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INSTITUT ZA NAUČNO ISTRAŽIVAČKI RAD I RAZVOJ

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U SLUŽBI VAŠEG ZDRAVLJA

Bosnia and Herzegovina was the fourth country in Europe that developed National version of HeartScore program !

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Novi Centralni medicinski blok - Klinički centar Univerziteta u Sarajevu
New Central Medical Building - Clinical Center University of Sarajevo

Novi Evropski vodič za prevenciju tromboembolizma kod A Fib

CHA_2DS_2-VASc skor za procjenu rizika od tromboembolizma kod A Fib!

Risk factor-based point-based scoring system - CHA_2DS_2 -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.

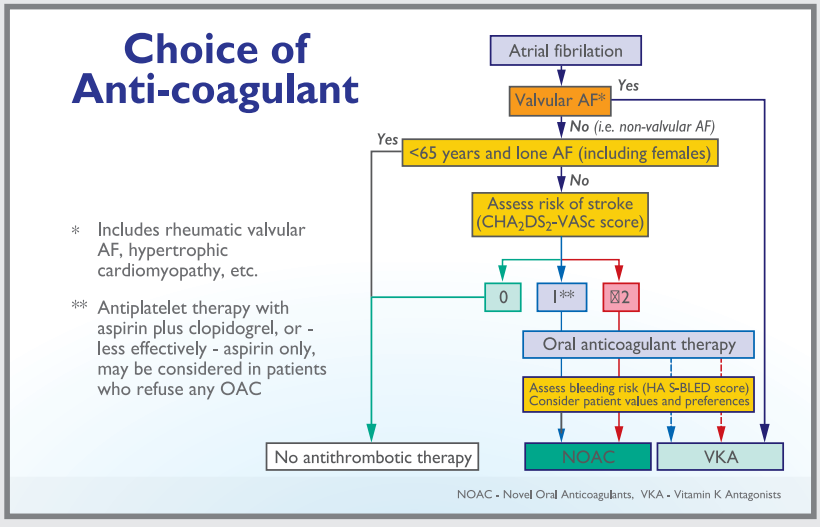
Major i non-major riziko fakori za procjenu tromboembolizma kod A Fib!

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 ⊠ 40%]
TIA or systemic embolism	Hypertension
Age ⊠75 years	Diabetes mellitus
	Age 65-74 years
	Female sex
	Vascular disease

AF = atrial fibrilation; EF = ejection fraction (as documented by echocardiography, radio nuclide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left venticular; TIA = trasient ischaemic attack.

Algoritam antikoagulantne terapije nakon procjene CHA_2DS_2VASc i major risk faktora!



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AIMS AND SCOPE

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Content

Original article

Algorithm of breast cancer treatment with review of histological types and reconstruction modalities 7
Sanela Salihagić, Lamija Gafurović, Ahmad Hemaidi, Adna Čelik

Long-term lamotrigine treatment and bone metabolism 12
Admir Mehičević, Enra Mehmedika-Suljić, Nevena Mahmutbegović

Efficacy of preemptive analgesia diclofenac in laparoscopic cholecystectomy 16
Aida Čorbeg

Nasal continuous positive airway pressure (NCPAP) versus mechanical ventilation in premature infants with respiratory distress syndrome (RDS) 21
Ismeta Kalkan, Amra Čengić, Raho Spahović, Sabina Terzić

Review article

Efficacy of beta agonists in comparison to other therapy options in acute bronchiolitis of infants and small children: systematic review 25
Ganimeta Bakalović, Jovana Nišandžić

Case Report

A case of incarcerated umbilical hernia - an unusual finding in the pediatric population 32
Alena Firdus, Edin Hodžić

The role of giant macroadenoma resection in psychotic vs. prolactin disorder: two year follow-up 35
Adi Ahmetspahić*, Bekir Rovčanin, Tarik Mašić, Ibrahim Omerhodžić

Instructions to authors 39

Uputstva autorima 41

Medical Journal (2018) **Vol. 24, No 1**, 7-11

Original article

Algorithm of breast cancer treatment with review of histological types and reconstruction modalities

Algoritam tretmana karcinoma dojke sa osvrtom na histološke tipove tumora i modalitete rekonstrukcije

Sanela Salihagić[1*], Lamija Gafurović[2], Ahmad Hemaidi[1], Adna Čelik[1]

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ABSTRACT

Introduction: Breast cancer is one of the major problems in the health care system considering its incidence and significance in terms of one of the major causes of mortality in the female population. Available diagnostic and treatment modalities require establishment of treatment algorithm as a significant guideline in clinical practice.

Aim:To establish applicable algorithm for breast cancer treatment at the Clinical Center of the University of Sarajevo, based on correlation of age factors, primary eradication mode, histological type and reconstruction modality. Materials and methods: we evaluated the results of surgical treatment of 547 patients diagnosed with breast cancer treated at the Clinical Center of the University of Sarajevo, period from 1 June 2014 to 31 January 2018. Statistical analysis was performed using the IBM SPSS program in 25.0 version and Microsoft Office Excel 2010.

Results: There is no statistically significant difference was evaluated between histological type of the tumor and extent of primary eradication, as well as histological type and reconstruction modality. Oncology and adjuvant therapy was administrated in all evaluated cases, with prevalence of neoadjuvant chemotherapy.

Conclusion: Histological type and invasiveness of tumor, extent of primary tumor eradication and modalities of reconstruction can be effectively used for the algorithm of breast carcinoma treatment as useful guideline in clinical practice.

Key words: breast cancer, reconstruction, algorithm

SAŽETAK

Uvod: Karcinom dojke je jedan od glavnih problema zdravstvenog sistema, uzimajući u obzir njegovu učestalost i značaj u smislu jednog od glavnih uzroka mortaliteta u zenskoj populaciji. Dostupni modaliteti dijagnostike i tretmana zahtjevaju ustanovljavanje algoritma tretmana, kao značajne smjernice u kliničkoj praksi

Cilj:Uustanoviti klinički primjenjljiv algoritam tretmana karcinoma dojke na Klinickom centru Univerziteta u Sarajevu, baziranog na korelaciji životne dobi pacijentica, modalitetu primarne eradikaacije tumora, histološkog tipa i modaliteta rekonstrukcije. Pacijenti i metode: evaluirali smo rezultate operativnog tretmana 547 slučajeva karcionoma dojke, tretiranih na Kliničkom centru Univerziteta u Sarajevu, u periodu od 01.06.2014. do 31.01.2018. godine. Statistička analiza podataka provedena korištenjem IBM SPSS programa verzija 25.0 i Microsoft Office Excel 2010.

Rezultati: Nema statistički značajne razlike između histološkog tipa tumora i opsega primarne eradikacije, kao i izmedu histološkog tipa i modaliteta rekonstrukcije. Onkološka i adjuvantna terapija primjenjena u svim slučajevima, sa prevalencom neoadjuvatne kemoterapije. Zaključak: Histološki tip i invazivnost tumora, opseg primarne eradikacije i modalitet rekonstrukcije mogu biti efektivno primjenjeni za algoritam tretmana karcionoma dojke kao smjernice u kliničkoj praksi.

Ključne riječi: karcinom dojke, rekonstrukcija, algoritam

INTRODUCTION

In order to find the most optimal modalities in diagnosis and treatment of breast cancer we established the algorithm of breast cancer treatment at Clinical Center University of Sarajevo as guidance to clinicians in selecting appropriate treatment regarding histological type and clinical behavior of tumor.

Early diagnosis of breast cancer is correlated with established screening tests.

The median age of breast cancer diagnosis has now risen to 61 years, so that localized tumors and in situ lesions that occur make majority of the diagnosed lesions (1). Breast cancer includes heterogeneous group of neoplasms with different morphology, molecular phenotype, response to the therapy, relapses and five year survival. Traditional pathohistological classification aims to categorize tumors into subgroups useful in clinical decision making, but the diversity within subgroups remains significant. Using a range of free-lance parallel technologies in clinical research the true depth of the problem was discovered in terms of diversity of the genetic, phenotypic, cellular structure of individual tumors, with the conclusion that each tumor is extremely unique (2).

The type of surgery depends on prognostic factors that are determinants of the Nottingham prognostic index, and these include tumor size and localization, lymph node involvement and tumor histological grade (3,4).

AIM

To establish a breast carcinoma treatment algorithm correlated with histological types of tumor, primary eradication modalities, breast reconstruction types and oncologic therapy as clinical guidance at Clinical Center University of Sarajevo after evaluation of clinical data in relation to age, histological type, eradication method, modality of reconstruction and oncologic therapy

MATERIALS AND METHODS

We evaluated the treatment results of 547 patients diagnosed with breast cancer and surgically treated at the Clinical Center University of Sarajevo in the period from 1 June 2014 to 31 January 2018. After primary tumor diagnostics and presentation of the cases at oncological consilium, time and the most optimal modalities of oncological and surgical treatment were determined.

Study inclusion criteria: cases of primary breast carcinoma, patients subjected to primary tumor eradication and patients subjected to primary or secondary breast reconstruction at the Clinical Center University of Sarajevo

Study exclusion criteria: metastases of other malignant tumors in the breasts, patients subjected to primary eradication and breast reconstruction in other medical centers, patients with complications of breast reconstruction done in other medical centers.

The research was based on data from medical records: age, gender, pathohistological diagnosis of tumors, modalities of primary and secondary breast reconstruction and type of oncologic therapy

Statistical analysis was performed using the IBM SPSS program in 25.0 version (SPSS-Statistical Package for Social Sciences) and all data were entered on a Microsoft Office Excel 2010 spreadsheet for statistical analysis. Significance of data was determined by Chi Squared method, and due to the small number of samples, Fischer´s test was used to confirm the significance of the data. Descriptive statistical data processing was also performed within the research. P values below 0.05 ($p<0.05$) were considered statistically significant. The results are presented in tables and figures.

RESULTS

According to our clinical data, average age of patients was 64 years (± 12.93). Patients over 65 years of age (≥65 years) made the largest group of the population in the study (49,7%), while midlife adults (45-64 years) made the second largest group in the examined population (40%).

Ratio between estimated age and histological type of tumor is presented in Figure 1. According to the presented data, Invasive Ductal Breast Cancer was the most common type in all groups. In adult age group (23-44 years) this cancer was present in 35 cases (62.5%), while other invasive cancers were present in less percentage: Invasive Lobular Carcinoma-ILC (1.7%), Invasive Mucinous Breast Carcionoma (1.7%), Invasive Mixed Breast Carcinoma (1.7%). Non-invasive Brest Carcinoma in adult group was presented in different percentages, Ductal Carcinoma in Situ- DCIS (30.7%) and Lobular Carcinoma in Situ-LCIS (1.7%). In group of midlife adults (45-64 years) out of all invasive breast cancers only Invasive Ductal Breast Carcionoma (77.6%) and Invasive Lobular Carcionoma (3,7%) were present. In this midlife adults group non-invasive cancers were present in 41 cases, Ductal Carcinoma in Situ in 35 cases (15,9%) and Lobular Carcinoma in Situ in 6 cases (2,8%). In third age group (≥65 years) invasive breast cancers were present in 239 cases: Invasive Ductal Carcinoma in 83.8%, Invasive Lobular Carcinoma in 1.8%, Invasive Mixed Carcinoma in 2.2%. In this group non-invasive breast cancers were present in 12.2% (Table 1).

Table 1 Correlation between age groups and percentage presentation of histological types.

Age Groups	Invasive Ductal Carcinoma	Invasive Lobular Carcinoma	Invasive Mucinous Carcinoma	Invasive Mixed Carcinoma	Ductal Carcinoma in Situ	Lobular Carcinoma in Situ
23-44 years	62.5%	1.7%	1.7%	1.7%	30.7%	1.7%
45-65 years	77.6%	3.7%	/	/	15.9%	2.8%
Over 65 years	83.8%	1.8%	/	2.2%	6.1%	6.1%

Figure 1 presents ratio between surgical modality of primary eradication and histological type of tumors in examined group of 547 patients. Based on Chi Squared test and Fischer's test we found that there was no statistically significant difference between the types of reconstruction modality that were used in examined population with different types of breast cancers ($p=0.165$; $\rho=-0.059$).

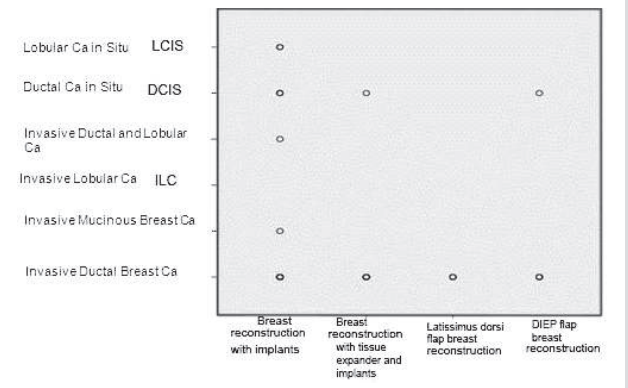

Figure 1 Correlation between histological type of tumor and method of primary eradication.

Percentage proportion of breast reconstruction in correlation to age group of examined groups is presented in Figure 2. Out of 547 patients, 41 breast reconstructions were performed (7.5%). Out of 41 breast reconstructions 6.0% related to primary breast reconstructions, while secondary reconstructions were performed in a much smaller percentage of 1.5%. Reconstruction was not performed in 506 cases (92.5%). Breast reconstruction was most commonly performed in younger patients, by their own decision, in the adult and middle aged groups at a percentage of 78%. Primary breast reconstruction was most prevalent at the age of 45-64 (middle aged adults, 63.6%). Sec-

ondary breast reconstruction was performed in 50% of cases in adult age group (23-44 years). In third life age patients' reconstruction was performed in 2 cases.

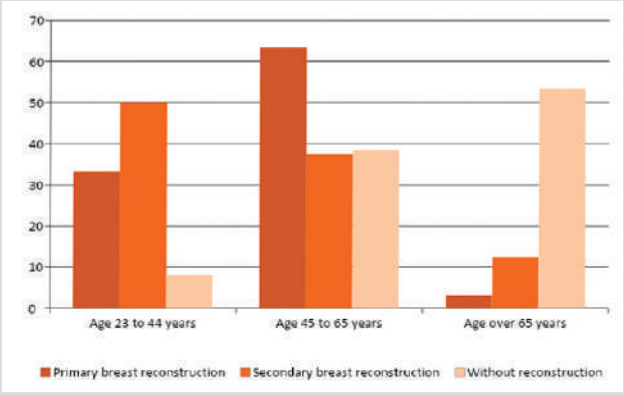

Figure 2 Time of breast reconstruction in correlation to the age groups.

Correlation of reconstruction modality and age group of patients is presented in Figure 2. Breast reconstruction using implants was prevalent in examined population and was performed in 33 cases (80%). Single phase reconstruction with silicone implant using titanium mesh was presented in 25 cases (60%), while biphasic reconstruction with the use of expanders, titanium meshes and implants was present in 8 cases (20%). Reconstruction of the latissimus dorsi lobe was performed in 3 patients (7.5%). Breast reconstruction of the DIEP lobe was performed in 5 patients (12.5%). Breast reconstruction of the latissimus dorsi lobe was present only in the middle-aged adult group (45-64 years). In this age group the highest number of reconstructions was performed using silicone implant (58.3%), while breast reconstruction using DIEP lobe was performed in 4 cases (16.6%). The highest percentage of total reconstruction of the DIEP lobe was presented in the group of middle-aged adults (80%). In the third age group (≥65 years), only 2 patients underwent reconstruction, with 1 case of simple breast reconstruction with a silicone implants (50%) and 1 case of two-phase reconstruction using expander titanium mesh and silicone implants (50%). In the youngest age group of adults (23-44 years), a total of 15 reconstructions were performed. Fourteen reconstructions were performed with implants (93.3%) and 1 reconstruction (6.7%) with the DIEP lobe (Figure 3).

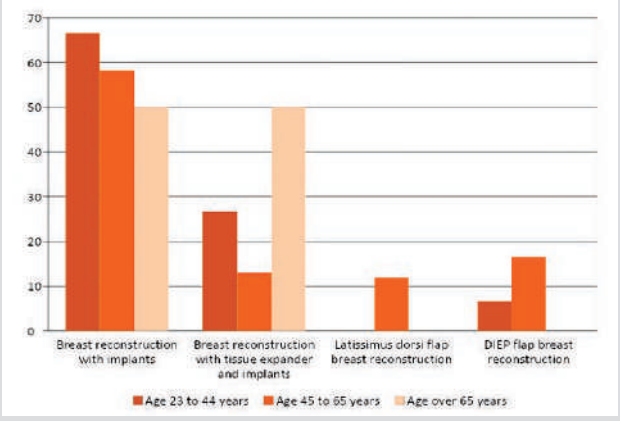

Figure 3 Correlation between breast reconstruction modality and estimated age groups.

