than >2/3 of usual portion during last two meals, respiratory rate < 60/min and CSS <4, oxygen supplementation and nasogastric tube feeding.	Infants younger than 12 months with mild bronchiolitis (Wang CSS 4 -19) requiring hospitalization	Cardiopulmonary disease, neurologic disease, prematurity (< 34 GA), asthma (at least third episode of wheezing), severe bronchiolitis, indications for ICU transfer in first 24 hours and corticosteroids or bronchodilators treatment.	3 days of 3 % NHS vs 1 day of 3% NHS	3 % hypertonic saline is more efficient during three days administration

DISCUSSION

NHS has been researched in last ten years though many randomized control studies but without clear consensus regarding its efficacy. It is claimed that this solution reduces mucous edema of respiratory airways, lowers constitution of mucous plugs, increases mucociliary clearance and rehydrates fluids on surface of respiratory tract. But regarding those previously mentioned claims, there are not clear experimental proves for supporting of claims (43). First examinations for treatment of bronchiolitis in newborns and infants with inhalation of hypertonic saline proved that it could be useful and subsequently conducted studies questioned the efficacy of this treatment. Accordingly, nebulised hypertonic saline was found on the list of controversial drugs in bronchiolitis therapy. The most common followed outcomes in this paper were clinical score of bronchiolitis and the length of hospital stay. According to descriptions of up here mentioned studies, hypertonic saline showed efficacy compared to NS regarding lowered clinical score of bronchiolitis patients in EDs as well as in hospitalized patients (31, 32, 34, 36, 37), but without significant difference. One study should be specially mentioned in this discussion regarding significant difference in term of outcome for group receiving NHS, conducted in EDs. It is the largest multicentric study which does not correspond with conclusions of AAP about hypertonic saline. AAP, in its guideline from 2014, stated that hypertonic saline does not have influence in treatment of children in EDs (1). Other studies showed NHS as less efficacious than NS (30) and it did not reduce clinical score of bronchiolitis compared to NS (38, 40). Regarding the length of hospital stay as outcome, it is not showed any difference between group receiving NHS and NS (31, 32, 33, 34, 35, 36, 37, 38, 40, 41). The result of multicentric study showed that NHS reduced the length of hospital stay in severe bronchiolitis and in case of hospitalization longer than 4 days. According to AAP, usage of NHS is indicated if the hospitalization is longer than 72 hours so results of the previously mentioned multicentric study do not correspond to AAP recommendations. It is needed to mention that the length of hospital stay is highly dependent on other factors to be compared with certain interventions. Also, there is another analyzed study showing that NHS is efficient compared to NS during administration at least 3 days in term of clinical score, clinical remission defined as a need for oxygen saturation above 92 % during wakefulness and more than 90 % during sleeping, spontaneous feeding for more than >2/3 of usual portion during last two meals, respiratory rate < 60/min and SCC <4, oxygen supplementation and nasogastric tube feeding (42). Analyzing admission rate for hospital treatments as outcome, it is showed that percentage of admitted patients on the hospital treatment was similar between groups (31), the admission rate in hospitals was significantly lower for patients receiving NHS (32) and NHS did not significantly decrease admission rate (34). Due to those aforementioned conclusions, it is needed to conduct more clinical trials on EDs to determine whether NHS decreases hospitalization rate. Some studies analyzed the influence of different NHS concentration - 3%, 5%, 7% and significant difference regarding

efficiency is not found (29,31,37). Therefore, a question about superiority of hypertonic saline in treatment should be answered. We may conclude about existence of mutual insufficiencies regarding analyzed studies. It includes an involvement of patient not being seriously ill, indeterminacies in term of drug dosages as well as concentration of administrating hypertonic saline, usage of different criteria for determination of clinical score (CSS and RDAI), big samples in certain studies. Albuterol, bronchodilators and racemic epinephrine were used in certain studies as wheezing relief. But it is possible to conclude that any difference is not found regarding outcomes in different treatment options (29,31,32,34,35,36). Usage of NS as comparator in those studies is not good choice. Hypertonic saline improves mucociliary clearance but either NS could be used in treatment of bronchiolitis. Therefore, usage of NS as comparator in most of studies represents obstacle for clearly determining of hypertonic saline efficacy. Because of previously mentioned reason, designed studies involving some nonirritating inhalatory solutions, which could serve as placebo, represent a great solution and on that way, it would be possible to differentiate real role of hypertonic and isotonic saline.

CONCLUSION

According to all analyzed studies in this review and AAP suggestions, NHS reduces clinical score of bronchiolitis and the length of hospital stay in patients hospitalized for more than 72 hours. Due to safety of this therapy and deficiencies of other efficient therapy options for bronchiolitis children patients, usage of hypertonic saline should be evaluated on a large sample and multicentric design using standardized dosage and concentration of NHS, with clearly defined outcomes, for final conclusion whether NHS gives clinical effects or not in the treatment of bronchiolitis.

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First clinical experience with neuronavigation system in Bosnia and Herzegovina: seven years results

Prvo kliničko iskustvo sa neuronavigacijskim sistemom u Bosni i Hercegovini: sedmogodišnji rezultati

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ABSTRACT

Introduction: stereotactic neuronavigation has become popular in 1980s and it represents a standard tool in brain and spinal surgery. In modern neurosurgical era, neuronavigation is commonly used to identify small brain lesions, deep seated lesions, sellar region tumors. Aim: to present clinical experience with neuronavigation system used at Clinic of Neurosurgery of the Clinical Center University of Sarajevo (CCUS). Materials and methods: this retrospective study includes analysis of patients treated in the period from 2012 to 2018. Patients operated with neuronavigation system assistance were included in this study. All information was collected from the patients' medical histories. Comparative analysis between neuronavigation and standard surgical resections was performed. Results: in the study period a total of 872 brain tumor operations were performed. Out of the total number of surgeries, 102 were performed with the assistance of neuronavigation system, there were 54 (52.9%) neuronavigation assisted resections, 36 (35.3%) biopsies and 12 (11.8%) tumor reductions. Without neuronavigation assistance 633 resections (82.5%) were performed, as well as 45 biopsies (5.9%) and 89 reductions (11.6%). There were statistically significantly more biopsies conducted in the neuronavigational group ($\chi^2=93.610$; $p=0.0001$). Conclusion: neuronavigation is one of the essential neurosurgical tools in the high volume centers. The results of the study demonstrate usefulness and effectiveness of neuronavigational system which contributes to the improvement of the final clinical outcome with small amount of complications.