Statistical correlation between the type of eradication of primary tumor and breast reconstruction modality is presented (Figure 4), which was confirmed based on Chi Squared test and Fischer's test ($p=0.089$; $\rho>0.275$).

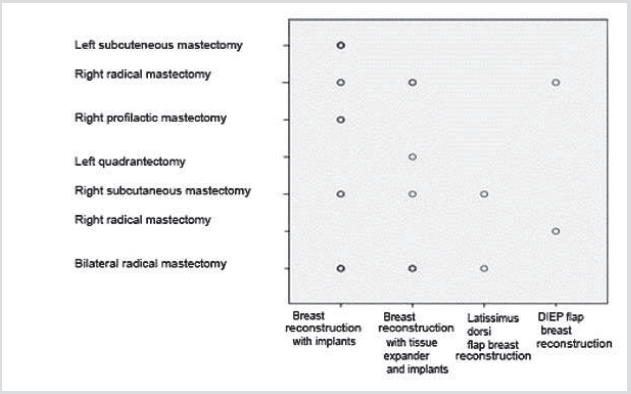

Figure 4 Correlation between the type of tumor eradication and modality of reconstruction.

Applied oncology therapy (Figure 5) was indicated in 234 cases (42.8%). Neoadjuvant therapy was administered in 207 cases (88.5%), and adjuvant therapy in 3 cases (1.3%). Radiotherapy was indicated in 10.3% of cases. Out of this percentage the adjuvant radiotherapy was performed in 2.6% and neoadjuvant therapy in 7.7% of cases. All types of breast cancers were most often treated with neoadjuvant chemotherapy (88.5%).

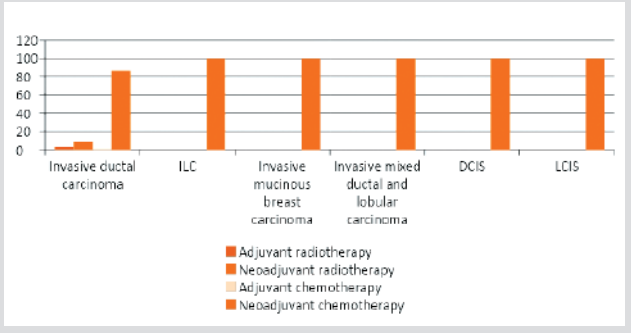

Figure 5 Correlation of applied oncology therapy with histological type of tumor.

DISCUSSION

The majority of patients in which implant for post-oncological breast reconstruction was used, had breast reconstruction with implant (94.8%). Lack of breast reconstruction in many cases could be explained by insufficient information and motivation of patients, while in the last three years the number of reconstructions has increased with the active involvement of a plastic surgeon, and definitely better informed patients regarding the possibilities of reconstruction.

Based on the 2010 data, the highest proportion of patients in the United States is currently among those of 60 years of age which is in accordance to our study (5). According to a study which included 2347 patients, invasive ductal breast cancer occurred in the highest percentage, 83.0% in the time period from 2011-2012, and 82.3% in period of 2014. ILC was presented in a percentage of 11.5% in 2011 and 2012,

and in 2014 in a percentage of 9.4%, which is similar to our study (6).

Rakha et al. in 2008 reported a study of 2304 patients with invasive breast cancer in Nottingham, Great Britain (7). Invasive ductal breast cancer was most prevalent with a percentage of 56.4%. ILC was presented by 8.2% and invasive mucinous breast cancer by 1.4%, which is consistent with the results of this study.

According to a study of Nowikiewicz T, at al., published in 2017, which included 2347 patients, sparing breast surgery was performed in 1245 patients (52.4%) in time period from 2011-2013, and 56.8% of patients in 2014 which is not in accordance with our data (6).

According to a research of Duriaud et al., conducted in the period from 2015 to 2016, 554 patients underwent radical breast cancer surgery at a ratio of 0.8:0.1 to conserving breast surgery, which is consistent with the results of this study (8).

In a 10 year study conducted by Magelia et al., published in 2012, breast reconsruction was performed in 59 cases. The largest percentage of patients had reconstruction performed with latissimus dorsi lobe (25 cases), followed by simple reconstruction with implants of 23 cases. Other patients had reconstruction with free abdominal lobe, which does not match the results of our study (9). In a study published in 2017, simple reconstruction was more prevalent than implant reconstruction after tissue expansion in a ratio reported over 23:184 which is consistent with the results of this study (10).

According to a study conducted by Nowikiewicz T, at al., neoadjuvant oncology therapy was not included in 87.6% of cases during 2011-2013, and in 84.7% of cases during 2014 (p=0.0409) which coincides with this study (6).

Throughout this study, a breast cancer treatment algorithm with reference to reconstruction modalities applied at the Clinical Center University of Sarajevo.

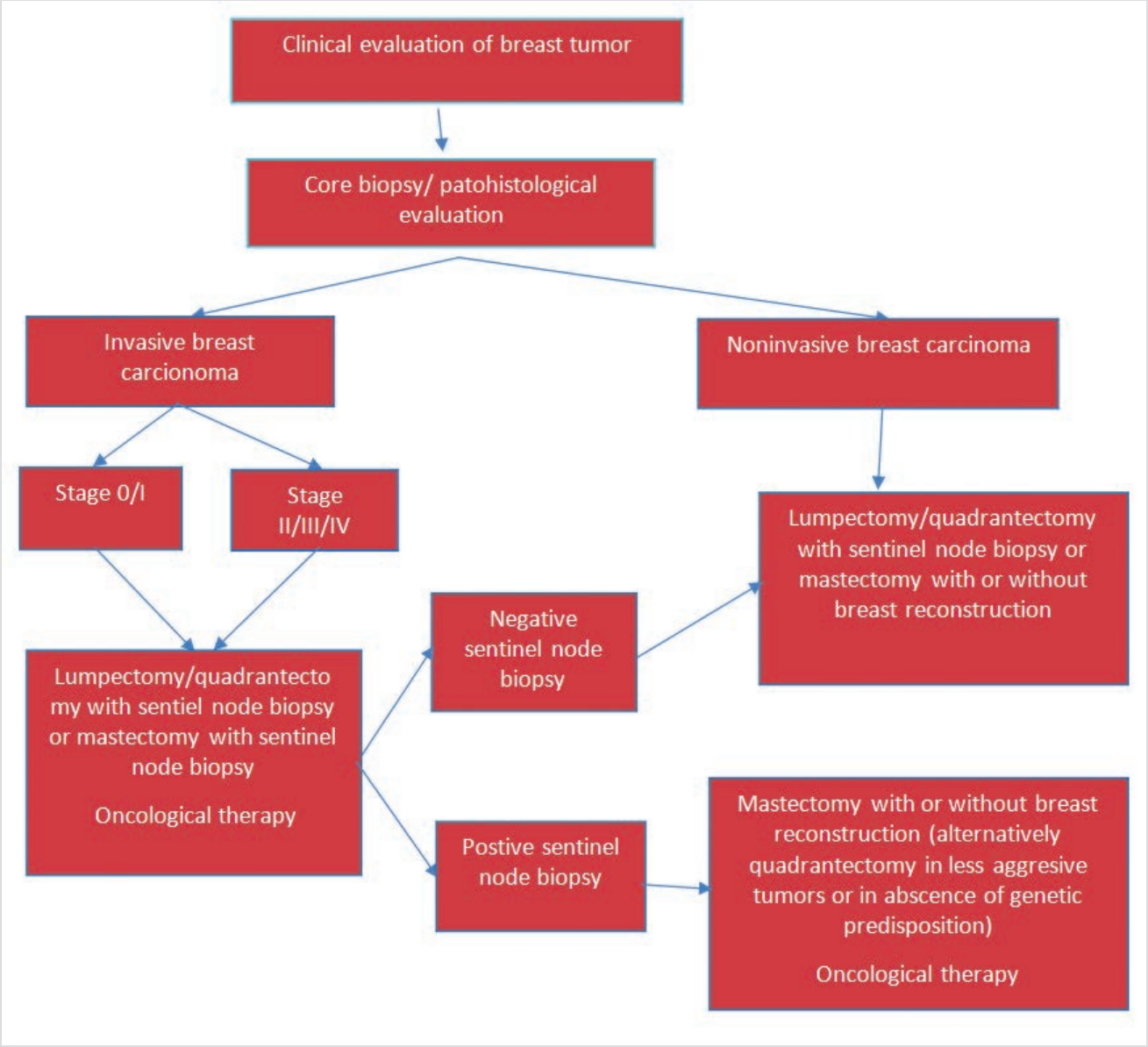

Figure 6 Algorithm of breast cancer treatment at Clinical Center University of Sarajevo.

CONCLUSION

Early diagnosis of breast cancer with multidisciplinary approach to each individual case is important factor of successful treatment. Each individual case of newly diagnosed breast cancer has to be carefully considered from point of the extent of primary eradication and acceptable modality of primary or secondary reconstruction. The initial stages of breast carcinoma are conditionally easier for treatment and reconstruction, which correlates with the histological type of tumor and genetic predispositions.. There is an increasing tendency of primary and secondary breast reconstruction due to changes in access to patient, consideration of every specific case, presentation of available breast reconstruction modalities and also due to active involvement of plastic surgeons in operation teams at Clinical Center University of Sarajevo. Establishing the algorithm of breast carcinoma treatment is a useful guideline in daily practice for clinicians in terms of uniquely aligning the views of diagnosis and treatment.

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Long-term lamotrigine treatment and bone metabolism

Dugotrajni tretman lamotriginom i metabolizam kostiju

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*Corresponding author

ABSTRACT

Introduction: data on antiepileptic drugs (AEDs) of newer generation and their effects on bone metabolism are insufficient and remain poorly understood. Aim: the aim of our study was to investigate the effects of lamotrigine (LTG) treatment on bone mineral density (BMD) as well as bone biochemical markers among epileptic patients (serum levels of 25-hydroxyvitamin D and serum levels of osteocalcin). Materials and methods: A cross-sectional study was performed in normal controls (n=30) and epilepsy patients taking lamotrigine (LTG) (n = 50) in monotherapy for a period of at least twelve months. For each participant, serum levels of 25-OHD and osteocalcin (OCLN) were measured and BMD was evaluated by dual-energy X-ray absorptiometry method. Results: the average value of vitamin D in serum was significantly lower in LTG group than in control group (Vit D 17.97±9.15 vs. 32.03 ±6.99, p=0, 0001). The average value of osteocalcin in serum was higher in LTG group than in control group (27.87±28.45 vs. 19.64±6,54, p=0,004) but this difference was not statistically significant. BMD value in LTG group was lower than in control group (T. score LTG: 0.37± 1.02 vs. T. score control: 0.73± 1.13, p= 0.031; Z score LTG: 0.38±0.96 vs. Z. score control: 0.55 ±0.79, p=0,015) but this difference was not statistically significant. Conclusion: even in the scarcity of evidence based data, patients on long-term LTG therapy could benefit of supplementation and regular control of biochemical markers of bone turnover, and BMD measurement. Further investigation of the effects of AED of new generation on bone metabolism is warranted.

Key words: anticonvulsants, lamotrigine, osteoporosis, bone mineral density

SAŽETAK

Podaci o antiepileptičkim lijekovima (AED) novije generacije i njihovim učincima na metabolizam kostiju su insuficijentni i još uvijek nisu potpuno razumljivi. Cilj našeg rada bio je istražiti učinke liječenja lamotriginom (LTG) na mineralnu gustoću kostiju (BMD) kao i biohemijske markere kostiju kod epileptičnih bolesnika (razina 25-hidroksivitamina D u serumu i razina osteokalcina u serumu). Pacijenti i metode: Presječna studija izvedena je na kontrolnoj grupi ispitanika (n=30) i epileptičnim bolesnicima (n=50) koji su koristili lamotrigin u monoterapiji u periodu najmanje 12 mjeseci. Svim ispitanicima mjeren je nivo serumskog 25-OHD i osteokalcina (OCLN) te izmjerena je mineralna gustoća kostiju (BMD) dvoenergetskom metodom rentgenske apsorpciometrije. Rezultati: prosječna vrijednost vitamina D u serumu bila je značajno niža u skupini s LTG-om nego u kontrolnoj skupini (Vit D 17,97 ± 9,15 u odnosu na 32,03 ± 6,99, p 0,0001). Prosječna vrijednost osteokalcina u serumu bila je viša u skupini s LTG-om nego u kontrolnoj skupini (27,87 ± 28,45 u odnosu na 19,64 ± 6,54, p=0,004), ali ta razlika nije bila statistički značajna. Vrijednost BMD-a u LTG skupini bila je niža nego u kontrolnoj skupini (T LTG: 0,37 ± 1,02 u odnosu na T. kontrolne grupe : 0,73 ± 1,13, p=0,031; Z LTG: 0,38 ± 0,96 u odnosu na Z. kontrolne grupe: 0,55 ± 0,79, p=0,015), ali ta razlika nije bila statistički značajna. Zaključak: čak i u oskudnosti podataka utemeljenih na dokazima, pacijenti na dugotrajnoj terapiji lamotriginom mogli bi imati koristi od suplementacije i redovite kontrole biohemijskih markera koštanog prometa i mjerenja BMD-a. Nepohodna su dalja istraživanja uticaja AED-a nove generacije na metabolizam kostiju.

Ključne riječi: antikonvulsanti, lamotrigin, osteoporoza, mineralna gustoća kostiju

INTRODUCTION

In recent years, there has been more and more evidence suggesting that epilepsy and its treatment may have negative effects on bone mineralization and calcium metabolism. Epilepsy itself represents unfavorable condition for bone health, given the fact that epileptic patients have up to 6 times higher risk of fracture than the general population (1). The risk of fractures is a function not only of bone mass, but also of various mechanisms such as reduction of physical activity, coexisting neurological deficits, and seizure-related falls (2). Additionally, fractures have been associated with antiepileptic treatment; the fracture risk increases significantly with the cumulative duration of antiepileptic therapy (3).

Long term antiepileptic therapy has been strongly associated with negative effects on bone mineralization and calcium metabolism. Multiple studies have reported the osteopenic effect of CYP450 inducing antiepileptic drugs (AEDs) threw their alteration of vitamin D metabolism leading to reduced calcium absorption, with consequent secondary hyperparathyroidism, increased bone resorption and accelerated bone mass loss (4-6). Novel studies have reported that AEDs may cause bone loss in the absence of vitamin D deficiency (7).

However, data on newer AEDs are insufficient and though their use has becoming increasingly prevalent, the effects on bone metabolism remain poorly understood. Previous studies on the effect of lamotrigine (LTG) monotherapy on bone health showed conflicting results. It has been suggested that LTG has limited (if any) effect on

bone health, but most of the studies have been conducted on pediatric population (8, 9) and premenopausal women (10).

Reduced BMD presents a critical concern in the selection of antiepileptic drug (AED) for patients with epilepsy therefore, more clarity in this field is essential.

AIM

The aim of our study was to investigate the effects of lamotrigine (LTG) treatment on bone metabolism at two levels: bone mineral density (BMD) as well as bone biochemical markers among epileptic patients (serum levels of 25-hydroxyvitamin D and serum levels of osteocalcin).

MATERIALS AND METHODS

A cross-sectional study in patients under treatment with LTG monotherapy was carried out in the period from 2016 to 2017, in Epilepsy Center of the Neurology Clinic in Sarajevo. Only patients on LTG monotherapy for a period of at least twelve months were entered in this study (n=50). Patients with any condition known to affect bone metabolism (e.g., renal disease, recent fracture, hyperparathyroidism, Paget disease, osteoporosis) or patients taking any drug known to cause or treat osteoporosis, were excluded. The results were compared with age-matched healthy controls, with no evidence of metabolic bone disease (n=30).

The study was conducted according to the standards of the Declaration of Helsinki (1975, revised 2000), and the protocol was approved by the local Bioethical Committee (decision reference numbers 0207-28784).

All participants were asked to complete a questionnaire which included medical history, fractures, falls and injuries, and vitamin D or calcium supplements. Bone mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry method called DXA technology. DXA was performed using a Hologic QDR-4000A densitometer (Hologic, Bedford, MA, U.S.A.). DXA measured bone mineral content (BMC in grams) and bone area (BA, in square centimeters), then calculated "area" BMD in g/cm2 by dividing BMC by BA. T-score, the value used for diagnosis osteoporosis, is the mean BMD of a young-adult reference population from the patients' BMD divide by the standard deviation (SD) of young-adult population. Z-score, used to compare the patients' BMD to a population of peers, was calculated by subtracting the mean BMD of an age, ethnicity and sex-matched referenced population from the patients' BMD and divide by the SD of the referenced population.

For each subject the level of vitamin D and osteocalcin in serum was determined in laboratory findings. Serum 1, 25-dihydroxyvitamin D (3) (normal range, 20-74 pg/ml) was measured by radioimmunoassay. Serum osteocalcin level was determined by Elisa. Due to laboratory errors, not every test was obtained for every patient. The precise n for each test in each patient group is noted in tables.

Statistical analysis

Statistical analyses were done using the SPSS for windows, version 16 (SPSS Inc., Chicago, IL). Continuous data were presented as mean ± standard deviation (SD). Student's t-test was used for continuous variables at baseline comparisons between the cases and controls. All continuous variables of interest (e.g., bone mineral parameters) were tested for normality using Kolmogorov-Smirnov test prior to data analysis. A p value of ≤ 0.05 was considered as significant.

RESULTS

The study involved 50 subjects, 15 males and 35 females with mean age 31.82±8.84 years.

Average duration of epilepsy was 11.32±6.86 years. Average duration of lamotrigine therapy was 4.27±2.52 years.

The average value of vitamin D in serum was significantly lower in LTG group than in the control group (Vit D 17.97±9.15 vs. 32.03 ±6.99, p-value: 0, 0001) (Table 1).

Table 1 Average value of 25-hydroxyvitamin vitamin D in serum in patients and control group.

Vitamin D (ng/ml)						
	N	X	SD	SEM	Minimum	Maksimum
Controls	30	32.03	6.99	1.28	21.30	50.30
Lamotrigine	49	17.97	9.15	1.31	4.10	39.10
Total	79	23.31	10.81	1.22	4.10	50.30

F=12,146; p=0.0001

The average value of osteocalcin in serum was higher in LTG group than in control group but it was not statistically significant (OCLN 27.87±28.45 vs. 19.64±6, 54, p-value: 0,124) (Table 2).

Table 2 Average value of osteocalcin in patients and control group.

Osteocalcin (ng/ml)						
	N	X	SD	SEM	Minimum	Maksimum
Controls	30	19.64	6.54	1.19	11.10	36.40
Lamotrigine	50	27.87	28.45	4.02	16.00	221.00
Total	80	24.79	23.10	2.58	11.10	221.00

F=2.422; p=0.124

BMD value in the LTG group was lower than in the control group but it was not statistically significant (T. score LTG: 0.37± 1.02 vs. T. score control: 0.73± 1.13, p-value: p=0,146; Z score LTG: 0.38±0.96 vs. Z. score control: 0.55 ±0.79, p value: p=0,418) (Table 3 and Table 4).

Table 3 T. scores in patients and control group.

T						
	N	X	SD	SEM	Minimum	Maksimum
Controls	30	0.73	1.13	0.21	-2.70	2.10
Lamotrigine	50	0.37	1.02	0.14	-2.70	2.40
Total	80	0.51	1.07	0.12	-2.70	2.40

F=2.158; p=0.146

Table 4 Z. scores in patients and control group.

Z						
	N	X	SD	SEM	Minimum	Maksimum
Controls	30	0.55	0.79	0.14	-1.00	1.80
Lamotrigine	50	0.38	0.96	0.14	-3.30	2.10
Total	80	0.45	0.90	0.10	-3.30	2.10

F=0.663; p=0.418

DISCUSSION

Antiepileptic therapy developed after the 1990s have generally being considered safer with less reported undesirable effects and drug interactions compared to traditional AEDs (11).

In general, it is believed that antiepileptic drugs that induce P450 cytochrome hepatic enzyme have negative impact on bone health, mostly by increase in the catabolism of vitamin D (7,12,13).

Previously, we investigated long term impact of carbamazepine therapy on vitamin D levels and biomarkers of bone turnover, and observed the significant reductions in 25-OHD levels and significant increases in the bone-formation marker OCLN (Vit D 17.03±12.86 vs. 32.03 ±6.99, p-value: 0, 0001) (OCLN 26.06±10.78 vs. 19.64±6.54, p-value: 0.004) (14).

However this cannot explain why non enzyme inducing agents have also been associated with reduced bone mass independent of low vitamin D levels (4).

Studies evaluating the influence of non-enzyme-inducing anticonvulsants on serum levels of vitamin D in epileptic patients showed contradictory results (9).

In this study, we demonstrated a significant decrease in 25-OHD levels in patients treated with LTG compared to the control group (Vit D 17.97±9.15 vs. 32.03 ±6.99, p-value: 0.0001).

However, most of the studies did not observe vitamin D-lowering effect of long term LTG treatment (15-18). Preliminary data indicate that prolonged use of lamotrigine gives no significant change in BMD and bone metabolism (19).

According to our results, lamotrigine treatment did not significantly affect bone strength and BMD, although we observed higher value of serum osteocalcin in LTG group and lower BMD value compared to the control group (Table 2). Our results are consistent with the results from previous research (20).

A recent study in 108 patients found an association between AEDs of newer generation and lower BMD. However, the patients were also on concomitant treatment with one of the traditional drugs (21).

On the other hand, retrospective cohort study on 560 patients reported that patients treated with non enzyme-inducing anticonvulsants were less expected to have osteoporosis (22).

Study conducted on pediatric patients on lamotrigine monotherapy did not observe any negative impact on bone growth (8).

A number of therapeutic options are available for the prevention and treatment of reduced BMD including calcium and Vitamin D supplementation, bisphosphonates, selective estrogen receptor modulators, hormone replacement therapy, recombinant forms of PTH, and calcitonin. Notably, very few studies are available on the prevention and treatment of bone disease in epileptic patients on long-term AEDs (23).

A recent systematic review and meta-analysis of randomized controlled trials in healthy children with normal levels of Vitamin D, in subgroup of patients found that supplementation of deficient children may be clinically useful, especially in the lumbar spine and total body bone mineral content (24,25).

It is generally recommended that serum 25(OH) D levels should be measured before the initiation of treatment and then at 6-12 months in patients on long-term treatment with enzyme-inducing AEDs. Monitoring of biochemical markers of bone turnover is not recommended in routine clinical practice (26).

CONCLUSION

Even in the scarcity of evidence based data, patients on long-term lamotrigine therapy could benefit of supplementation and regular control of biochemical markers of bone turnover, and BMD measurement. Further investigation of the effects of new generation AED on bone metabolism is warranted.

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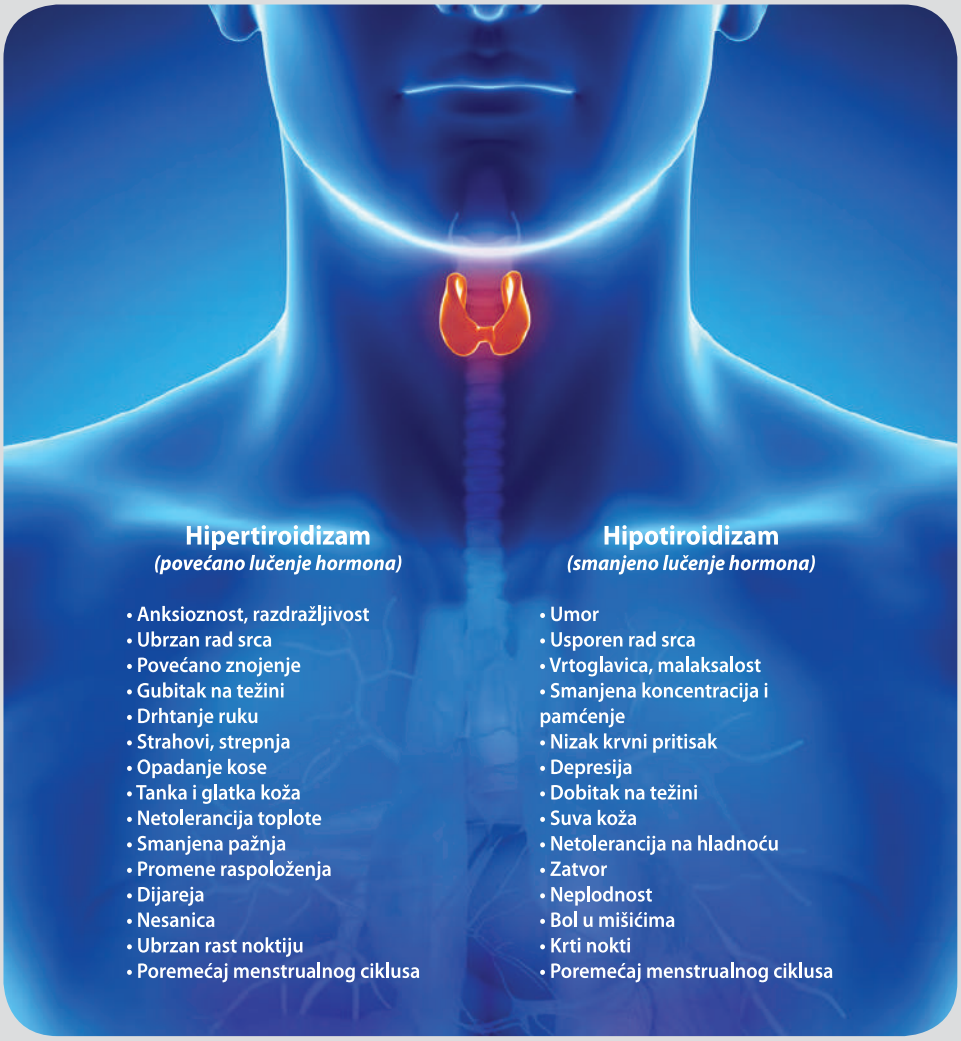

Efficacy of preemptive analgesia diclofenac in laparoscopic cholecystectomy

Efikasnost preemptivne analgezije diklofenakom kod laparoskopskih holecistektomija

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ABSTRACT

Introduction: preemptive analgesia is a treatment that prevents the establishment of changes, so-called sensitive processing of the aphasic signals which increase post-operative pain. It is a treatment that prevents the creation of central hypersensitivity caused by dissection or inflamed tissue injury. Preemptive analgesia prevents or reduces the "pathological" pain that differs from physiological pain in some characteristics: it is too extensive in intensity and expansion can be triggered by low intensity stimuli (hyperalgesia) or even typical painless sensations recognized as painful (allodynia). Aim: to compare the effectiveness of pre applied diclofenac in reducing post operative pain following laparoscopic cholecystectomy and to prove how adequate preemptive analgesia, diclofenac reduces the use of pain reliever (analgesic) in the postoperative period. Within the study we also examined the characteristics and qualities of the effect of applied analgesic depending on the following factors: age, body mass index and the presence of comorbidity in patients at the Public Hospital Travnik in Travnik. Materials and methods: this prospective study included 90 patients who underwent laparoscopic cholecystectomy. The study was realized by dividing the patients into 3 groups: Group I included 30 patients, who received pre operatively diclofenac in the amount of 1 mg/kg intramuscular; Group II consisting of 30 patients who received diclofenac in the amount of 1mg/kg in a form of suppositories and Group III consisted of 30 patients who were not given diclofenac. The study included the total of 90 patients. Results: the research showed that patients' age and weight did not have any influence on subjective pain assessment either in the overall sample or in individual groups. There was statistically significant difference in the estimation of pain intensity after 15, 20, 30, 45 and 60 minutes and 2, 3 and 6 hours after the surgery. There was a difference among the individual groups regarding the pain occurrence after 15, 30, 45 and 60 minutes, and 2, 3 and 6 hours after the surgery, among the control and other two groups, but not between Group I (diclofenac intramuscularly) and Group II (diclofenac suppository). Conclusion: preemptive analgesia administered intramuscularly or in the form of suppositories, significantly reduced the intensity of pain postoperatively, but we could not confirm significant difference in the manner of analgesia administration (intramuscular injection or suppository).

Key words: preemptive analgesia, diclofenac, laparoscopic cholecystectomy

SAŽETAK

Uvod: preemptivna analgezija je antinociceptivni tretman kojim se spriječava uspostavljanje promjene, tzv. preosjetljive obrade aferentnih signala, koji pojačavaju postoperativnu bol. To je tretman koji prevenira stvaranje centralne preosjetljivosti uzrokovane incizijskom ili inflamacijskom povredom tkiva. Preemptivna analgezija prevenira ili reducira "patološku" bol koja se od fiziološke boli razlikuje po nekim karakteristikama: preobimna je u intenzitetu i širenju, te se može aktivirati podražajima slaba intenziteta (hiperalgezija) ili čak tipične bezbolne senzacije prepoznaje kao bolne (alodinija). Preemptivna analgezija smanjuje intezitet hiperpatije. Ispitati efikasnost preemptivno apliciranog diklofenaka na smanjenje postoperativne boli nakon laparoskopske holecistektomije. Cilj: dokazati da adekvatna preemptivna analgezija dikolofenakom smanjuje upotrebu analgetika u postoperativnom periodu. Ispitati karakteristike ili odlike uticaja primjenjenog analgetika u zavisnosti od sljedećih faktora: dobi, indeksa tjelesne mase, prisustva komorbiditeta kod pacijenata u JU Bolnica Travnik. Materijali i metode: u ovoj prospektivnoj studiji obrađeno je 90 pacijenata podvrgnutih laparaskopskoj holecistektomiji podjeljenih u 3 skupine: I skupina od 30 pacijenata kojima je preoperativno intramuskularno aplicirano diklofenak 1mg/kg, II skupina od 30 pacijenata kojima je u vidu supozitorije aplicirano diklofenak 1mg/kg, i III skupina od 30 pacijenata kojima nije apliciran diklofenak. U istraživačkom radu vršena su istraživanja na 90 pacijenata gdje smo dobili rezultate koji pokazuju da dob i tjelesna težina pacijenata nemaju uticaja na subjektivnu ocjenu boli kako u ukupnom uzorku, tako i u pojedinim skupinama. Rezultati: pokazalo se da postoji razlika između pojedinih skupina o pojavi boli nakon 15, 30, 45, 60 minuta, te 2, 3 i 6 sati nakon operativnog zahvata, i to između kontrolne i ostale dvije skupine, ali ne i između skupine I (aplikacija diklofenaka intramuskularno) i skupine II (aplikacija diklofenaka supozitorije). Zaključak: preemptivna analgezija intramuskularno aplicirana ili u vidu supozitorije, signifikantno smanjuje intenzitet bola postoperativno, ali ne može se utvrditi značajna razlika u načinu aplikacije analgezije (intramuskularno ili supozitorij).