Key words: neurosurgery, neuronavigation, brain tumor, biopsy, resection

SAŽETAK

Uvod: stereotaksijska neuronavigacija je postala popularna 1980-ih i predstavlja standardni alat u hirurgiji mozga i kičme. U modernoj neurokirurškoj eri neuronavigacija se najčešće koristi za detekciju malih moždanih lezija, duboko smještenih lezija, tumora selarne regije. Cilj: predstaviti kliničko iskustvo sa neuronavigacijskim sistemom koji se koristi na Klinici za neurohirurgiju Kliničkog centra Univerziteta u Sarajevu (KCUS). Materijali i metode: ovo retrospektivno istraživanje uključuje analizu pacijenata koji su se liječili u razdoblju od 2012. do 2018. U ovu studiju uključeni su pacijenti operisani uz pomoć neuronavigacijskog sistema. Svi podaci su prikupljeni iz historija bolesti pacijenata. Izvršena je usporedna analiza između neuronavigacijskih i standardnih hirurških resekcija. Rezultati: u istraživanom periodu izvedene su 872 operacije tumora na mozgu. Od ukupnog broja operacija, 102 su izvedene uz pomoć neuronavigacijskog sistema. Od ukupnog broja, imali smo 54 (52,9%) resekcije uz pomoć neuronavigacije, 36 (35,3%) biopsija i 12 (11,8%) redukcija tumora. Bez neuronavigacijske asistencije izvršili smo 633 resekcije (82,5%), 45 biopsija (5,9%) i 89 redukcija tumora (11,6%). U neuronavigacijskoj grupi smo imali statistički značajno više provedenih biopsija ($\chi^2=93,610$; $p=0,0001$). Zaključak: neuronavigacija je jedan od bitnih neurokirurških alata u visokovolumnim centrima. Naši rezultati pokazuju benefit i efikasnost neuronavigacijskog sistema, koji doprinosi poboljšanju konačnog kliničkog ishoda sa malim udjelom komplikacija.

Ključne riječi: neurohirurgija, neuronavigacija, tumor mozga, biopsija, resekcija

INTRODUCTION

Neuronavigation is a computer assisted technology used in neurosurgery based on preoperative magnetic resonance (MRI) or computed tomography (CT), to guide the neurosurgeon in brain and spine surgery (1). Neuronavigation became popular in 1980s and today it represents a standard neurosurgical tool (1,2). One of the main surgical issues is how to safely and accurate approach to the brain lesion, without damaging vital structures surrounding it. First stereotactic neuronavigation surgery was performed in 1947

by Spiegel and Wycis (1,3,4). Nowadays, radiological diagnostic tools are standard in neurosurgery, but neuronavigation occupies an irreplaceable role. In modern neurosurgical era, neuronavigation is most commonly used to identify small brain lesions, deep seated lesions, brain abscess, sellar region tumors. However, it is used in intracranial endoscopy as well as in functional neurosurgery. One of the most important surgical value of neuronavigation is intraoperative identification of the key brain vessels during skull base surgery (1,5). There are some limitations of neuronavigational system according to precision. Majority of neuronavigation systems

used today give an accuracy of approx. 2 mm (6). The first neuronavigation assisted operation in Bosnia and Herzegovina was performed in 2012 by neurosurgeon Avduh Hasanagic in brain tumor surgery, which has since become routinely used by each neurosurgeon at our Clinic.

AIM

The aim of the study was to present clinical experience with neuronavigation system used at Clinic of Neurosurgery of the Clinical Center University of Sarajevo (CCUS). The study will present indications where neuronavigation system, navigation accuracy was used, pathohistological results, complications related to the use of neuronavigation and functional outcome of the patients.

MATERIALS AND METHODS

This retrospective study includes first results obtained in the seven years period, from 2012 to 2018. Patients surgically treated at our Clinic using frameless neuronavigation system (Medtronic™) were included in the study. However, frame based stereotactic device (14,15) was used at our Clinic from 1980 to 2012. All data were collected from the patients' medical histories. Patients without a complete data were excluded from the study. From medical histories the following was documented: sociodemographic data, type of surgery, radiological preoperative diagnosis, definitive pathohistological diagnosis, rate of reoperation due to inaccurate biopsy sample, postoperative complications, reoperation rate and intrahospital functional outcome according to the modified Rankin score (mRs) and Karnofsky Performance Score (KPS). Postoperative complications were defined as events requiring

prolonged multidisciplinary treatment at Neurosurgery Intensive Care Unit (NICU). Following the surgery, all patients were admitted to NICU for 24 hours monitoring. A postoperative CT brain scan with iodine contrast was performed 24-48 h after the surgery. Significant postoperative CT was considered in the case of CT verified brain edema with brain midline shift (more than 5 mm) or significant amount of blood in the operative field (compressive effect on surrounding brain). In patients where neuronavigation was performed radiological findings were correlated with the definitive pathohistological finding match rate. The statistical analysis used Excel 2003 and SPSS 13. The data were statistically processed to determine the following values: mean (M) and standard deviation (SD), minimum and maximum value (min – max), Chi square test. The results were presented in the form of tables and figures. The significance of the difference for continuous variables was tested by an independent Student t-test. Values of $p < 0.05$ were considered as statistically significant.

RESULTS

This article analyzed 872 brain tumor operations performed at the CCUS Clinic of Neurosurgery in the seven years period (annual rate of 125). Out of total number of brain tumor operations 102 were performed with neuronavigation assistance.

Within the group of tumors operated without the neuronavigation there were 375 males (48.7%) and 395 females (51.3%) (Table 1). On the other hand, neuronavigation assisted operation were performed in 56 males (54.9%) and 46 females (45.1%). According to the Chi-square test results there was no statistically significant difference in gender representation between the groups ($\chi^2 = 1.385$; $p = 0.142$).

Table 1 Gender distribution of patients operated with and without neuronavigation assistance (number and percent within the group and total).

	NEURONAVIGATION GROUP		WITHOUT NEURONAVIGATION		TOTAL	
	Number	Percent (%)	Number	Percent (%)	Number	Percent (%)
MALE	56	54.9	375	48.7	431	49.4
FEMALE	46	45.1	395	51.3	441	50.6
TOTAL	102	100	770	100	872	100

Mean (M) age of the patients operated with neuronavigation assistance was 52.30 ± 14.2 years. In the group of patients operated without neuronavigation assistance the mean age was 51.46 with

the oldest patient being 87 years of age and the youngest in the first year of life. There was no statistically significant difference in mean age between the two groups; ($F = 0.230$; $p = 0.632$) (Table 2).

Table 2 Age distribution of patients operated with and without neuronavigation assistance.

		Neuronavigation	Without neuronavigation
Median		56.50	51.46
Mean		52.30	51.46
Percentiles	25	42.50	42.75
	50	56.50	55.0
	75	63.00	63.0

Great majority of neuronavigation assisted operations (96.1%) were performed for a brain tumor, with only 4 patients having different final diagnosis (3.9%). In the group of lesions operated without neuronavigation, there were 764 tumors (99.2%).

According to the type of lesions there was statistically significant difference related to other types of lesions in nonneuronavigational group ($\chi^2=8.030$; $p=0.018$) (Table 3).