Ključne riječi: preemptivna analgezija, diklofenak, laparoskopska holecistektomija

INTRODUCTION

The biliary calcullosis is the most frequent disease of the hepatobiliary system, and the cholecystectomy is one of the most frequently performed surgical procedures. Preemptive analgesia is an antinociceptive treatment that prevents the formation of afferent nociceptive signals, which leads to the intensification of postoperative pain. Many reviewed studies have shown different results, partially and because of different focus of studies using various protocols of analgesia after the procedure, various combinations of analgesics with different methods of applying (parietal blockade, visceral blockade or peripheral block, local infiltration), therefore the great diversity of results were shown, from very favourable, partially better results in the early postoperative period to the lack of efficiency (1-3). A large number of studies indicate systematic technique on opoid administration or local analgesia to prevent the onset of central sensitization and hyperalgesia prior to painful stimulation and pain similar to behavioural pain. Preemptive analgesia refers to administration of analgetics, in any given moment and any possible regime in preoperative setting in order to provide analgesia by preventing the onset of central sensitization and hyperalgesia. Preemptive analgesia is treatment that prevents the establishment of a central response to pain caused by incision and inflammatory tissue injuries beginning before the surgical incision and covering the surgery period and the initial postoperative period (4,5). Pain is a normal pathophysiological response of the body due to tissue damage. It is a protective mechanism which function is to make the body aware of the danger and react to eliminate painful stimuli. The International Association for the Study of Pain (IASP) defines pain as unexplained sensory, emotional experience associated with current or potential tissue damage (6-8). According to the agreement of the ASA (American Society of Anesthesiologists), acute postoperative pain is described as pain present in patients treated surgically due to previous illness, surgery, or pain related to the disease and surgery. IASP (International Association for the Study of Pain) defines chronic pain as pain lasting at least three months. Post-operative pain-related changes may affect the levels of insulin, cortisol, catecholamines and other hormones (9-10). Reduced physical mobility due to pain can lead to the development of pneumonia, muscles can be damaged by decreased metabolism. The muscles that control bladder function can be disrupted resulting in urinary retention. Coronary vasoconstriction resulting from activation of the sympathetic nervous system can cause cardiovascular adverse effects such as angina or ischemia. Also, untreated postoperative pain can lead to sleep deprivation and psychological problems such as anxiety or depression (11-15). It is estimated that around 234 million surgical procedures are performed worldwide each year, which gives this type of pain great importance. Studies have shown that 80% of patients experience acute postoperative pain, and as many as 86% rate pain as moderate to severe. Poorly treated postoperative pain leads to the development of complications and a prolonged recovery time with increasing rates of morbidity and mortality. Proper pain management contributes to shorter hospitalization time, lower hospital costs and increased patient satisfaction. Given that the World Health Organization (WHO) and the IASP consider the treatment of pain as a basic human right, it is not surprising that the management of postoperative pain (15-20) is used as a measure for quality of hospital care. In order to be successfully treated, pain must be adequately quantified. The gold standard is the patient's self-assessment, which is performed routinely after surgery to evaluate the success of pain management. One-dimensional scales are generally used for the evaluation of postoperative pain, the most famous of which are the Visual Analog Scale (VAS), the Speech Scale (VRS), the Numerical Scale (NRS) and the Facial Pain Scale (FPS) (20-22).

AIM

The aim of this study was to compare the effectiveness of pre applied diclofenac in reducing post operative pain following laparoscopic cholecystectomy and to demonstrate how adequate preemptive analgesia, diclofenac reduces the use of pain reliever (analgesic) in the postoperative period.

MATERIALS AND METHODS

This prospective randomized study was conducted from in the period from July 2015 to July 2016 at the Public Hospital Travnik, and it included 90 patients divided into two experimental and one control group. Respondents age ranged from 20 to 73 years. All patients included in the study were treated with laparoscopic cholecystectomy, with surgery duration up to 90 minutes, and the same principle of general anesthesia, ASA status I-III.

I Group of respondents included:
- Patients given intramuscular diclofenac, 1 mg/kg per body weight, one hour before the surgery.
- A total of 30 patients.

II Group of respondents included:
- Patients given diclofenac as a suppository, 1 mg/kg per body weight, one hour before the surgery.
- A total of 30 patients.

III Group of respondents - Control group included:
- Patients who were not given diclofenac preoperatively.
- A total of 30 patients.

Patients in all three groups were examined for the severity of pain in the postoperative period, from the time of extubation, precisely after 15, 30, 45, 60 minutes, and after 2, 3, and 6 hours.

The level of postoperative pain was determined according to the numerical analogue scale, indicated on the data collection questionnaire. In the postoperative period, all patients who rated pain level higher than 3 on the numerical analogue pain scale received an appropriate dose of metamizole (Figure 1).

Figure 1 Numerical analog pain scale.

All data collected was analysed using a MS Excel 2013 and programme tool IBM SPSS Statistics v. 20.0 for Windows and are present as mean ± SD (range) or frequency. For all analyses by Chi-square test, statistical significance was defined as $p < 0.05$.

RESULTS

Following data processing, the following results were obtained: the group of subjects who received diclofenac pre-operatively and intramuscularly were marked as IM, while the group of subjects who was administered diclofenac preoperatively as suppository was marked as SUP group.

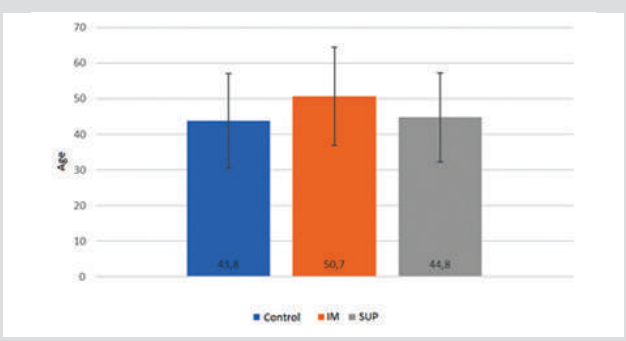

Figure 2 Average age of respondents.

Correlation analysis of the effect on age group showed that the age group did not have any influence on pain rating, either in the total sample or in the individual study groups (all p> 0.05).

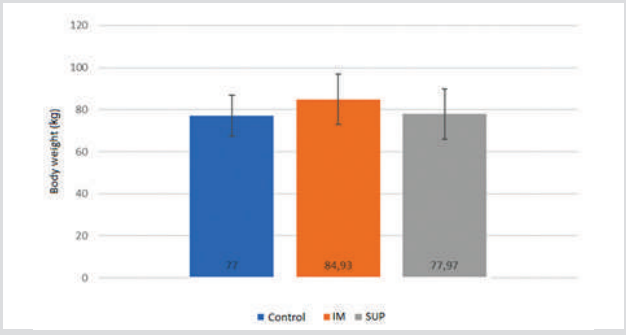

Figure 3 Average body weight of respondents.

As with the age, correlation analysis of the influence of body weight on pain score results showed that body weight did not have any influence on pain score in either the total sample or the individual groups (all p> 0.05).

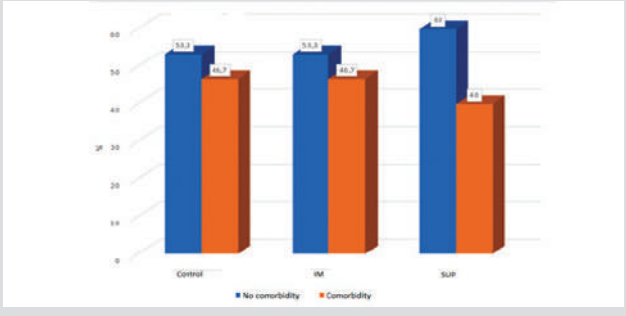

Figure 4 Presence of comorbidity in respondents.

Statistical analysis by Chi-square test indicated that there was no significant difference between the observed groups in respect of the presence of comorbidity (p>0.05). The sample was homogeneous regarding the presence of comorbidity.

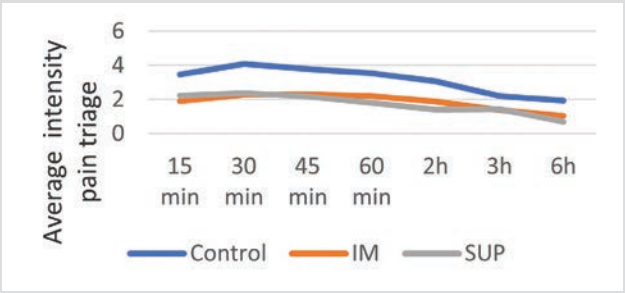

Figure 5 Average scores on the pain scale during the observed postoperative course.

Figure 5 shows the average scores on the pain scale over the entire postoperative period (preoperative period was not included given that it was almost equal to 0 - no pain) in all three observed groups. A statistically significant difference was found between the experimental and control group.

Post hoc analysis of differences between the individual groups indicated that there was a difference between the control and other two groups ($p < 0.05$), but not between the IM and SUP group ($p < 0.05$).

The pain in the control group was much severe during the entire postoperative period.

In the postoperative period, all patients who rated pain levels higher than 3 on a numerical analogue pain scale received an appropriate dose of metamizole intravenously. Statistical analysis of data shows that after extubation, metamizole sodium was more frequently used in the control group than in other two groups.

DISCUSSION

About 600 laparoscopic cholecystectomies are annually performed in the Public Hospital Travnik in Travnik. The results of our study showed that there was a significant differential effect on the onset of pain between the control group and the analgesic group prior to anesthesia. There was significant difference between the effect and the response in the groups, between the control group and the group administered analgesic, but the mode of administration of analgesics (intramuscular or suppository) was shown to be of no significant difference. The most intensive pain occurred 30 minutes after the extubation, which was the time when we applied painkillers, but in other time intervals need for additional analgesia was significantly reduced in experimental groups in respect to the control group.

Mazhar I et al. (23) conducted a study which included 200 patients divided into 2 comparable groups. In their conclusion the authors stated that preemptive analgesia in patients undergoing laparoscopic cholecystectomy with diclofenac sodium was efficient with minimal side effects and decreased need for additional analgesia in the early postoperative period, which was in correlation with the results of our study.

The aim of the research conducted by Gulcin Ural S et al. (24) was to compare the effectiveness of applied oral, intramuscular and

transdermal Diclofenac sodium for the management of pain in patients undergoing laparoscopy cholecystectomy and their effect on post-operative consumption of opoids. The study obtained the following findings: post-operative analysis where VAS was included, showed that the intensity of pain was at lower scale at all current interval points in the IM and TD group compared to PO group. The same was found in the results of our study.

A study which results correlated with ours was conducted by Goyal et al. (25). They analyzed whether diclofenac suppository administered immediately after induction could reduce pain after surgery, the need for analgesia and the side effects associated with opioid administration. The study included 69 respondents. The authors conclude that diclofenac suppository at a dose of 100 mg significantly reduces the VAS score, the need for analgesia, as well as side effect for patients after laparoscopic cholecystectomy.

In the study carried out in Sweden by Lars E et al. (26), where the preemptive use of diclofenac was investigated in reducing postoperative pain after gynecological laparoscopic procedures, statistical data collected was in correlation with the results of our study. After the surgery, the intensity of pain was higher in the control than in the diclofenac group during 24 hours of postoperative monitoring ($P < 0.05$).

In order to examine the effects of preventively administered low-dose ketamine, diclofenac and their combination on postoperative pain in patients undergoing laparoscopic cholecystectomy Nasek-Adam et al. (27) conducted a study involving a total of 80 patients, ASA I or ASA II status. Patients receiving diclofenac had a significantly lower pain score between 2 and 6 hours post-operatively as compared to patients receiving placebo, which correlates with the results of our study.

Although perceptual analgesia has proven to be practical and useful method in reducing postoperative pain in patients, this research should be extended to discover new practical modalities for medication and analgesic doses, with the final goal to reduce postoperative pain in patients.

CONCLUSION

Our study has shown that diclofenac is suitable for preemptive approach and has proven to be an effective drug, as part of balanced analgesia which helps reducing analgesic consumption in the postoperative period. The route of administration, whether intramuscular or suppository, did not show any difference in the test results. Preemptive analgesia with diclofenac prior to laparoscopic cholecystectomy significantly reduces the intensity of postoperative pain and the length of pain duration compared to Control group of patients without applied procedure, thus confirming our primary hypothesis. It was shown that there was no statistically significant difference between the groups, the sample was homogeneous by age. Correlation analysis on the age group effect on pain assessment results showed no influence on pain score, either in the total sample or individual study groups. Correlation analysis on the influence of body weight on pain assessment results showed that it did not influence the subjective assessment of pain in the total sample or in individual groups. In relation to the presence of comorbidity, there was no significant difference between the observed groups, nor did comorbidity affect the intensity of pain or the final consumption of analgesia.

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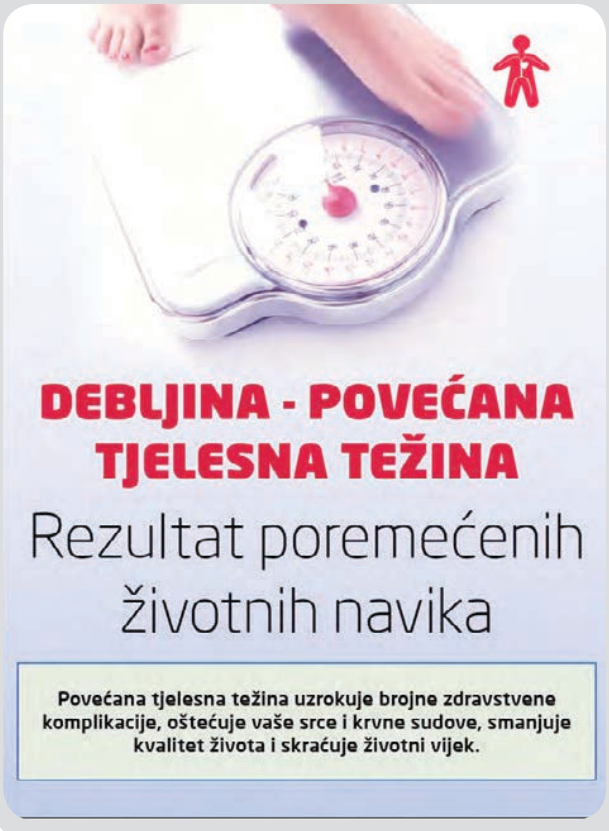

Nasal continuous positive airway pressure (NCPAP) versus mechanical ventilation in premature infants with respiratory distress syndrome (RDS)

Neinvazivna ventilacija nazalnim kontinuiranim pozitivnim pritiskom u odnosu na mehaničku ventilaciju u tretmanu sindroma respiratornog distresa kod prijevremeno rođene djece

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ABSTRACT

Introduction: significant progress in treating respiratory distress syndrome (RDS) can be attributed to prenatal identification of high-risk pregnancies, prenatal use of glucocorticoid, administration of surfactant, progression in respiratory support, application of noninvasive ventilation by nasal continuous pressure trough nasal prongs. These measures resulted in the reduction of mortality and morbidity rates in preterm newborns. Aim: to study the effect of nasal continuous positive airway pressure (NCPAP) in preterm newborns with RDS. Materials and methods: the research included 236 preterm newborns with respiratory distress syndrome hospitalized in Neonatal Intensive Care Unit (NICU), Pediatric Clinic, Clinical Center University of Sarajevo. The study group consisted of 118 preterm newborns, treated with NCPAP. The control group consisted of 118 preterm newborns of approximately the same gestational age and weight. They were intubated and received conventional mechanical ventilation. Results: treatment with nasal continuous positive airway pressure (NCPAP) significantly reduced mortality rate (p=0.05). There was a significant difference in the incidence of pneumonia, pulmonary hemorrhage and intracranial hemorrhage in the group of preterm newborns treated with NCPAP in comparison to the group of newborns treated with conventional mechanical ventilation (p=0.05). Conclusion: the use of NCPAP significantly reduces mortality and morbidity rate of preterm newborns with RDS compared to newborns of approximately same gestational age with RDS treated with conventional mechanical ventilation. Application of NCPAP leads to a reduction in lung complications: pneumonia, pulmonary hemorrhage and extrapulmonary complications such as intracranial hemorrhage.

Key words: preterm infant, respiratory distress, NCPAP, mechanical ventilation

SAŽETAK

Uvod: značajan napredak u liječenju respiratornog distres sindroma (RDS) može se pripisati prenatalnoj identifikaciji trudnica visokog rizika, prenatalnoj primjeni glukokortikoida, primjeni surfaktanata, napretku u respiratornoj potpori, neinvazivnoj ventilaciji kontinuiranim nazalnim pritiskom putem nazalnih nastavaka. Ove mjere dovode do smanjenje mortaliteta i stope morbiditeta kod prijevremeno rođene djece. Cilj: ispitati efekate tretmana kontinuiranim pozitivnim pritiskom putem nosnih nastavaka a (NCPAP) kod djece sa respiratornim distres sindromo. Materijali i metode: istraživanje je uključilo prijevremeno rođenu djecu s RDS-om hospitaliziranu na Neonatalnoj intenzivnoj njezi, Pedijatrijske klinike, Kliničkog centra Univerziteta u Sarajevu. Ispitivana skupina sastojala se od 118 nedonoščadi liječenih NCPAP-om. Kontrolnu skupinu činilo je 118 prijevremeno rođenih novorođenčadi približno iste gestacijske dobi i težine. Djeca su bila intubirana i mehanički ventilirana. Rezultati: upotreba NCPAP je značajno smanjila stopu mortaliteta (p = 0,05). U skupini prijevremno rođene novorođenčadi koja se liječila NCPAP-om postojala je značajna razlika u učestalosti upale pluća, plućnog krvarenja i intrakranijalnog krvarenja u odnosu na skupinu novorođenčadi koja su liječena konvencionalnom mehaničkom ventilacijom (p = 0,05). Zaključak: upotreba NCPAP značajno je smanjila mortalitet i morbiditet prijevremeno rođene novorođenčadi s RDS-om u usporedbi s novorođenčadima približno iste gestacijske dobi s RDS-om tretiranim konvencionalnom mehaničkom ventilacijom. Primjena NCPAP-a dovodi do smanjenja komplikacija: upale pluća, plućnog krvarenja i ekstrapulmonalnih komplikacija poput intrakranijalnog krvarenja.