Table 3 Type of operated lesions in the group of patients operated with and without neuronavigation assistance (number and percent within the group).

TYPE OF LESION	NEURONAVIGATION ASSISTED		WITHOUT NEURONAVIGATION	
	Number	Percent (%)	Number	Percent (%)
TUMOR	98	96.1	764	99.2
APSCES	1	1.0	2	0.3
ELSE	3	2.9	4	0.5
TOTAL	102	100	770	100

Majority of brain lesions operated with neuronavigation assistance were on the right side of the brain (38.2%; $n=39$), (36.3%; $n=37$) were on the left side, while medial localization was recorded in 22 cases (21.6%). Four patients were with bilateral lesions (3.9%). Analysis of the non-neuronavigation group showed that 308 lesions (40.00%) were on the right side, 307 (39.90%)

were on the left side, 151 (19.60%) lesions were in medial structures and 4 (0.50%) of them were bilateral. There was statistically significant difference in side of the brain localization of lesions between the two groups ($\chi^2=11.903$; $p=0.008$) with more medially and bilaterally located lesions in the neuronavigational group (Table 4).

Table 4 Side of the brain lesion localization in patients operated with and without neuronavigation assistance (number and percent within the group).

SIDE	NEURONAVIGATION ASSISTED		WITHOUT NEURONAVIGATION	
	Number	Percent (%)	Number	Percent (%)
RIGHT	39	38.2	308	40.0
LEFT	37	36.3	307	39.9
MEDIAL	22	21.6	151	19.6
BILATERAL	4	3.9	4	0.5
TOTAL	102	100	770	100

Regarding tumor location, 18 (17.6%) neuronavigation assisted operations were performed on sellar region (pituitary gland), with the same number on parietal region and on multilobar localizations. Parietal lobe and multilobar lesions were most

frequent localizations of non-neuronavigation operated tumors with 124 lesions (16.2%) each. There was statistically significant difference in tumor localizations between the two compared groups ($\chi^2=38.116$; $p=0.0001$) (Table 5).

Table 5 Localization of the operated lesion in group of patients operated with and without neuronavigation assistance (number and percent within the group).

LOCALISATION	NEURONAVIGATION ASSISTED		WITHOUT NEURONAVIGATION	
	Number	Percent (%)	Number	Percent(%)
FRONTAL LOBE	12	11.8	118	15.4
TEMPORAL LOBE	11	10.8	73	9.5
PARIETAL LOBE	18	17.6	124	16.2
OCCIPITAL LOBE	6	5.9	90	11.7
INTERHEMISFERIC	1	1.0	9	1.2
MULTIPLE LOBES	18	17.6	124	16.2
BASAL STRUCTURES	12	11.8	17	2.2
SELLAR/PITUITARY GLAND	18	17.6	89	11.6
PINEAL GLAND	0	0	1	0.1
PONTOCEREBELLAR ANGLE	0	0	19	2.5
TOTAL	102	100	770	100

From the total of 102 lesions operated with neuronavigation assistance, radiologists assumed that 26 (25.5%) of lesions related to high grade gliomas, 23 lesions (22.5%) to secondary tumor deposits, and 18 lesions (17.6%) related to adenomas. In the group of tumors operated without the neuronavigation assistance,

preoperative radiology diagnose for 179 (23.25%) patients was meningioma and for 177 (23.0%) of them it was metastatic disease. Statistically significant difference in radiology diagnosis between the two groups was noted ($\chi^2=73.268$; $p=0.0001$) (Table 6).

Table 6 Type of lesion based on radiology scans in the group of patients operated with and without neuronavigation assistance (number and percent within the group).

			Neuronavigation (% within group)	Without neuronavigation (% within group)
Radiology	Abscess	Count	1 (0,1%)	1 (0,1%)
	High grade glioma	Count	141 (18,3%)	141 (18,3%)
	Low grade glioma	Count	65 (8,4%)	65 (8,4%)
	Metastasis	Count	177 (23,0%)	177 (23,0%)
	Adenoma	Count	86 (11,2%)	86 (11,2%)
	Paraganglioma	Count	1 (0,1%)	1 (0,1%)
	Cavernoma	Count	5 (0,6%)	5 (0,6%)
	Lymphoma	Count	14 (1,8%)	14 (1,8%)
	Meningeoma	Count	179 (23,2%)	(23,2%)
	Schwannoma	Count	19 (2,5%)	19 (2,5%)
	Craniopharyngeoma	Count	4 (0,5%)	4 (0,5%)
	Dermoid cyst	Count	8 (1,0%)	8 (1,0%)
	Teratoma	Count	3 (0,4%)	3 (0,4%)
	Colloid cyst	Count	1 (0,1%)	1 (0,1%)
	BCC	Count	1 (0,1%)	1 (0,1%)
	Choroid plexus papilloma	Count	1 (0,1%)	1 (0,1%)
	DNET	Count	2 (0,3%)	2 (0,3%)
	Choroid plexus carcinoma	Count	1 (0,1%)	1 (0,1%)
	Ependymoma	Count	6 (0,8%)	6 (0,8%)
	Neurocytoma	Count	2 (0,3%)	2 (0,3%)
	Hemangioma	Count	1 (0,1%)	1 (0,1%)
	Angiofibroma	Count	1 (0,1%)	1 (0,1%)
	Hemangioblastoma	Count	2 (0,3%)	2 (0,3%)
	Dysplasia	Count	1 (0,1%)	1 (0,1%)
	Lypoma	Count	1 (0,1%)	1 (0,1%)
	Radiologist did not give an opinion	Count	47 (6,1%)	47 (6,1%)

In our Clinic 54 (52.9%) neuronavigation assisted resections, 36 (35.3%) biopsies and 12 (11.8%) tumor reductions were performed. 633 resections (82.5%), 45 biopsies (5.9%) and 89 reductions (11.6%) were performed without neuronavigation

assistance. There were statistically significantly more biopsies performed in the neuronavigational group ($\chi^2=93.610$; $p=0.0001$) (Table 7).

Table 7 Type of surgery performed in the group of patients operated with and without neuronavigation assistance.

TYPE OF SURGERY	NEURONAVIGATIONAL			WITHOUT NEURONAVIGATION	
	Resection	N	54	633	
		%	52.9	82.5	
	Biopsy	N	36	45	
		%	35.3	5.9	
	Reduction	N	12	89	
		%	11.8	11.6	

In the group of tumors operated with neuronavigation assistance, out of 26 radiologically diagnosed high grade glioma lesions, 23 (22.5%) of all neuronavigation assisted tumors were confirmed in patohistology analysis, 16 (15.7%) of all neuronavigation assisted tumors were confirmed as hypophyseal adenomas, and 15 (14.7%) of all neuronavigation assisted tumors were patohistological verified as metastatic deposits.

Surgically non-significant findings on the control CT was noted on the scans of 100 patients (98%) operated with neuronavigation assistance, and only 2 patients had surgically significant findings on postoperative control scan. Great majority of patients ($n=90$; 88.2%) operated with neuronavigatinal assistance was without postoperative complications and only 2 patients (2%) underwent reoperation due to postoperative complications. In the group of

lesions operated without neuronavigation, there were 61 (7.9%) patients with surgically significant findings on postoperative CT and 164 (21.3%) patients with postoperative complications where 64 (8.3%) of them underwent reoperation. There were statistically significantly more surgically significant postoperative CT scans (regarding blood in operative field, edema or hydrocephalus) in the non-neuronavigation group - 7.9% compared to 2% in the neuronavigation group ($\chi^2=4.775$; $p=0.029$). Also, there was more need for repeated operation in the non-neuronavigation group - 8.3% compared to 2% in neuronavigation group ($\chi^2=5.193$; $p=0.023$). Significantly more complications were noted in the non-neuronavigation group - 21.3% compared to 11.8% in the neuronavigation group ($\chi^2=5.082$; $p=0.013$) (Table 8).

Table 8 Surgically significant postoperative CT scan finding, complications and reoperations in patients operated with and without neuronavigation assistance (number and percent within the group).

Significant finding on postoperative CT					Postoperative complications				Reoperation			
Neuronavigation assisted		Without neuronavigation			Neuronavigation assisted		Without neuronavigation		Neuronavigation assisted		Without neuronavigation	
Numbe r	Perce nt (%)	Numbe r	Perce nt (%)		Numbe r	Perce nt (%)	Numbe r	Perce nt (%)	Numbe r	Perce nt (%)	Numbe r	Perce nt (%)
Yes	2	2.0	61	7.9	12	11.8	164	21.3	2	2.0	64	8.3
No	100	98.0	709	92.1	90	88.2	606	78.7	100	98.0	706	91.7
Tot.	102	100	770	100	102	100	770	100	102	100	770	100

The final clinical outcome was measured by both modified Rankin (mRs) score and Karnofsky Permormance Score (KPS). Better outcome was found on mRs in neuronavigational - 2.05 ± 1.53 compared to the non-neuronavigation group 2.42 ± 1.64 (Figure 1).

According to the final PHD diagnosis the most common type of lesion was glioblastoma in 22,5% of cases followed by pituitary adenoma in 15.7% of cases and metastases in 15 or 14.7% of cases (Table 9).

Table 9 Pathohystological findings in navigational and nonnavigational group.

			Group		Total
			Neuronavigational	All tumours	
PHD	Puss/inflammation	N	2	1	3
		%	2.0	7.7	2.6
	Anaplastic oligodendroglioma	N	2	0	2
		%	2.0	0.0	1.7
	Oligodendroglioma gr 3	N	1	1	2
		%	1.0	7.7	1.7
	Astrocytoma gr	N	5	0	5
		%	4.9	0.0	4.3
	Astrocytoma pylociticum who gr 1	N	1	0	1
		%	1.0	0.0	0.9
	Astrcytoma diffusum who gr 2	N	2	0	2
		%	2.0	0.0	1.7
	Adenoma hypophyseos	N	16	1	17
		%	15.7	7.7	14.8
	BCC of the baseos crani	N	1	0	1
		%	1.0	0.0	0.9
	Metastasis	N	15	3	18
		%	14.7	23.1	15.7
	Glioblastoma	N	23	0	23
		%	22.5	0.0	20.0
	Lymphoma	N	7	3	10
		%	6.9	23.1	8.7
	A-V malformation	N	1	0	1
		%	1.0	0.0	0.9
	Cavernoma	N	2	0	2
		%	2.0	0.0	1.7
	Meningeoma	N	2	4	6
		%	2.0	30.8	5.2
	Gliosarcoma	N	1	0	1
		%	1.0	0.0	0.9
	Myxopapillary ependymoma	N	1	0	1
		%	1.0	0.0	0.9
	Mucocoele	N	1	0	1
		%	1.0	0.0	0.9
	Sample not suitable for PHD	N	8	0	8
		%	7.8	0.0	7.0
	PHD missing	N	11	0	11
		%	10.8	0.0	9.6
Total	N	102	13	115	
	%	100.0	100.0	100.0	

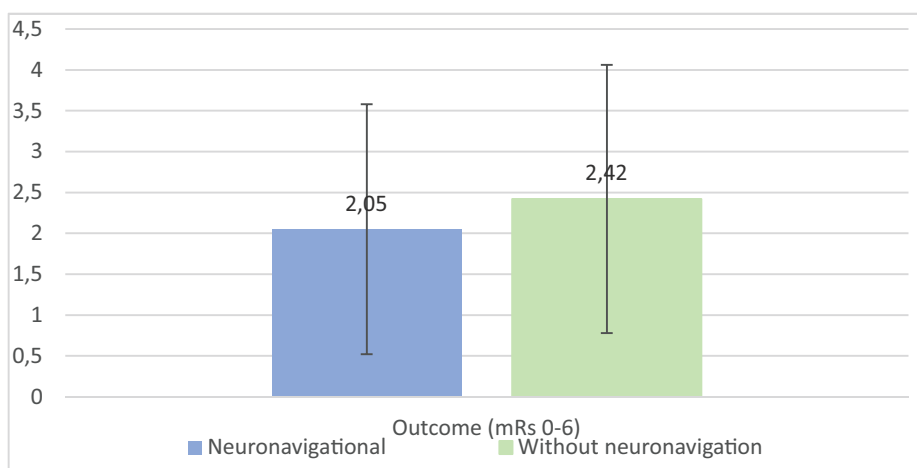


Figure 1 Outcome presented by mRs in the group of patients operated with and without neuronavigation assistance.

Furthermore, Karnofsky performance score (KPS) over 80 was found to be good outcome and 47 of patients who underwent neuronavigation assisted surgery (46.08%) had good outcome. Nine

(8.8%) of them had excellent outcome by 100 and one patient had post-operative lethal outcome (10).

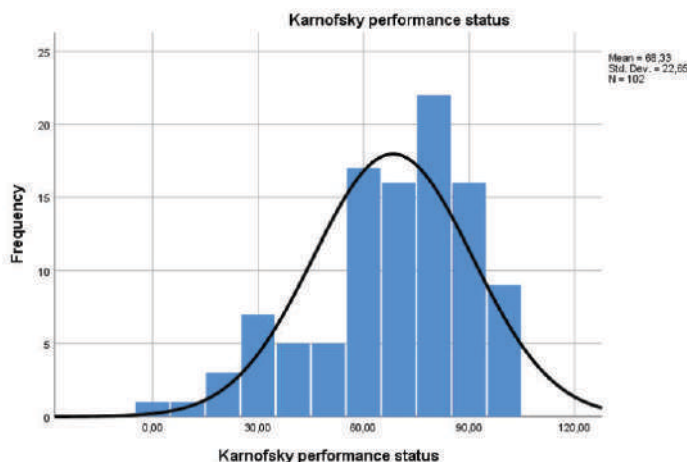


Figure 2 Outcome measured by Karnofsky performance score in patients operated with neuronavigation assistance.