Ključne riječi: prematurus, respiratorni distres, NCPAP, mehanička ventilacija

INTRODUCTION

Respiratory distress syndrome (RDS) is the leading cause of mortality in preterm newborns. It primarily affects preterm newborns and is in reverse proportion to gestation age and weight (1,2). Surfactant deficiency is the primary cause of RDS. RDS is „almost unchangeable" in newborns under 28 weeks of gestation (80% of affected newborns) and it presents significant problem in newborns under 34 weeks of gestation. Preterm newborns are at higher risk of developing RDS and sometimes require mechanical ventilation to be kept alive (3,4,5).

There are various complications related to mechanical ventilation most of which are iatrogenic. Ventilator Induced Lung Injury (VILI) is reported to be a cause for developing bronchopulmonary dysplasia (BPD) or chronic lung disease (6,7). Accordingly, there is an increased interest for the application of continuous positive airway pressure (CPAP) as a „gentle" respiratory support in the efforts to decrease mortality rate and reduce long-term respiratory morbidity. The use of intermittent positive pressure ventilation (IPPV) in preterm newborns with respiratory insufficiency saves life but is, however, associated with number of complications (7,8,9). Use of non-invasive mechanical ventilation with continuous positive airway pressure may result in minor lung damage, reduced mortality rate and other complications associated with prematurity and assisted ventilation in preterm newborns subjected to positive-pressure mechanical ventilation due to RDS.

AIM

The aim of article was to study the effect of nasal continuous positive airway pressure (NCPAP) in preterm infants with RDS.

MATERIALS AND METHODS

The study included 236 preterm newborns with RDS, between 25 and 37 weeks of gestation, treated in the Neonatal Intensive Care Unit (NICU), Pediatric Clinic, Clinical Center University of Sarajevo, Bosnia and Herzegovina, in period from June 2015 and May 2017. Sample were divided in two groups. First group included 118 preterm newborns with clinical (cyanosis at the room air, tachypnea) and radiological RDS symptoms (ground glass on X ray). Control group consisted of 118 premature newborns of approximately same gestation age and weight intubated and ventilated with conventional mechanical ventilation „standard method". Infant flow CPAP (SiPAP) device (Viasys Respiratory Care Inc, United States of America) was used with the possibility of applying one or alternatively two (biphasic) values of continuous pressure. RDS diagnosis was set up both clinically and radiologically (diffuse granular opacities, ground glass). Clinical diagnosis was based on the presence of tachypnea, cyanosis at the room air and need for oxygen support in the absence of other respiratory insufficiency causes. Newborns were intubated according to standard criteria (need for oxygen support, FiO2 >40%, stopped breathing, respiratory acidosis). Chi square test, student t test, F tests and analysis of variance (ANOVA) was used for statistical analysis of data. Microsoft Excel (version 11 Microsoft Corporation, Redmond, Washington, USA) was used in analysis, along with the SPSS Windows software package (version 21.0, SPSS Inc., Chicago, Illinois, USA). All tests were performed with the accuracy level of 95% ($p<0.05$). Ethical approval was obtained from the Ethics Committee of the Clinical Center of the University of Sarajevo.

RESULTS

We compared results of preterm newborns treatment with CPAP with the results of preterm newborns treatment with mechanic ventilation in respect to mortality rate, pulmonary complications (pneumonia and pulmonary haemorrhage), and extrapulmonary complications (intracranial haemorrhage). A total of 236 newborns was examined. Outcome of the treatment in both study and control group is presented in Table 1. There was a significant difference in the treatment outcome (survive/deceased) by groups. In the group of premature newborns treated with NCPAP, 95% (112) of them survived and 65% (77) in the group treated with mechanical ventilation.

Table 1 Structure of the study and control group by mortality rate.

Group	Survive		Deceased		Total
	No.	%	No.	%	
CPAP	112	95.00	6	5.00	118
MV	77	65.00	41	35.00	118
Total	189	80.00	47	20.00	236

Table 2 shows results of pneumonia incidence in the study groups. In the group of patients treated with NCPAP, pneumonia occurred in 7.63% (9), whereas in patients treated with mechanical ventilation it occurred in 22.03% (26) of newborns.

Table 2 Incidence of pneumonia in the study and control group.

Group	Pneumonia (Yes)		Pneumonia (No)		Total
	No.	%	No.	%	
CPAP	9	7.63	109	92.37	118
MV	26	22.03	92	77.97	118
Total	35	14.83	201	85.17	236

The results show that there was statistically significant difference in the incidence of pneumonia (Table 3).

Table 3 Incidence of pulmonary haemorrhage in the study and control group.

Group	Pulmonary haemorrhage (Yes)		Pulmonary haemorrhage (No)		Total
	No.	%	No.	%	
CPAP	8	6.78	110	93.22	118
MV	22	18.64	96	81.36	118
Total	30	12.71	206	87.29	236

In the group treated with CPAP, incidence of pulmonary haemorrhage was 7.63% (8) and 18.64% (22) in the group treated with mechanical ventilation.

Table 4 Incidence of intracranial haemorrhage in the study and control group.

Group	Intracranial Haemorrhage (Yes)		Intracranial Haemorrhage (No)		Total
	No.	%	No.	%	
CPAP	16	13.56	102	86.44	118
MV	44	37.29	74	62.71	118
Total	60	25.42	176	74.58	236

Intracranial haemorrhage (HIC) grade III and IV is detected on ultrasound. Table 4 show incidence of HIC grade III and IV in the

study and control group where significant differences were observed (p=0.05). In newborns treated with CPAP incidence of HIC grade III and IV was reported in 13.65% (n=16) and in 37.29% (n= 44) of preterm newborns on mechanical ventilation.

DISCUSSION

Treatment of RDS uses different ventilation techniques, but currently there is no clear recommendation as to which technique is the most efficient. Each mechanical ventilation model can cause lung damage (10). Increasing interest in the ,,open lung "concept in RDS and the role of mechanic ventilation in the development of lung damage and chronic pulmonary disease arouse interest in the use of CPAP as a primary respiratory support in preterm newborns worldwide. Its use in the word is increasing partly based on the reported effective evidence but largely based on clinical experience showing that CPAP is a safe, cheap and efficient alternative for endotracheal and mechanical intubation (7,11,12).

Our study analyzed data related to the outcome of the initial treatment of preterm newborns with respiratory stress syndrome who were postpartum treated with CPAP at NICU (118 newborns). Data was compared to those obtained on the outcome of the initial treatment of the same number of preterm newborns (118) with mechanical ventilation, total of 236 newborns. All newborns were born as prematurus, with clinically and radiologically diagnosed RDS symptoms.

Progress in respiratory distress syndrome therapy enables survival of the most immature newborns (13-16). The mean gestational age of the examined newborns was 30 weeks in the CPAP group and 30.33 weeks in the group of newborns treated with mechanical ventilation. The results show that very small newborns can benefit from NCPAP. The best results in our study were shown in newborns treated with NCPAP in the gestational age from 31 to 33 weeks. The survival rate in that group of newborns was 97.30%. In the group of newborns with extreme law gestation age (from 24 to 26 weeks) the survival rate was 93.33%.

We observed significant decrease in mortality rate of premature newborns with respiratory distress syndrome treated with NCPAP. Mortality rate in newborns treated with CPAP was 5% whereas mortality rate in newborns treated with mechanical ventilation was 35%. Based on our results there was statistically significant difference in the treatment outcome between the two compared groups, newborns treated with mechanical ventilation and newborns treated with NCPAP.

Our study compared results obtained before and after NCPAP application for the initial treatment of RDS in preterm newborns admitted to NICU. We found significant difference in decrease of complications and lower mortality rate which resulted in reduction of invasive ventilation.

There was significant difference in pneumonia incidence in our study groups. In the group of patients treated with CPAP pneumonia occurred in 22.03% (26) of patients, which can be explained with less invasive treatment of newborns treated with NCPAP. Pulmonary haemorrhage was present in 7.63 % (8) of patients in the CPAP group whereas in the group of patients treated with mechanical ventilation it occurred in 18.64% (22) of patients. There were significant differences in the incidence of pulmonary haemorrhage by groups (p=0.05). Lower prevalence of intracranial haemorrhage of third and fourth grade was observed in the group of newborns treated with NCPAP. In newborns treated with NCPAP, HIC grade III and IV was present in 13.56% (16) of premature newborns and in 37.29% (44) of premature newborns on mechanical ventilation. There was statistically significant differences in the incidence of intracranial haemorrhage of III and IV grade between the groups (p=0.05).

Recent study conducted in Boston, USA, and in Stockholm, Sweden, compared newborns in 28 gestation week. The study observed that newborns intubated in delivery room more significantly required oxygen supplement in the 40th week in relation to Sweden where NCPAP was more frequently used, which pointed to better outcome with less invasive approach (17,18-23). Data published by Avery, et al., related to North American neonatal intensive care units, where NCPAP was used instead of mechanical ventilation, pointed to reduced mortality rate when using NCPAP (24,25).

Our results show significant differences in the incidence of pulmonary complications, such as pneumonia and pulmonary haemorrhage.

When applied on birth, NCPAP reduces need for surfactant therapy and mechanical ventilation in newborns with less severe RDS (26-29).

CONCLUSION

Respiratory distress syndrome is the most common cause of mortality and morbidity in premature newborns. Use of IPPV in premature newborns with respiratory insufficiency saves life but is also associated with number of complications. NCPAP can result in lower level of lung damage, lower mortality rate and lower incidence of other complications associated with prematurity and assisted ventilation in preterm newborns treated with CPAP due to respiratory distress syndrome. The use of NCPAP results in increased survival rate of premature newborns with small gestational age and weight. Various ventilation techniques are used in the treatment of RDS but currently there is no clear recommendation as to the most efficient one. However, the most efficient technique is the one that stabilizes p02, pC02 and pH to reduce trauma caused by pressure and volume, to reduce possible lung damage and shorten hospitalization duration.

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Efficacy of beta agonists in comparison to other therapy options in acute bronchiolitis of infants and small children: systematic review

Efikasnost beta agonista u odnosu na druge terapijske opcije kod akutnog bronhiolitisa dojenčadi i male djece: sistematski pregled

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ABSTRACT

Introduction: bronchiolitis is the most common respiratory infection of the early infancy and the most common cause for hospitalization of children up to six months of age. Therapeutic options in this disease are rather limited. In everyday clinical practice, beta agonists are widely used in the treatment of this disease, although it has been shown that neither the number of hospitalizations nor the length of the hospitalization is reduced. In 2014, the American Academy of Pediatrics (AAP) has published an updated guide to diagnosis and treatment of bronchiolitis without any recommendation for this type of therapy. The aim of this paper is to examine the efficacy of beta agonists in acute bronchiolitis compared to other therapeutic options. Materials and methods: Pubmed and Cochrane databases have been searched. The search was limited to the last 10 years and to clinical studies. The analysis included nine studies evaluating the efficacy of using beta agonists in hospital and outpatient conditions. Each study was critically evaluated in order to determine the efficacy and safety of the therapeutic use of these drugs. Results: nine studies involved 796 infants and small children up to two years of age. All studies were carried out in the period from 2008 to 2016. The size sample varied from 22 to 186 respondents. Five studies included examination of hospitalized patients whereas four of them were implemented on patients treated in out patient clinics. Based on the study comparing the efficacy of nebulized salbutamol and nebulized epinephrine, the hospitalization lasted longer in the group treated with salbutamol ($p=0.03$). According to the study comparing the efficacy of the therapy with 3% NaCl and salbutamol, the hospitalization was also longer in the groups treated with salbutamol ($p<0.001$). The study which compared the efficacy of nebulized salbutamol and epinephrine, Respiratory Distress Assessment Instrument (RDAI) was lower in the groups treated with salbutamol ($p=0.03$), whereas the study which compares application of therapy with 3% NaCl and salbutamol, RDAI was significantly lower in the groups treated with 3% NaCl. Based on the study which compared the efficacy of combined inhalations applying salbutamol together with saline and hypertonic solutions, the oxygen saturation was significantly lower (in statistical terms) in the groups treated with hypertonic NaCl ($p=0.0001$) and saline solutions ($p=0.037$), while the pulse was statistically significantly lower in the group treated with hypertonic solution ($p=0.044$) and statistically significantly higher in the groups treated with salbutamol ($p=0.0001$). Conclusion: over the last decades, numerous researches on therapeutic options in bronchiolitis have been conducted. Beta agonists, although still widely used, have not demonstrated long-term efficacy in the treatment of infants and young children with bronchiolitis.

Key words: bronchiolitis, infants, beta agonists, oxygen saturation

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 dosta ograničene. U svakodnevnoj kliničkoj praksi beta agonisti se široko upotrebljavaju u terapiji ovog oboljenja, iako je dokazano da ne smanjuju niti broj hospitalizacija niti dužinu hospitalnog boravka. Godine 2014. Američka Akademija za Pedijatriju (AAP) je objavila ažurirani vodič za dijagnozu i tretman bronhiolitisa u kojem ne stoje preporuke za ovu vrstu terapije. Cilj ovog rada je ispitati efikasnost beta agonista kod akutnog bronhiolitisa u odnosu na druge terapijske opcije. Materijali i metode: pretraživali smo Pubmed i Cochrane baze podataka. Pretraživanje smo ograničili na posljednjih 10 godina i na kliničke studije. Analizom je obuhvaćeno 9 studija koje su evaluirale efikasnost upotrebe beta agonista u hospitalnim i ambulantnim uslovima. Kritički je evaluirana svaka studija kako bi se odredila efikasnost i bezbjednost terapijske upotrebe ovih lijekova. Rezultati: u ukupno devet studija bilo je uključeno 796 dojenčadi i male djece dobi do 2 godine. Sve studije su provedene u periodu od 2008. do 2016. godine. Veličina uzorka se kreće od 22 do 186 ispitanika. Pet studija se odnosi na istraživanje na hospitalizovanim pacijentima, a četiri na ambulantno liječenim pacijentima. Kos studije koja poredi efikasnost nebulizovanog salbutamola i nebulizovanog epinefrina, hospitalni boravak je bio duži u grupi koja je primala salbutamol ($p=0.03$). Studija koja poredi efikasnost 3% NaCl i salbutamola, hospitalni boravak je akođer

bio duži u grupi sa salbutamolom (p<0.001). Studija koja poredi efikasnost nebulizovanog salbutamola i epinefrina, RDAI je bio niži u grupi sa salbutamolom (p=0.03), dok u studiji koja poredi 3% NaCl i salbutamol, RDAI je bio signifikantno niži u grupi koja je primala 3% NaCl. Studija koja poredi efikasnost kombinovanih inhalacija salbutamola sa fiziološkim i hipertonim rastvorom i hipertonog i fiziološkog rastvora, saturacija kiseonikom je bila statistički značajno niža u grupama koje su primale hipertoni NaCl (p=0.0001) i fiziološki rastvor (p=0.037), dok je puls bio statistički značajno niži u grupi koja je primala hipertoni rastvor (p=0.044), a statistički značajno viši u grupama sa salbutamolom (p=0.0001). Zaključak: posljednjih decenija provedena su mnogobrojna istraživanja terapijskih opcija kod bronhiolitisa. Beta agonisti, iako i dalje u širokoj upotrebi, nisu pokazali dugoročno efikasnost djelovanja u tretmanu dojenčadi i male djece sa bronhiolitisom.

Ključne riječi: bronhiolitis, dojenčad, beta agonisti, saturacija kiseonikom

INTRODUCTION

Bronchiolitis is the most common respiratory infection in early infancy and the most common cause for hospitalization of children up to six months of age. In the USA, every winter 1-3% of infants are hospitalized due to this respiratory illness. There is no specific bronchiolitis therapy. Beta agonists have been tested in numerous clinical studies. In 2014, the American Academy of Pediatrics (AAP) published an updated guide for diagnosis and treatment of bronchiolitis without any recommendation for this type of therapy.