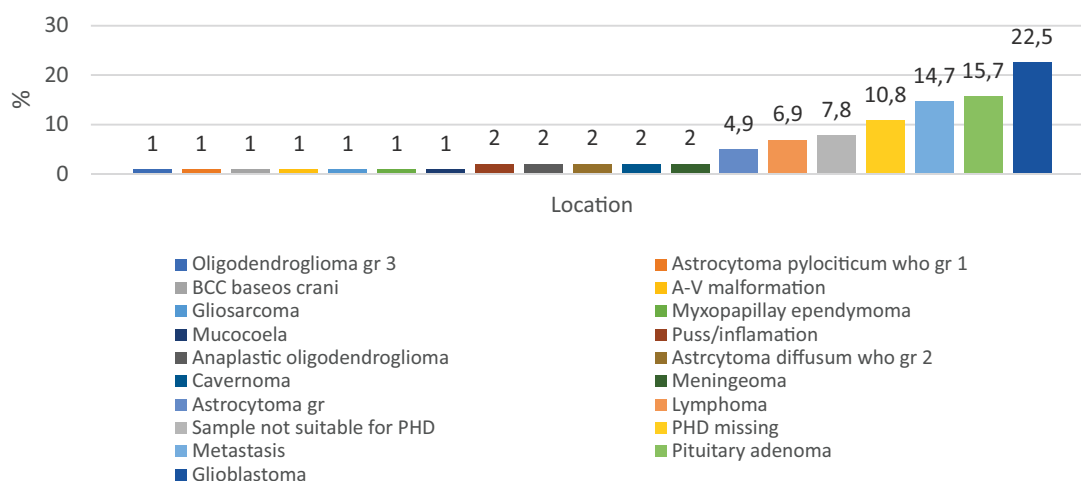


Figure 3 PHD types of lesions after neuronavigational assisted surgery.

DISCUSSION

This article analyzed 872 brain tumor operations performed at the CCUS Clinic of Neurosurgery, in the seven year period. Around 130 operations of brain tumors are performed annually. Out of the total number of brain tumor surgeries, 102 of them were performed with the assistance of the neuronavigation system. One of the most common procedures using neuronavigation system is neuronavigational guided tumor biopsy (35.3%) for deep seated lesions, where open surgical approach carries high risk for neurological injury. One meta-analysis of 7471 reported cases demonstrated that a positive histological diagnosis can be obtained by performing stereotactic biopsy in 91% of all cases and in another studies from 88.9% to 97.4% by using neuronavigation guided needle biopsy (7,8). In a case series of 33 patients, intraoperative MRI obtained during biopsy confirmed that in 32 patients biopsy needle was at the right position with correct sampled diagnostic tissue (9). Each surgical intervention navigation guided needle biopsy has a rate of mortality and complications. One study showed that biopsy had a major morbidity rate of 3.5% and an operative mortality rate

of only 0.7% (7). However, in our series only a single patient had lethal outcome. Most common complication after neuronavigation guided biopsy was bleeding, in symptomatic and asymptomatic patients found on the postoperative CT. However, in majority of cases bleeding was not found to be serious and was usually resolved spontaneously without the need for surgical exploration. Intraoperative bleeding complications and 3 cm or smaller lesions were correlated with a higher incidence of postoperative intracerebral hemorrhage or mismatch. Additional patients risk factors are serum glucose levels more than 11.1 mmol/l, size of the needle, pathological diagnosis as lymphoma, basal ganglia tumors, thalamic tumors, and frontotemporal locations in general (8).

Today, neuronavigation has become an obligatory tool in neurosurgery, especially for the planning approach route and the brain tumors resection margins determination. Neuronavigation is used in awake surgeries in eloquent area and functional neurosurgery. Neuronavigation in these surgeries is used for planning operative trajectories to avoid eloquent areas, or as adjunct to brain mapping and similar techniques (9).

With neuronavigation system every type of tumor surgery can be optimized in relation to the preoperative MRI or CT (biopsy, subtotal resection, gross total resection and supra total resection). This issue is very important in infiltrative tumors like high grade gliomas. It is well known from volumetric studies that the amount of resected primary brain tumor like glioblastoma directly correlates with survival rate. The fact that there is a strong correlation between extent of resection and survival, with combination of radiotherapy and temozolomide (10) guides the neurosurgeons to endeavor maximal safe tumor resection. A single study of 52 patients operated with the neuronavigation in comparison with matching cases operated without its usage showed that neuronavigation increases radicality in glioblastoma resection without prolonging operating time (11). Another study with 750 craniotomies with neuronavigation assistance in brain metastases surgery showed that neuronavigation improved extent of resection with less damage to the surrounding eloquent brain structures (12). Our study showed minimal morbidity for the patient, with a single lethal outcome in 102 cases. Also, surgery with neuronavigation had better final outcomes regarding postoperative brain CT findings, reoperations and clinical outcomes measured by mRs and KPS. Our radiological findings have a high matching rate with definitive pathohistological diagnosis, for high grade gliomas (88.5%).

One of the greatest limitations that can impact an accuracy of neuronavigation is an intraoperative brain shift. Brain shift can occur during dural opening, after giving mannitol or other antiedematous drugs, cerebrospinal fluid drainage, or after brain tumor reduction. Some studies have reported brain shift as much as 2.4 cm during brain surgery. This issue can impact precise tumor resection, because neuronavigation is installed before surgery itself (13). This study found that pathohistological sample was not suited for definitive diagnosis in 7.8 % of patient while we did not find it in any case compared to the open surgical approach. This limitation is possible due to the inappropriate needle position or small number of tumor samples. If the needle is placed in the central part of the tumor where the necrosis occurred, an adequate sample will most likely not be obtained especially in high grade glioma. This issue can be overcome by taking tumor samples from the periphery of the tumor (where the tumor is contrastingly enhanced). Furthermore, it is necessary to take as many samples from different directions by rotating the needle also preferably from more depths of the tumor. Our rule is to take samples from 3 different tumor levels and at least 7-8 directions in order to get an adequate sample and increase the chance of definitive pathohistological diagnosis. If the tumor is cystic, a fluid sample is sent for cytological analysis. However, the patient should always be warned that there is a chance that an adequate sample will not be obtained and that an open surgical biopsy or repeated procedure will be required. Our experience is in favor of preparing for an open microsurgical biopsy in the same act, unless we receive ex tempore confirmation of the histological diagnosis.

This study had some limitations. Data were collected from previous patient histories, with the possibility of missing some data. It is a pilot study which showing the first clinical results, followed by prospective part of neuronavigational study in ten year experience.