Definition, epidemiology and patophysiology

The AAP defines bronchiolitis as a prodromal viral infection of the upper respiratory tract followed by the appearance of respiratory effort and wheezing in children up to two years. (1)

Ninety percent of children are infected with respiratory syncytial virus (RSV) by the end of the second year of life, and 40% of them will manifest infection of the lower respiratory tract during primo infection (2). About 100.000 children with bronchiolitis have been annually hospitalized in the United States and the cost of the treatment is estimated at about $ 1.73 billion. Out of the total number of hospitalized children, 2-5% require mechanical ventilation, mainly children with RSV bronchiolitis and present risk factors such as chronic cardiopulmonary disease. Mortality is lower than 1% in children without risk factors, while significantly higher (3-10%) in children with chronic pulmonary disease and congenital heart defects.

The most common cause of bronchiolitis is RSV, in 60% to 75% of all illness cases. (3)

In everyday clinical practice, it is sufficient to know the epidemiological characteristics, age, eventual presence of risk factors and physical finding in the child for the diagnosis of bronchiolitis as a clinical entity (4).

Pathophysiological events are very important in explaining the clinical manifestations of this disease as the purpose of individual therapeutic options. Pathologically there is an inflammation of the small respiratory pathways, bronchioles. The virus has tropism for the bronchial epithelium. These small (up to 300 micron) breathing pathways are completely obliterated by cellular debris and dense mucus, as well as epithelial cells fused in syncytium. Due to non-existence of collateral ventilation, development of disseminated atelectasis and hyperinflation zones occurs.

Therapy for bronchiolitis

Although bronchiolitis, as an entity, has been known for nearly seventy years, unique and clear pharmacotherapeutic guidelines have not been developed yet. Therapeutic options for this disease are quite limited. There are many doubts and controversial data in a daily clinical practice and available literature, and a small number of evidence-based recommendations on effective treatment for this disease that occur frequently and can endanger life. There is no specific therapy for bronchiolitis caused by RSV or other viruses. Treatment includes measures ensuring the child to take enough fluid and to breathe sufficiently independently without significant difficulty (2).

Bronchodilators, such as salbutamol, are still commonly used in treatment of this disease in a daily clinical practice and in primary health care, although it has been shown that they have no significant therapeutic effect. Beta agonists are widely used in the treatment of this disease, although neither the number of hospitalizations nor the length of hospitalization is reduced. In 2014, the AAP published an updated guide for diagnosis and treatment of bronchiolitis without any recommendation for this type of therapy.

In the recent literature, there are many clinical studies focusing on newer therapeutic choices such as hypertonic NaCl in bronchiolitis therapy. Given the pathophysiological events of bronchiolitis which involve inflammation of the pathways and the formation of mucous plugs, the improvement of the mucociliary clearance can be of benefit in the resolution of the disease. Hypertonic solution retracts water by osmosis into the mucus layer thereby reducing its viscosity, and also reduces edema of mucosa and improves mucociliary clearance. The ACP supports the use of nebulized hypertonic NaCl for infants and children hospitalized due to bronchiolitis (6).

This article presents a review of literature that encompasses the efficacy of beta agonists in treating bronchiolitis compared to other therapeutic options.

MATERIALS AND METHODS

Literature review is carried out using the instructions recommended by the PRISMA guide.

Criteria

The criteria for inclusion in the studies was therapeutic effect of nebulized salbutamol compared to other nebulized drugs used in the treatment of acute bronchiolitis in infants and young children. The filters used were: clinical studies, available abstract, last ten years, without any restrictions on the country or languages. Originally, the five-year filter was used, but only two randomized clinical trials were found. Duplicates and all studies primarily related to the therapeutic effect of other nebulised drugs were excluded.

Sources of data and search strategy

We searched the Cochrane and Pubmed databases in the period from 8th to 14th March 2017. The PubMed search strategy was as follows: (bronchiolitis OR acute wheezing) AND (Salbutamol OR Beta agonists) AND (menagament OR treatment) AND (infants OR children).

Selection of studies

Searching for the aforementioned databases 191 articles were found. 16 duplicates were removed. Including the filters: clinical studies, 10-year period and available abstracts, 25 papers were found. Sixteen papers were further excluded because they referred primarily to the study of the efficacy of other therapeutic options in the treatment of bronchiolitis. Therefore, to be included in this systemic review, the study had to meet the following criteria: 1. Study design: clinical studies 2. Respondents: infants up to 24 months of age diagnosed with acute bronchiolitis with the first episode of wheezing and without severe comorbidities such as chronic cardiopulmonary diseases, immunodeficiency, severe neurological diseases, positive family history of asthma, etc. We classified patients to "hospitalized", those who had to be hospitalized and "outpatient" who were admitted and treated in a pediatric outpatient clinic or emergency unit. 3. Interventions and comparisons: salbutamol diluted in saline or hypertonic NaCl solution, distilled water, which was compared to 3% NaCl, saline, epinephrine, magnesium sulfate, ipratropium bromide. 4. The outcomes monitored included: length of hospitalization, clinical score of the bronchiolitis, oxygen saturation, pulse, time needed for bronchiolitis symptom resolution, adverse effects.

Selected and chosen data

Out of nine studies included in this systematic review, the following data were extracted: 1. Characteristics of the study: year of publication, state and author's name. 2. Methods: study design, type of random group sorting, double blind, concealment of group spacing. 3. Characteristics of respondents: sample size, age of respondents, inclusion and exclusion criteria. 4. Interventions and controls: concentration and volume of given nebulized solutions, administration intervals, duration of treatment and co-intervention. 5. Outcomes.

Assessment of the risk of bias

Of all the studies included in the analysis, only one randomized study describes respondents randomly classified in groups by using random number tables (11). In two studies we did not have access to full texts or detailed descriptions (13,15). One of the studies was prospective randomized double blind and other was prospective double blind placebo control study. Seven of the nine listed studies were double blind, which reduced the research bias (8,9,10,11,13,14,15).

RESULTS

Literature search and study selection

Searching the databases based on selected words, 191 articles were found. After eliminating duplicates, adding filters: clinical studies, available abstracts and the five years period, 9 articles were found. Five studies were eliminated because they analyzed the difference in efficacy of nebulized 3% and 0.9% NaCl, (this fact remains unclear), one because it investigated the efficacy of dexamethasone, one because it analyzed the efficacy of 3% and 6% NaCl versus 0.9% NaCl and one because it tested the efficacy of nebulized N acetylcysteine. Only one study remained which analyzing the efficacy of magnesium sulphate compared to salbutamol. Afterwards, the 10 years filter was included and 25 articles were found. Ten articles were eliminated because they studied the effects of hypertonic NaCl, one because it was examining acetylcysteine, one because it examined epinephrine, one helium oxygen, two dexamethasone, and one study because it investigated the effects of respiratory physical therapy. Our study involved 9 studies. The inclusion criteria did not vary significantly between the studies. They maninly included infants with the first episode of wheezing, a mild or moderate clinical picture of bronchiolitis.

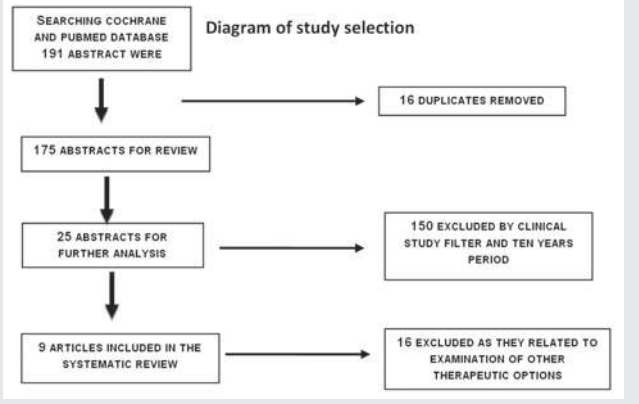

Table 1 Characteristics of the involved studies.

Author of the study, country type of the study	Hospitalized/ Out-patient care	Number of respondents Inclusion criteria	Experimental and control groups	Manner of medicine administration	Results
Modoresi MR, at al. 2012, Iran Controlled clinic study	Hospitalized	40 1–24 months old Acute bronchiolitis	Epinephrine 0.1 ml/kg Salbutamol 1.5 mg/kg	Three doses of each medicine were administered in duration of 10 minutes in the interval of 20 minutes.	LOS longer p=0.03 RDAI lower p=0.03
Kose M at al., 2014,Turkey Double blind prospective study	Outpatient treatment	56 1-24 months old. Retraction, first episode of wheezing CSS 4-8	Salbutam/ Saline MgSO4/ Saline Salbutam/ MgSO4	Inhaled two times in the interval of 30 minutes	Post-treatment mean CSS results were significantly lower than pre-treatment scores in all groups at 4 h with no significant difference within groups
AliZamani M, at al., 2015, Iran Double blind clinical study	Hospitalized	70 < 24 months old First episode of wheezing, RDAI lower then 9	Ventolin / distilled water 3% NaCl/ distilled water	Administered every 4 hours	Shorter LOS and lower RDAI P<0.001

Author of the study, country type of the study	Hospitalized/ Out-patient care	Number of respondents Inclusion criteria	Experimental and control groups	Manner of medicine administration	Results
Ipek IO, et al., 2011, Turkey Double blind randomized controlled clinical study	Outpatient treatment	120 12-24 months old Wheezing, BSS 4-8	Salbutam/ saline Salbutam/3% NaCl, 3% NaCl, 0.9%NaCl	Administered every 20 minutes up to 3 doses. The assessment made 20 minutes after the third dose.	P higher (p=0.0001) P higher (p=0.0001) SpO2 lower (p=0.0001), P lower (p=0.044) SpO2 lower (p=0.037)
Anil AB at al., 2010, Turkey Double blind randomized clinical study	Outpatient treatment	186 1.5– 24 months old First episode of wheezing Clinical score 1-9	Epinephrine/ Saline Epinephrine/ 3% NaCl Salbutam./ saline Salbutam./ 3% NaCl saline	The examined medicine was applied in 0.30 minutes after the patient was received.	BSS, Sao2,P After 120 min were significantly better than initial values (p<0.05), but there was not significant difference in results amongst the groups.
Luo Z. at al., 2010., China Randomized Control Study	Hospitalized	93 1-16.5 months old First episode of wheezing	Salbutam./ 3% NaCl Salbutam./ Saline	Inhaled every 8 hours until release from hospital	Cough, wheezing, crepitation, LOS Better results (P<0.01)
Dli L at al., 2008, the USA Prospective randomized double blind, controlled study	Hospitalized	22 RSV bronchiolitis respiratory insufficiency	Norepinef levalbuterol racemic albuterol Saline	Inhaled every 6 hours	Statistically significant bronchodilation in groups with bronchodilators.
Gupta P, at al., 2008, India Randomized double blind, placebo controlled study	Outpatient treatment	140 infants acute bronchiolitis. R Spo2≥95% RDAI skor≤10.	oral salbutamol placebo	Administered three times a day in seven days or until full resolution of symptoms.	Time of resolution of illness, duration of increased body temp, cough, wheezing, time needed to reassume normal sleeping and feeding, frequency of hospitalization and adverse effects. No sign. diff. in results.
Bulent K., at al. 2008, Turky Randomized double blind, placebo controlled study	Hospitalized	69 Wheezing crepitation	Salbutam/ saline Ipratrop. Bromide/ saline placebo/ saline	Every six hours	Clinical score of illness, Sao2 better in the groups with bronchodilatator There is no diff. in length of hospit.

Characteristics of the study

Table 1 summarizes the characteristics of 9 included studies. The studies were conducted in the USA, Turkey, India, Iran, and China. They were clinical studies, both prospective and randomized, of which seven were double blind. In the total of nine studies, 796 infants and young children aged up to 2 years were included. All selected studies were conducted in the period from 2008 to 2016. The sample size ranged from 22 to 186 respondents. Five studies refer to analysis on hospitalized patients (7,9,12,13,15), one of which relates to pediatric intensive care unit (13). Four studies were conducted on patients who visited the pediatric outpatient clinic and the emergency medical unit (8,10,11,14). Regarding the age of patients included in the study, six of them decisively stated to have included children from one month to two years of age, i.e. from 6 weeks up to two years and one month to 16.5 months. In five of the nine studies, the inclusion criteria was the exact value of the clinical score of the disease (8,9,10,11,14), in one study it was the pulse rate ≤200, the number of respiration ≤70 and the oxygen saturation ≥95% in the room air (14).

Characteristics of ordered therapies

In all studies, therapy was administered in the form of nebulized drugs except for one where salbutamol was administered orally (14). The effect of salbutamol in the bronchiolitis therapy was compared to the effects of other nebulized drugs such as epinephrine, magnesium sulphate, hypertonic NaCl, ipratropium bromide or placebo. In seven out of nine studies we had access to full text, where the concentrations of nebulized drugs given to patients, the amount of nebulized drug in milliliters, as well as the time intervals in which they were ordered were described in detail. In four out of nine studies oxygen was ordered in the form of supportive therapy (7, 8, 10, 11), and in three stidies it was emphasized that parenteral rehydration was given and in one study it was antipyretics for elevated body temperature. Another type of therapy, such as antibiotics, etc., was not ordered to children who were included in any of the above studies. Salbutamol was diluted in saline, hypertonic NaCl solution and distilled water. In four studies combined therapy with magnesium sulphate, hypertonic NaCl and saline was investigated (8,10,11,12). In two studies we only had access to available abstracts with no detailed study methods.

Efficacy of beta agonists in hospitalized patients
Length of hospitalization

Out of the total of nine studies selected for this systematic review of literature, five studies were conducted on hospitalized patients, involving 294 respondents. Four of five studies considered the duration of the hospital stay (7,9,12,15). One study did not have access to full text, so we did not have insight into methods, detailed procedures and outcomes. In the study which compared efficacy of nebulized salbutamol and nebulized epinephrine, length of hospital stay was longer in the group receiving salbutamol, which was statistically significant difference, p=0.03 (7). In the study which compared the efficacy of hypertonic 3% NaCl and salbutamol, the length of hospital stay was longer in the salbutamol group, which was also statistically significant difference, p<0.001 (9). The study which compared the efficacy of ipratropium bromide and salbutamol to the physiological solution, it was concluded that bronchodilators did not shorten the length of the hospital stay (15) and the study which compared efficacy of combined salbutamol and hypertonic NaCl to combined salbutamol and saline, the combination of salbutamol and hypertone solution was shown to be more efficient in terms of shortening the hospital stay (12).

RDAI

*RDAI (Respiratory Distress Assessment Instrument) is a scale for assessing the severity of the disease in infants. Includes scoring scale involving wheezing and retractions.

In the study that compared the efficacy of nebulized salbutamol to nebulized epinephrine, RDAI was lower in the salbutamol group, which was statistically significant difference, p= 0.03 (7). Furthermore, in the study which compared 3% NaCl and salbutamol, RDAI was significantly lower in the group receiving 3% NaCl (9), and in the study comparing ipratropium bromide to salbutamol with saline, clinical score was lower in patients who were on bronchodilator therapy (15).

Other outcomes

In the study investigating the effect of various bronchodilators (norepinephrine, levabuterol, racemic albuterol) in sedated children, intubated on mechanical ventilation, upper inspiratory pressure and inspiratory pulmonary resistance were followed. In the end it was concluded that bronchodilators decrease which led to statistically significant bronchodilation. However, these changes were small and probably clinically insignificant. When considering adverse effects, such as tremor and tachycardia, it was concluded that the benefit of the bronchodilator was small, questionable and did not differ among the tested bronchodilators (13). Bronchodilators improve oxygen saturation, clinical score but do not shorten the length of hospital stay (15).

Efficacy of beta agonists in outpatient respondents

Hospital admissions

Out of nine studies included in this systemic review, four were conducted in the primary health care conditions including the total of 502 children with mild clinical picture of bronchiolitis. Only one of the aforementioned studies as an outcome considers the number of patients admitted after the treatment. Respondents received oral salbutamol and control group received placebo three times a day. There was no statistically significant difference in relation to this outcome between the groups (14).

RDAI, BSC

*BSS (Bronchiolitis severity score) scale for the evaluation of the severity of the clinical picture in bronchiolitis, which includes the respiration rate, wheezing evaluation, retractions and the condition of the child in general.