CONCLUSION

Neuronavigation is a standard minimal invasive and indispensable neurosurgical tool in high volume centers which offers anatomical orientation in brain tumor surgery. The study results demonstrate neuronavigational safeness and effectiveness which improves final clinical outcomes. However, strong clinical predictors of precision limitation due to the brain shift are still to be overcome in the future.

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Surgical treatment of aggressive intra-abdominal fibromatosis

Hirurški tretman agresivne intraabdominalne fibromatoze

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ABSTRACT

Introduction: desmoid tumors are rare benign non metastatic neoplasms which occur isolated or within familiar polyposis and have a very unpredictable outcome. In approximately 10% of cases they show aggressive nature. **Aim:** to present a case of surgically treated patient with pathologically verified desmoid tumor. **Case report:** we present a case of a 64 years old male patient which is diagnosed with a tumor mass situated in the peritoneal cavity, clinically with signs of an acute abdominal condition. **Discussion:** this rare condition is associated with numerous treatment modalities but so far none has been declared as the most successful one. **Conclusion:** surgical treatment with histologically clear margins, when feasible, is the method of choice in such cases.

Keywords: aggressive fibromatosis, desmoids tumor, surgery, prognosis

SAŽETAK

Uvod: dezmoidni tumori su rijetki benigni, nemetastazirajući tumori koji mogu nastati samostalno ili u sklopu familijarne polipoze sa veoma nepredvidljivom prognozom. U otprilike 10 posto slučajeva pokazuju agresivnu formu. **Cilj:** predstaviti slučaj pacijenta tretiranog hirurški zbog patohistološki verificiranog dezmoidnog tumora. **Prikaz slučaja:** prezentuje se slučaj 64-godišnjeg muškog pacijenta, kojem se dijagnosticira tumorska masa, smještena u peritonealnoj šupljini, sa klinički prisutnim znacima akutnog abdomena. **Diskusija:** ovo je rijetko oboljenje, koje se povezuje sa više modaliteta tretmana, ali do sada se nijedan od tih modaliteta nije pokazao kao najbolji. **Zaključak:** hirurški tretman sa patohistološki čistim marginama, kada je izvediv, je metoda izbora u takvim slučajevima.

Ključne riječi: agresivna fibromatoza, dezmoidni tumor, hirurgija, prognoza

INTRODUCTION

Aggressive fibromatosis (AF), also known as desmoid tumor, is a rare type of fibrous tumor with low-grade malignancy and high potential of recurrence (25-77%) although it usually recurs in situ and does not metastasize distantly (1). It can occur isolated and/or with familiar polyposis. AF can be divided into sporadic and hereditary cases, with sporadic cases accounting for the higher percentage of new AF cases which occur at an annual rate of ~4–6 cases/1,000,000 population (2). As regards the site, aggressive fibromatoses can be divided into: extra-abdominal in the area of the shoulder and pelvic girdle or chest and neck wall; abdominal in abdominal wall muscles; intra-abdominal concerning pelvis, mesentery connective tissue or retroperitoneal space (3). Locally aggressive DF can lead to complications like gastrointestinal obstruction and bowel ischemia (4). A case of a 64-year-old male was reported with an infiltrative intra-abdominal DF in the left hypochondriac region, status post cholecystectomy, associated with gastric outlet and colon obstruction as well as signs of pneumoperitoneum.

AIM

To present a case of successfully surgically treated patient with pathologically verified desmoid tumor.

CASE REPORT

A 64-year-old male complained of persistent left upper quadrant (LUQ) pain starting early that morning, status post cholecystectomy. This pain was radiating to epigastric region and associated with nausea, loss of appetite, vomiting and causing signs of acute abdominal pain, followed by defense of anterior abdominal wall musculature. The patient denied any other symptoms, and had regular stool and urination. Cholecystectomy was performed without any complications, two years prior, and the patient was discharged safely. After the LUQ pain started, he underwent extensive workup, which included abdominal ultrasound (US), computed tomography (CT) and standard laboratory tests. Review

of the initial CT (Figure 1) revealed a heterogeneous enhancing solid mass in the left hypochondriac region, 1140x90x40 mm in diameter, placed between the anterior abdominal wall, greater contour of the stomach and transverse colon which was infiltrating the latter. The mass exerted compression over stomach, with associated signs of pneumoperitoneum and bowel obstruction. Explorative laparotomy was performed and intraoperatively an ovoid tumor mass was found, located between transverse colon and anterior abdominal wall, infiltrating the colon. The mass was completely excised and a TT anastomosis of the transverse colon with a protective colostomy was performed, as well as the splenectomy. The patient was postoperatively in a good condition, with stable vital parameters, regular laboratory check-ups, wound healing properly, and a functional colostomy. He was discharged eight days after the surgery.

The histological examination revealed an aggressive intra-abdominal fibromatosis, completely excised, with negative margins in the length of 65 and 80 mm. Microscopically a mesenchymal, rich on cellularity mass was observed, built of spindle and bland cells with light eosinophil cytoplasm, long nuclei, with no signs of pleomorphism, and sporadic mitosis (10 per 50 high-power fields). Tumor cells were arranged in fascicles. Tumor tissue had plenty of blood vessels, congested with foci of recent hemorrhage. In general, all of these pathology findings were compatible with the diagnosis of desmoid fibromatosis.

The case was presented in a multidisciplinary oncologic meeting and the decision was made in favor of imaging follow-up with no further oncological treatment.

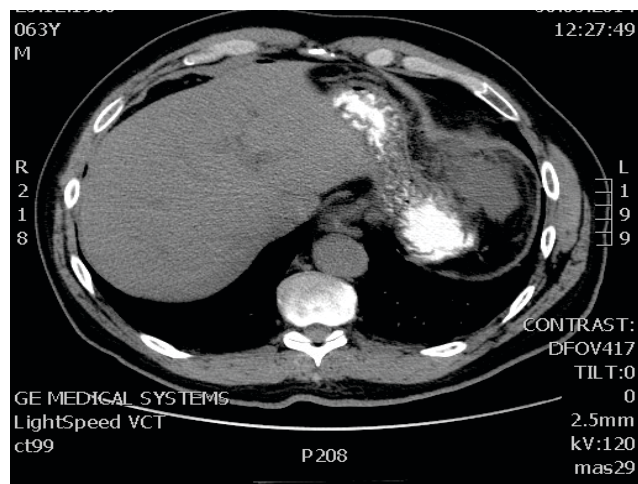


Figure 1 Preoperative CT scan of the patient.

DISCUSSION

AF accounts for 0.03% of all neoplasms; < 3% of all soft tissue tumors, 10-30% of familial adenomatous polyposis (FAP) patients have desmoid type fibromatosis (also called Gardner syndrome); 7.5-16% of patients with fibromatosis have FAP (5). These tumors are commonly associated with prior trauma, prior surgery, irradiation and high estrogen levels such as pregnancy (4). Desmoid tumor is a neoplasm which rarely turns malignant and is non-metastasizing but demonstrates ability to local infiltration into

tissue and is characterized by high risk of recurrence (25-65%) after surgical treatment (3).