Clinical bronchiolitis score was taken as an outcome in three of four included studies (8,10,11). Researchers have concluded that salbutamol improves clinical score rapidly short-term. Concerning these outcomes, the combination of salbutamol with magnesium sulphate is superior to magnesium sulphate itself but not compared to the nebulized salbutamol itself (8). The combination of salbutamol and hypertonic NaCl and the combination with saline significantly improve the clinical score, but it has not been shown to be superior to the hypertonic NaCl itself or to the saline itself (10). The combination of salbutamol with saline and hypertonic NaCl solutions was also not shown to be superior to the combination of nebulized epinephrine with saline and hypertonic NaCl (11).

Sodium saturation, pulse

In the study which compared efficacy of combined inhalation of salbutamol with saline and hypertonic NaCl and saline and hypertonic NaCl itself, oxygen saturation was statistically significantly lower in groups receiving hypertonic NaCl (p=0.0001) and saline (p=0.037), while the pulse was statistically significantly lower in the group receiving hypertonic NaCl (p=0.044) and statistically significantly higher in salbutamol groups (p=0.0001) (10). In the study which compared the efficacy of combined inhalation of epinephrine with saline and hypertonic NaCl to salbutamol in combination with saline and hypertonic NaCl, pulse and saturation were significantly lower than initial values ($p<0.05$), but there was not significant difference between the groups. In the study which compared efficacy of salbutamol, magnesium sulfate and their combinations, the pulse was significantly lower in the group that received magnesium sulphate and combined inhalation magnesium sulphate and salbutamol as compared to initial values. There was no significant difference in the salbutamol group compared to the initial pulse rate (8).

When observing outcomes such as the time needed for resolution of the disease, the time needed to establish neat sleep and feeding, no statistically significant difference between placebo and salbutamol was recorded (14).

DISCUSSION

The most controversies in the therapeutic approach in children with bronchiolitis refer to the use of salbutamol and corticosteroids in treatment (2). Several meta-analysis and systemic studies have shown that they can improve clinical score and transient improvements in the clinical picture may be noticed, yet they do not affect the resolution of the disease, the need for hospitalization and length of hospital stay. In everyday clinical practice, beta agonists are widely used in the treatment of this disease, although it has been shown that neither the number of hospitalizations nor the length of hospital stay is reduced. The recently updated Cochrane systematic study evaluates the effect of bronchodilators on oxygen saturation values through 30 randomized control studies including 1992 infants in 12 countries. The results of this study indicate that there is no benefit in terms of clinical score in infants with bronchiolitis receiving bronchodilators. Thus, bronchodilators such as salbutamol or albuterol do not improve oxygen saturation, do not reduce the number of admissions to hospital after outpatient treatment, do not shorten the length of hospitalization, and do not shorten the period of illness resolution at home. Potential adverse effects (tachycardia and tremor) and the cost of these medicines outweigh any potential benefit of them (2). In a study conducted in Canada, where doctors working on pediatric emergency department were surveyed on the use of bronchodilators in bronchiolitis treatment, 66.5% of respondents answered that they "typically" treat children with bronchodilators. Among the respondents, there were two groups: those who preferred to give salbutamol because they could be prescribed for home use and were in a slightly larger number, and the other epinephrine

for this reason proved to be more effective than salbutamol (17). Thus, bronchodilators are still used in the therapy of this disease, although it has been proven through many studies that they have no sufficient therapeutic effect.

From the studies included in this systemic review, salbutamol does not result in shortening of the hospital stay, nor does it reduce the number of hospitalizations after the treatment of outpatient patients. In studies of efficacy of epinephrine with 3% NaCl to salbutamol, the length of hospital stay is longer in those receiving salbutamol (7.9). With regard to the clinical score, it leads to improvements in relation to initial values, but overall, this efficacy is only current and there is no major difference in efficacy compared to other nebulized drugs. And it is indeed questionable, still so widespread, its use in everyday clinical practice. It seems that the clinicians, deciding on the immediate improvement of the clinical condition of small children suffering from bronchiolitis, choose to order this type of therapy. But considering the outcomes such as length of the hospital stay, there is no evidence of the efficacy of this bronchodilator in any study. On the other hand, when we observe the adverse effects of these therapeutic options and their costs, there is a question of cost-benefit in their use.

Del Vecchio MT et al. published the results of a retrospective study in 2012 conducted on 316 subjects during a five year period involving children aged 11 to 90 months admitted to the Temple University Children's Medical Center in Philadelphia, Pensylvania, USA. The aim of this study was to evaluate the effects of albuterol use in infants with RSV positive bronchiolitis in relation to the length of oxygen supplementation and length of hospital stay. Four of the five groups who received albuterol in therapy required longer period of oxygen supplementation and longer hospitalization. In the end, it was concluded that, according to previous research, beta agonists have no place in the treatment of this disease, whatsoever can be harmful, as they prolong the time required for oxygen supplementation and length of hospital stay (18).

This systematic review includes studies from both developed and the less developed countries, so the conclusions made in this way are more valid. Depending on the available literature, the results of this systematic review are summarily consistent with the results of the previous research.

We can say that there are some common shortcomings in all the studies conducted. These include, for example, the inclusion of patients who were not seriously ill, exclusion of patients with asthma, uncertainty regarding dose rates, and similar, and also using different criteria for determining the clinical score. Since only the children with milder and moderately severe clinical presentation were involved in the study, and not children who had severe comorbidities beside bronchiolitis, we needed to be very careful regarding extrapolation of results for all children with bronchiolitis. Furthermore, the saline as a control in the study is not suitable because it improves the mucociliary clearance and affects the clinical picture improvement so it is also useful in treating bronchiolitis. Accordingly, designing a study which would include some irresistible inhaled placebo would be ideal and would make it possible to express the actual role of other nebulized drugs but is ethically questionable.

CONCLUSION

In the last decades, numerous researches on different therapeutic options in bronchiolitis have been conducted. Beta agonists, although still in broad use and leading to short-term improvement in the clinical picture, did not show long-term efficacy in the treatment of infants and young children with bronchiolitis.

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A case of incarcerated umbilical hernia - an unusual finding in the pediatric population

Inkarcerirana umbilikalna kila - neuobičajan nalaz u dječijoj populaciji

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ABSTRACT

Introduction: a hernia is protrusion of any organ through the wall of the cavity in which it normaly reside. Umbilical hernia occurs in 10-30% of white children at birth, decreasing to 2-10% in the first year of life. Although umbilical hernia is common in children, total incarceration rate is considered low, estimated from 0.07 to 0.3%. Aim: The aim of this study was to present statistically unusual case of incarcerated umbilical hernia in the pediatric population, surgically treated at Clinic of Pediatric Surgery of the Clinical Center University of Sarajevo. Case report: a 21-month-old male toddler, referred by the appointed pediatrician, was admitted at the Clinic of Pediatric Surgery suspected with incarcerated umbilical hernia. He had one regular bowel movement on the day of admission and stool was of normal consistency. The vomited matter was yellow. The problem was noticed two months before the admission. Clinically, examination of the abdomen revealed umbilical hernia the size comparable to that of a larger walnut, solid consistency with a bluish skin color above the hernia, irreducible. Surgical procedure in general anesthesia was performed on the day of the admission. Skin and subcutaneous tissue was opened by arch incision in the area of approx 0.5 cm above the upper umbilical region, exposing small intestine, approx. 3-4 cm long, preserved trophic and peristalsis. Intestines were returned into the abdominal cavity. Abdominal wall defect was repaired by linea alba closure (Mayo's repair). Postoperative follow-up was uneventful and the patient was discharged three days after surgery. Six month's follow up did not show any signs of recurrence, surgical incision was healed with good cosmetic appearance. Conclusion: more active monitoring of children with umbilical hernia on primary and secondary healthcare level for preventing incarceration related morbidity is imperative.

Key words: umbilical, hernia, pediatrics, treatment

SAŽETAK

Uvod: Kila je izbočenje bilo kojeg organa kroz zid šupljine u kojoj fiziološki boravi. Umbilikalna kila javlja se kod 10-30% djece bjelačke populacije pri rođenju, smanjujući se na 2-10% u prvoj godini života. Iako je pupčana kila uobičajena kod djece, ukupna stopa inkarceracije smatra se niskom, a procijenjena je na 0,07 do 0,3%. Cilj: prikazati slučaj inkarcerirane umbilikalne kile u dječijoj populaciji koji je hirurški tretiran na Klinici za dječiju hirurgiju Kliničkog centra Univerziteta u Sarajevu. Prikaz slučaja: dječak starosti godinu i devet mjeseci upućen od strane nadležnog pedijatra, primljen na Kliniku za dječiju hirurgiju pod kliničkom sumnjom na inkarceriranu umbilikalnu kilu. Imao jednu uobičajnu stolicu u jutarnjim satima na dan prijema. Povratio dva puta žuti sadržaj. Promjena se javila dva mjeseca pred prijem. U statusu, umbilikalna hernijacija veličine većeg oraha, tvrde konzistencije sa plavičastom kožom iznad, nereponibilna. Učini se operativni zahvat u opštpj anesteziji na dan prijema. Lučnom incizijom u predjelu oko 0,5cm iznad gornje usne umbilikusa otvori se koža i potkožno tkivo kada se ukaže tanko crijevo dužine oko 3-4cm, očuvane trofike i peristaltike. Uslijedi rekonstrukcija trbušnog zida Majo tehnikom. Postoperativni tok se odvija uredno, a pacijent se trećeg postoperativnog dana otpuša kući urednog općeg i lokalnog statusa. Na kontroli nakon šest mjeseci ne nađe se znakova recidiva, operativni rez zarastao uz uredan kozmetski izgled. Zaključak: aktivnije promatranje djece s umbilikalnom kilom na primarnom i sekundarnom nivou zdravsvene zaštite kako bi se spriječila pojava morbiditeta zbog inkarceracije treba da bude imperativno.

Ključne riječi: umbilikus, hernija, pedijatrija, tretman

INTRODUCTION

A hernia is protrusion of any organ through the wall of the cavity in which it normaly reside. Hernias in pediatric population are common development disorder requiring different approach in regard to their equivalents in adults (1).

Umbilical hernia occurs in 10-30% of white children at birth, decreasing to 2-10% in the first year of life (2,3). Incidence of umbilical hernia in African population is estimated to 23-85% (4-6). Exact ethiology exposing the African population to higher incidence has remained unknown (4,5). Risk factors related to the occurrence of umbilical hernia are presented in Table 1.

Table 1 Risk factors for hernia in pediatric population (5).

Risk factors	Umbilical hernia	Inguinal hernia
	• Permaturity • Low birth weight • Down's syndrome • Beckwith-Weidemann syndrome • Hypothyroidism • Children od African descent	• Premature, low birthweight infants (<1kg) (increased rates of up to 30%), 4 x more common in: • males • patinents with connective tissue disorders • patients with conditions which raise intra-abdominal pressure (eg, cystic fibrosis)

Umbilical ring serves to enable the passage of blood vessels through abdominal wall muscles and enable communication between mother and fetus. After the birth, and following umbilical cord disintegration, the ring remains, regressing spontaneously, normally up to the age of five, by development of abdominal muscles and fusion of peritoneum and fascia layers.

Failure or delay in this process leads to the formation of an umbilical hernia. The etiology is unknown, but mostly occurs through the component of umbilical vein (5). Diagnosis of strangulated hernia may be set based on anamnesis and physical examination. Sometimes ordinary abdominal radiographs may show signs of bowel obstruction (6-10).

Although umbilical hernia is common in children, total incarceration rate is considered low, estimated from 0.07 to 0.3%. It has been noted that the incarceration rate in some African populations is high, amounting to even 40% (11-16).

Standard surgical procedure includes infraumbilical or periumbilical incision. A blunt and sharp dissection is performed up to the hernia sac level, which is subsequently opened and explored. Umbilical hernia may contain preperitoneal fat tissue, omentum, small intestine, colon or their combination. Linea alba is closed with individual stitches, as the skin above (17-19). Some surgeons perform laparoscopic correction of the umbilical hernia, although there is no evidence in favor of this approach (20). It is important to warn both patients and parents to eventual bad cosmetics, scars and recurrence possibility. A large cohesion prospective study reported a 2% recurrence rate after the age of 13 (16).

AIM

The aim of this report was to present statistically rare case of incarcerated umbilical hernia, implemented therapeutic procedure and treatment outcome after six-month follow-up, as well as review of literature related to this data.

CASE REPORT

A 21-month-old male toddler, referred by the appointed pediatrician, was admitted at the Clinic. His mother stated his uncontrolled crying on the day of the admission. He had a regular bowl movement in the morning and on the way to hospital he vommited yellow matter twice. When changing his diapers the mother noticed a bluish swelling, the size comparable to that of a larger walnut, which she could not suppress (Figure 1). The problem occurred two months before the admission, which was regularly followed by the appointed pediatrician. Clinical examination showed the following: abdomen under the chest level, soft, insensitive to pain on palpation, umbilical hernia the size comparable to that of a larger walnut, solid consistency with a bluish skin color above, irreducible. Following the usual emergency preoperative preparation, surgical procedure in general anesthesia was performed on the day of the admission.

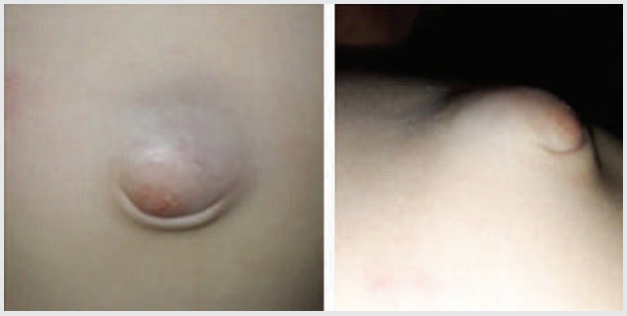

Figure 1 Umbilical hernia at admission.

Skin and subcutaneous tissue was opened by arch incision in the area of approx 0.5 cm above the upper umbilical region, exposing small intestine, approx. 3-4 cm long, preserved trophic and peristalsis (Figure 2). Hernia aperture was enlarged with partial blunt and sharp preparations followed by exploration of the intestine: pathological substrate was not found. Intestines were returned into the abdominal cavity. Abdominal wall reconstruction was done by Mayo's repair technique. Adequate hemostasis is achieved and suture of the subcutaneous tissue and skin and umbilical dressing is done. Postoperatively, patient tolerates food intake, spontaneous stool passage was established, wound regullary bandaged, dry, healing "per primam intentionem". On the third postoperative day the patient was discharged from hospital with normal general and local status, with recommendations related to bandaging and follow up for sutures removal, and taking painkillers if required.

At the six-month follow-up examination, no signs of hernia recurrence were found. Surgical incision was healed with good cosmetic appearance.

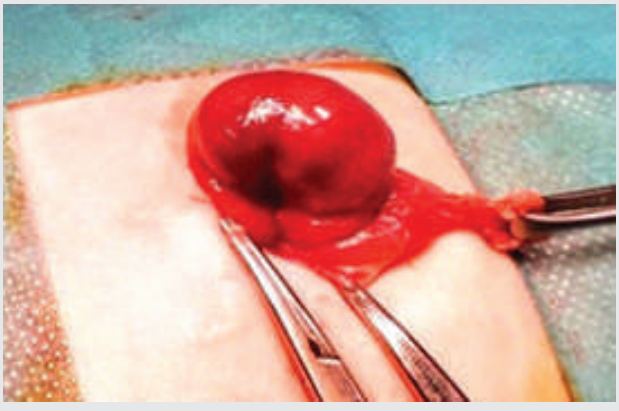

Figure 2 Intraoperative finding

DISCUSSION

A literature review involving different size and quality studies from several countries showed a complication rate of 1:1500 for an umbilical hernia (14). A large observational Nigerian study conducted over the period of 15 years on the sample of 2542 children surgically

treated for umbilical hernia reported two cases of children with strangulated hernia (15).

A retrospective cohort study conducted in the Western Australia on the sample of mixed population reported the 1:3000 risk of incarceration requiring urgent reparation. During the monitoring period, the hospital reported fifty-two children with umbilical hernia. Twenty-three of them (44.2%) were with incarcerated hernia. Seventeen (32.7%) were with acute incarcerated hernia, whereas 6 (11.5%) had recurrent incarcerated hernia. The age of children with acute incarcerated hernia was from 3 weeks to 12 years (median 4 years), whereas the age of children with recurrent incarcerated hernia was from 3 to 15 years (median 8.5 years). Incarceration occurred in 1.5 cm diameter hernias (in those in which size of the defect is measured). Twenty-one children (15 with acute and all six of them with recurrent incarcerated hernia) were subjected to standard treatment of umbilical hernia (21).