The most commonly used imaging techniques for desmoids are computed tomography (CT) and magnetic resonance imaging (MRI). Desmoids show similar or slightly higher attenuation compared to skeletal muscle in a non-contrast CT scan and contrast-enhanced CT generally exhibits mild-to-moderate enhancement (1). MRI is the preferred imaging modality to assess extra-abdominal and intra-abdominal DF. The MRI signal intensity pattern reflects the proportion of different tissues present microscopically. It most commonly presents heterogeneously with hypo/hyperintense signal on T2 images and iso/hypointense signal on T1 images (4). Following surgery, CT and MRI are used for detecting recurrence and to monitor tumor response to radiotherapy or medical therapy for unresectable or recurrent tumors (6).

This neoplasm is composed of spindle (fibrocyte-like) cells. (3) Immunohistochemical studies of desmoid tumors have demonstrated a fibroblastic-myofibroblastic phenotype. Muscle-specific actin, SMA and desmin are expressed in varying proportions of cases (4). Histology shows long, sweeping fascicles with thin walled vessels and microhemorrhages; bland cells with mild to moderate cellularity and minimal atypia (5). Histological review is always required in order to confirm the diagnosis and thus avoiding differential diagnosis.

Surgery is the standard treatment for DF in symptomatic patients without significant morbidity (4). The current results suggest that the attainment of microscopically negative surgical margins at the initial surgical treatment is associated with a significantly improved prognosis. A conservative surgical approach involving the attainment of narrow negative margins while preserving function should be sought in patients in whom tumor resection is indicated (8). However, there is a very high chance of local recurrence with surgical resection. Long-term prognosis is currently unknown (7). Considering its infiltrate characteristics, it is difficult to distinguish the boundaries of desmoids. Simultaneously, an aggressive excision for negative margin cannot exactly assure a better outcome, which may sacrifice important function or even lives (1).

Radiotherapy alone and surgery plus adjuvant radiotherapy have shown improved local control over surgery alone; however, long-term effects of radiation therapy prevent standard use, especially in young patients (5). Other treatment modalities include chemotherapy, hormone therapy and cryoablation.

CONCLUSION

Intra-abdominal aggressive fibromatosis is a benign tumor with a high recurrence rate. Surgery still remains an effective technique with a clear surgical margin being an imperative in achieving low risk of local recurrence rate in cases where it is feasible.

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Myocardial infarction with non-obstructive coronary arteries - ghost hunting in cardiology - case report

Infarkt miokarda bez opstrukcije krvnih žila - "lov na duhove" u kardiologiji - prikaz slučaja

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ABSTRACT

Introduction: myocardial infarction with non-obstructive coronary arteries (MINOCA) is a syndrome with several causes, characterized by clinical evidence of myocardial infarction and without significant coronary disease (stenosis $\leq 50\%$). Aim: to present a patient with verified myocardial infarction with non-obstructive coronary arteries (MINOCA), and complexity of diagnostic and therapeutic modality. Case report: the article presents a 33-year-old male patient admitted due to chest pain with elevated high-sensitive cardiac troponin-T (hs-TnT) and electrocardiographic (ECG) signs of anterior myocardial infarction. Coronary angiography verified normal findings but intracoronary acetylcholine provocation testing confirmed diagnosis of MINOCA. The patient was discharged with calcium channel blockers, trimetazidine and antiaggregant in therapy. Conclusion: MINOCA has complex diagnostic and therapeutic modalities. Individual approach to the patient is an imperative, with the aim of finding an etiological cause, with obligatory review of anamnestic data, physical examination, ECG, elevated enzymes of cardiac necrosis, echocardiography, along with coronary and left ventricular angiography, that can lead to a clearer picture of the onset and prognosis.

Keywords: acute coronary syndrome, angiography, treatment, troponin

SAŽETAK

Uvod: infarkt miokarda bez opstrukcije krvnih žila (MINOCA) je sindrom s nekoliko uzroka, karakteriziran kliničkim dokazima infarkta miokarda i angiografski bez koronarne bolesti (stenoz $\leq 50\%$). Cilj: prikaz pacijenta sa dijagnozom infarkta miokarda bez opstrukcije krvnih žila (MINOCA), uz osvrt na kompleksnost dijagnostičkog i terapijskog modaliteta. Prikaz slučaja: rad prezentuje muškog pacijenta, 33 godina starosti, koji je hospitaliziran zbog bola u grudnom košu sa povišenim vrijednostima visoko-specifičnog srčanog troponina-T (hs-TnT) i elektrokardiografskim (EKG) znacima prednjeg infarkta miokarda. Koronarografija je verificirala uredan koronarni status, a intrakoronarna acetilholin provokacija potvrdila dijagnozu MINOCA-e. Pacijent je otpušten sa blokatorom kalcijevih kanala, trimetazidinom i anatiagregansom u terapiji. Zaključak: MINOCA ima kompleksan dijagnostički i terapijski modalitet. Individualni pristup pacijentu je imperativ s ciljem identifikacije uzroka i osvrtom na anamnestičke podatke, fizikalni pregled, EKG, povišene vrijednosti enzima srčane nekroze, nalaz ehokardiografije, koronarografije i lijeve ventrikulografije, što može voditi ka jasnijoj slici uzroka i prognoze.

Ključne riječi: akutni koronarni sindrom, angiografija, tretman, troponin

INTRODUCTION

Term myocardial infarction with non-obstructive coronary arteries (MINOCA) is related to patients who meet following criteria: clinical documentation of a myocardial infarction, the

exclusion of obstructive coronary artery disease with no obvious cause of acute myocardial infarction (1,2). The pathophysiology of MINOCA is difficult to understand and diagnostics as well as treatment is a challenge for cardiologists and interventional cardiologists (3). The cause can be found in coronary

(thromboembolism, thrombotic disorders (factor V deficiency, protein C and S deficiency), plaque disruption, vasospasm caused by exogenous substances (cocaine), microvascular dysfunction in the form of microvascular spasm, angina or coronary slow flow phenomenon) and non-coronary factors (renal impairment, myocarditis, pulmonary embolism, Takotsubo cardiomyopathy) (3,4). Elevation of troponin is monitored and must be present, but interpretation should be made with caution as the elevation can occur in the presence of some other pathological conditions (sepsis, heart failure, myocarditis, pulmonary embolism) (3). The aim of this case report was to present a patient with verified MINOCA, and complexity of diagnostic and therapeutic modality. The article presents a 33-year-old male patient admitted for chest pain at Intensive Care Unit, Clinic of Heart, Blood Vessel and Rheumatic Diseases of the Clinical Center University of Sarajevo who was monitored over the period of one year after admission to the Clinic. Patient consent form was obtained.

CASE REPORT

A 33-years old patient was admitted due to chest pain which started one hour before the admission. The pain spread into the jaw and was followed by the loss of breath. Anamnestic data was neat, negative family history, smoker. On admission, electrocardiogram (ECG) verified sinus rhythm, ST segment elevation in VI-V4 leads and reciprocal depression in inferior leads. Laboratory values of high-sensitivity cardiac troponin-T (hs-TnT) was 1199 ng/L (reference range 0-14 ng/L). Coronary angiography showed left main artery, left anterior descending artery, circumflex artery and right coronary artery without significant stenosis along with preserved systolic function of the left ventricle (Figure 1-2). Intracoronary acetylcholine provocation testing was positive (a sign of vasospasm, as the cause of symptoms).

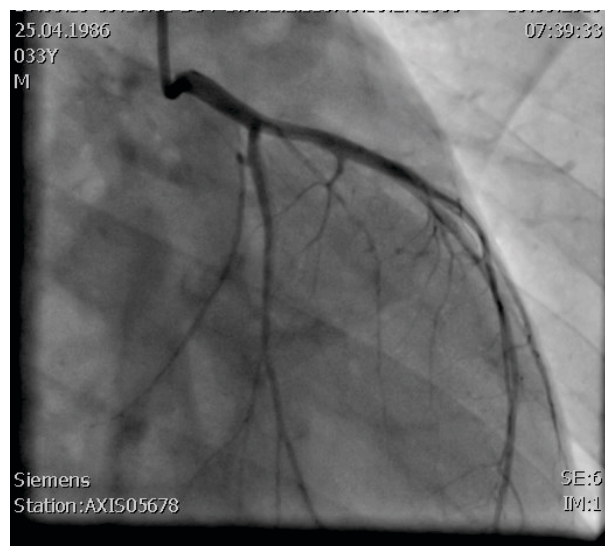


Figure 1 Coronary angiography - left coronary system.

Echocardiographically left ventricle had normal dimensions, left ventricular anteroapical and medioapical hypokinesia was noted, with left ventricular ejection fraction of 45%. Elongation of the

anterior mitral leaflet was also verified, with consequent mild mitral regurgitation. The patient was hemodynamically and electrically stable during hospitalization. He was discharged with acetylsalicylic acid 100 mg once a day (OD), diltiazem 60 mg twice a day (BID), trimetazidine 35 mg BID and magnesium effervescent OD in therapy. After a month, echocardiography finding was the same.

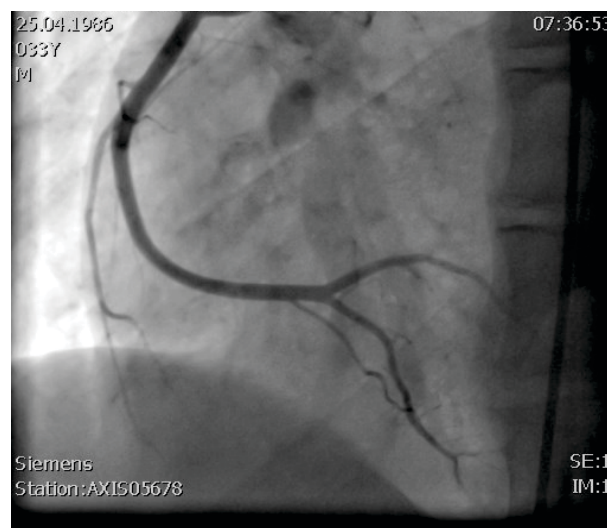


Figure 2 Coronary angiography - right coronary artery.

DISCUSSION

Patients with MINOCA clinically differ from all other patients with acute myocardial infarction (AMI). In most cases they are younger and the disease affects both sexes equally (6). Patients with MINOCA have fewer cardiovascular risk factors, and their serum markers of myocardial damage are lower (6). Analysis of Delay in AMI-Spanish Society of Intensive Care Medicine and Coronary Unit (ARIAM-SEMICYUC) register higher rate of female gender and less severe changes in the electrocardiogram (ECG) along with lower values in the Killip class, thrombolysis in myocardial infarction (TIMI) and global registry of acute coronary events (GRACE) scores in comparison with AMI with coronary obstruction (8). Although pulmonary embolism is often taken as a cause, Collste et al. in 100 consecutive MINOCA patients did not find pulmonary embolism (9). MINOCA diagnosis should be made with caution in patients who have comorbidities like renal impairment (8,9). Particular attention should be made in case of postinfarction angina pectoris, as it connected to the MINOCA incidence (9,10). Cardiac Magnetic Resonance (CMR) has been suggested as a standard in the evaluation of cause of MINOCA (11). Stockholm Myocardial Infarction With Normal Coronaries (SMINC)-2 study stated that the use of CMR could find the cause of MINOCA in 87% of the cases (it was performed one month after the incident) (11). CMR can detect plaques that are not visible on coronary angiography and can make distinction of the plaque whether it is stable or unstable (11). The SMINC-2 study suggested that in evaluation of MINOCA catecholamines (to exclude pheochromocytoma), D-dimer (to exclude pulmonary embolism) and tests to exclude inherited causes of thromboembolism should be analyzed (11). About one third of patients with MINOCA have myocarditis in the background (9,11). Epicardial spasm was detected in more than two-thirds of patients and microvascular

spasm in about one-third of patients (12). Prevalence of MINOCA is 1-14% (13), and with complex diagnostic tools in recent period term TpNOCA (Troponin-positive non-obstructive coronary arteries) was introduced to describe patients with an apparent myocardial infarction in the absence of obstructive coronary artery disease (2). MINOCA should be used only for those patients who have evidence of ischemia-related myocardial necrosis (2). During period January 2017 - January 2019 at Clinical Center University of Sarajevo 6 cases with diagnosis of MINOCA were confirmed from total number of 863 patients with diagnosis of AMI (0.7%). Pharmacological treatment is dubious, but use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, with use of beta blockers, anti-aggregation therapy and statins is suggested (8,9,10,12,13). Use of calcium channel blockers is indicated for coronary artery spasm (2,10). Lindhal et al. in 9,466 consecutive patients with MINOCA showed that the use of statins or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers was associated with reduced Major adverse cardiovascular events (MACE) in follow up period of 12 months (14). Beta-blockers were useful, with benefit in reducing of MACE, but that benefit was not proved for dual antiplatelet therapy (14). Mortality is about 5 %, which was confirmed in analysis of 897 patients with MINOCA (15).

CONCLUSION

MINOCA has unknown pathophysiological mechanism, and presents a challenge to clinicians in their daily work, with complex diagnostic and therapeutic modalities. Individual approach to the patient is an imperative, with the aim of finding an etiological cause, with obligatory review of anamnestic data, physical examination, ECG, elevated enzymes of cardiac necrosis, echocardiography, along with coronary and left ventricular angiography, that can lead to a clearer picture of the onset and prognosis.

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