A strangulated umbilical hernia is not as rare as thought. Active monitoring of children with umbilical hernia is necessary for preventing incarceration related morbidity (16).

CONCLUSION

It is a common opinion that incarcerated umbilical hernia is rare and that natural course of the disease involves spontaneous closure of the defect within the first five years of life. We report a rare case of strangulated umbilical hernia with preserved intestine vitality, treated with Mayo technique. Active monitoring of children with umbilical hernia is necessary for preventing morbidity related to incarceration is imperative.

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The role of giant macroadenoma resection in psychotic vs. prolactin disorder: two year follow-up

Uloga resekcije gigantskog makroadenoma u psihotičnom naspram prolaktinskog poremećaja: dvogodišnje praćenje - prikaz slučaja

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ABSTRACT

Introduction: psychosis is defined by presence of hallucinations, delusions or both. Sometimes, the only presentation of brain tumours in general may be psychosis. However, pituitary tumours are also found in association with psychosis. Aim: to present the patient outcome with psychosis associated macroadenoma two years after resection. Case report: 36-year-old male psychiatric patient was managed for acute polymorphic psychotic disorder with symptoms of schizophrenia. After stabilization of disease the therapy was excluded in 2009. In 2016, the patient had been examined by neurosurgeon due to recurrence of psychotic episodes. One month prior to admission to our department disconnected speech, restlessness and aggression with sleep disturbance were found. A giant skull base tumour in the sphenoidal sinus, sellar, parasellar and clival region was found with hyperprolactinemia of 255,000 μIU/ml (reference values for males 78-380 μIU/ml). The patient underwent a transfacial skull base approach with subtotal tumour resection. Postoperatively, the prolactin level decreased to 96,280 μIU/ml initially and 10230 μIU/ml in last control examination. In 2017 the patient was re-hospitalized due to anxiety and stereotyped behaviour. Conscious and disorientation were major complaints while it was difficult to establish contact due to distant thought flow followed by agitation and aggression. Regression of symptoms was achieved through antipsychotic therapy. After two years, final magnetic resonance imaging (MRI) scan showed a satisfactory postoperative finding with tumour regression and a residual component in both cavernous sinuses with no signs of compressive effect to the basal forebrain. Conclusion: Pituitary tumours and psychiatric disorders are quite rare in association. While the presence of endocrinological disturbances is a good indication for the possible need of surgery, diagnosis of psychiatric disorders is not. According to extreme hyperprolactinemia and tumour location surgery provides good results and a fast decline in prolactin level. Even though symptoms were found in regression, the exact relation between giant adenomas resection and psychotic disorder regression could not be well established for two years follow up. Cases like this require a multidisciplinary approach due to possible adverse effects of drugs and potential substitute therapy requirements.

Key words: pituitary adenoma, hyperprolactinemia, psychotic disorder

SAŽETAK

Uvod: Psihoza je definisana prisutnošću halucinacija, deluzija ili oboje. Nekada se, kao jedina manifestacija tumora mozga može javiti psihoza. Također, pituitarni tumori se mogu javiti u korelaciji sa psihozom. Cilj: Prikazati ishod pacijenta sa makroroadenomom povezanim sa psihozom dvije godine nakon resekcije. Prezentacija slučaja: Pacijent starosne dobi 36 godina je tretiran od 2004. godine kao akutni polimorfni psihotični poremećaj sa simptomima šizofrenije. Nakon stabilizacije bolesti terapija je isključena 2009. Godine 2016., pacijenta je pregledao neurohirurg zbog recidiva psihotičnih epizoda. Mjesec dana prije prijema na naš odjel pojavili su se nepovezan govor, nemir i agresija sa poremećajem spavanja. Pronađen je giganstski tumor baze lobanje u sfenoidalnom sinusu, selarnoj, paraselarnoj regiji i klivusu, je evidentiran uz hiperprolaktinemiju od 255, 000 μIU/ml (ref vrijednosti za muškarce 78-380 μIU /ml). Pacijent je tretiran transfacijalnim skull base pristupom sa subtotalnom resekcijom tumora. Postoperativno, nivo prolaktina smanjio se na 96,280 μIU/ml u početku i 10230 μIU/ml na posljednjem kontrolnom pregledu. U 2017 godini pacijent je ponovno hospitaliziran zbog anksioznosti i stereotipnog ponašanja. Svijest i dezorijentacija bile su dominantne tegobe dok je bilo teško uspostaviti kontakt zbog distanciranog toka misli praćenog uznemirenošću i agresivnošću. Regresija simptoma postignuta je antipsihotičkom terapijom. Nakon dvije godine, kontrolno snimanje magnetskom rezonancom (MRI) pokazalo je zadovoljavajući postoperativni nalaz s regresijom tumora i manjom rezidualnom komponentom u oba kavernozna sinusa bez znakova kompresijskog učinka na bazalni mozak.

Zaključak: Pituitarni tumori i psihotični poremećaj su veoma rijetki u korelaciji. Dok su endokrinološki poremećaji dobro definirani kao indikacija za hirurgiju, psihijatrijski poremećaji su veoma upitni. Posmatrajući ekstremne vrijednosti prolaktina i lokaciju tumora, hirurgija pruža dobre rezultate i brzu deklinaciju prolaktinskih vrijednosti. Iako su psihotični simptomi u regresiji, tačan odnos resekcije giganstkog adenoma i psihotičnog poremećaja se ne može uspostaviti, nakon dvije godine praćenja. Slični slučajevi zahtjevaju multidisciplinarni pristup shodno mogućim sporednim efektima lijekova i potrebe za supstitucionom terapijom.

Ključne riječi: adenomi hipofize, hiperprolaktinemija, psihotični poremećaj

INTRODUCTION

According to DSM-5, disordes is classified as psychotic or on the schizophrenia spectrum if presented symptoms include hallucinations, delusions, disorganized thinking, grossly disorganized motor behavior, or negative symptoms (1). Rarely, the only presentation of brain associated tumours may be psychosis and this is most common for tumours found in the pituitary gland region (2). As stated in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), F06.2 is classified as Organic delusional (schizophrenia-like) disorder, which primarily occurs due to cerebral disease. Additionally, diagnosis F23.1 is classified as an acute polymorphic psychotic disorder with symptoms of schizophrenia, for which there is no indication of organic causation (3). Pituitary adenomas are the most common form of tumour occurring in the sellar region and are also the most common cause for pituitary disease in adults (5). In pituitary disease, some of the presented symptoms include acromegaly, severe depression, strong headaches, drug-seeking behaviour and other psychological disturbances (6). Therefore, the aim of this case report is to observe the correlation between sellar tumours and psychosis and other cognitive processes.

AIM

To present the patient outcome with psychosis associated macroadenoma two years after resection.

CASE REPORT

We present a 36 years old psychiatric patient managed since 2004 as acute polymorphic psychotic disorder with symptoms of schizophrenia. After stabilization of disease the therapy was excluded in 2009. The patient was evaluated by a neurosurgeon in 2016 after psychotic episodes. One month prior to admission to our department disconnected speech, restlessness and aggression with sleep disturbance were found. The patient was admitted and treated at the Psychiatric Clinic. However, Computed Tomography (CT) followed by brain Magnetic Resonance Imaging (MRI) was performed. A giant skull base tumour in the sphenoidal sinus, sellar, parasellar and clival region was found with hyperprolactinemia of 255,000 μIU/ml (reference values for males 78-380 μIU/ml). The patient underwent a transfacial skull base approach with subtotal tumour resection. A residual part of the tumour in both cavernous sinuses was left intentionally as a part of surgical strategy. The pathohistological finding confirmed pituitary adenoma. The early postoperative course was uneventful with regular control examinations by a psychiatrist. Postoperatively, the prolactin level decreased to 96,280 μIU/ml. The patient was transferred to the Department for Endocrinology for further treatment. The early postoperative brain MRI showed tumour subtotal resection. Still, disorientation with impaired cognitive function and dementia were presented and antipsychotic therapy was administered.

The patient was re-hospitalized at the Psychiatric Department in 2017, due to appearance of anxiety and symptoms of schizophrenia. Patient's major complaints were conscious disorder and disorientation. Also, it was difficult to establish contact due to patients agitation and aggression. If endocrinological therapy (cabergoline - a dopamine receptor agonist) influenced psychotic decompensation, the same therapy was excluded by a psychiatrist until the end of hospital treatment. Regression of symptoms was achieved through antipsychotic therapy. At the last annual check by an endocrinologist (in 2019), prior to planned monthly therapy prolactin levels of 10230 μIU/ml and low testosterone values of 1.2 nmol/L (reference values 4.6-23.2 nmol/L) were noticed. Regular hormonal substitution therapy with thyroxine and testosterone was ordinated. After two years final MRI showed a satisfactory postoperative finding with tumour regression and a residual component in both cavernous sinuses with no signs of compressive effect to the basal forebrain. The patient's current therapy includes Clozapine to be taken three times a day and a control examination every two months. In the final neurosurgical control exam, the patient was fully conscious without neurological disturbances.

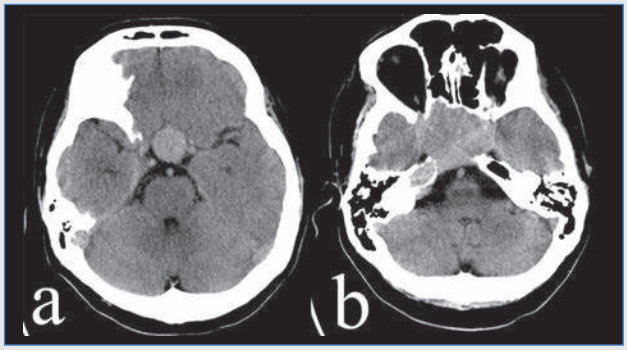

Figure 1 Image A and B: Preoperative CT scans. Hyperdense zone in the sellar region marks the tumour.

Note the tumour extension in the parasellar region. The tumour involves both cavernous sinuses.

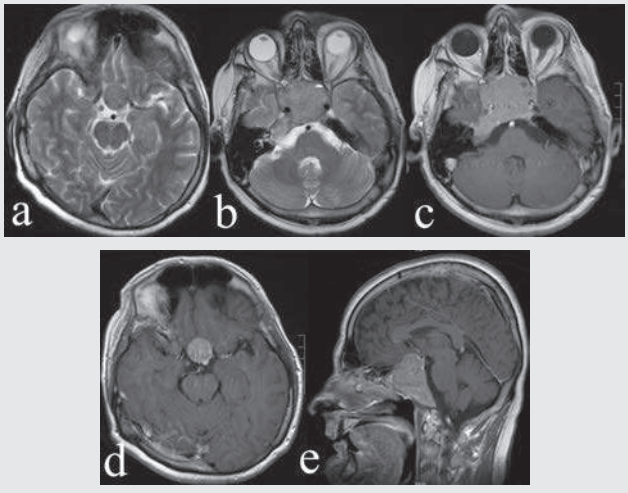

Figure 2 Image A and B: Preoperative MRI scans.

Note the tumour in the sellar region with lateral extensions in both cavernous sinuses. Both Internal Carotid Arteries are seen in their cavernous part. Image C, D and E. Gadolinium contrast MRI sequence in axial and sagital planes. Please note the contact between the tumour and the basal frontal lobe in the sagital scan. The tumour is extended distally in the clival region. The whole sphenoidal sinus area was involved in the tumour.

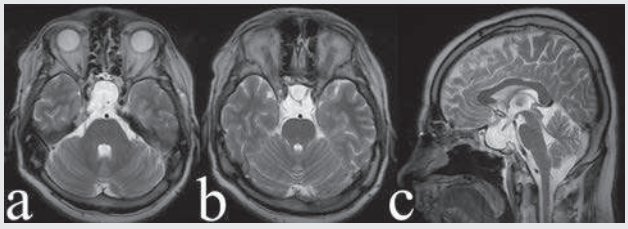

Figure 3 Images A, B and C: Postoperative T2 MRI images axial and sagital scans.

Postoperative residual cavum in sellar region after tumour resection. Note the optic chiasm in image B. There is no more compressive effect by tumour to the basal frontal lobe.

DISCUSSION

Brain tumours are a relatively frequent with the incidence of 10.82 per 100,000 persons per year (7). Presence of brain tumours may be followed by psychiatric symptoms (8), particularly in frontal or temporal regions. According to a meta-study analyzed by Madhusoodanan et al, in 22% of cases psychotic symptoms have been found in brain tumour patients (4). Nowadays, sellar tumours are rarely associated with psychotic syndrome.

In this illustrated case, the patient suffered from tumour in sellar region with psychiatric diagnosis as well (F 23.1). As one of the main symptoms was hyperprolactinemia, the patient underwent endocrinological treatment. Whether his endocrinologist treatment or macroadenoma caused any symptoms is uncertain. There are multiple case reports showing possible correlation between cabergoline and psychosis (9, 10, 11). However, our patient was presented with a giant skull base tumour with suprasellar extension which produced loss of visual aquity. We noticed in preoperative MRI scans that there was a direct contact between the basal frontal lobe and the tumour with possible compressive effect. (Figure 2C) It has been previously reported that tumor located in frontobasal region, due compressive effect on the frontobasal brain, could lead to psychiatric symptoms (12).

The patient underwent subtotal tumour resection by transfacial approach with usual postoperative outcome.

Some reports found most likely localized tumour in the pituitary gland if a patient experiences psychotic symptoms (8). In the period after the surgery, significant improvement in psychotic symptoms was not noticed in our case, an assumption that a correlation between psychosis and presence of pituitary tumour with suprasellar extension could not be proposed. We have noticed tumour reduction in early MRI scans but without expected descensus of the suprasellar component. However, visual improvement was noted. In a recent review done by Pertichetti et al, it is claimed that in patients with pituitary adenoma, after the operation, short-term memory, psychomotor speed and general quality of life had improved (13). Since our surgical strategy to prevent cerebrospinal fluid (CSF) leak is packing of the sphenoidal sinus with adipose tissue it could be the reason for still presented partial compressive effect to the basal part of frontal lobe followed by symptoms (Figure 3).

The other possible mechanism of symptoms presence was that we surgically blocked the pathway for the prolactin-inhibiting factor from the hypothalamus to the prolactin-secreting cells in anterior pituitary lobe.

Patient's initial prolactin levels were 255,000 μIU/ml. These extremely elevated levels could be explained by the presence of functional macroadenoma. After surgery, the patient's prolactin levels have decreased to 96, 280 μIU/ml, and are now 10230 μIU/ml. Although they are still above the normal value, they have overall decreased by 96%. Furthermore, there is a suggestion that tumour formation could be promoted with usage of first generation of antipsychotic drugs (14) which acts as dopamine antagonists (15,16). However, our patient was treated only with second generation antipsychotic drug clozapin what seems to increase pituitary hormone levels in general but without prolactin influence (14,17). Since the patient's last MRI scan shows that there is no residual tumour except in cavernous sinuses, it could be proposed that the absence of "functional" tumour leads to a decrease in prolactin levels. The value of 10230 μIU/ml was possibly related to existing adenoma in cavernous sinuses or decreased hypothalamic inhibition. However, we have not discussed additional surgery or stereotactic radiosurgery due to increased risk of cranial nerves deficit and satisfactory results with substitutional therapy.

Seven months after surgery, the patient was administered back to Psychiatry Department with similar symptoms but now organic delusional (schizophrenia-like) disorder. We could not find a correlation between tumour removal and diagnosis code shift. An earlier study by Mamta Sood et al. presented a patient who, even after surgery, still suffered from psychiatric disorder and consequently had to be treated with psychiatric approach but with the same IDC code (6). There are studies suggesting that tumours could be the underlying etiology of psychiatric disorders with an emphasis being on high values of prolactin (18,19,20). This study shows that more research should be done on the correlation between psychosis and pituitary adenomas and leads us to the conclusion that macroadenoma could have affected hyperprolactinemia, but psychotic symptoms could not be excluded to hyperprolactinemia only.

CONCLUSION

Pituitary tumours and psychiatric disorders are quite rare in association. While endocrinological disturbances are well defined as an indication for surgery, psychiatric disorders are quite doubtable. According to extreme hyperprolactinemia and tumour location surgery provides good results and a fast decline in prolactin level. Even though the symptoms were found to be in regression during the two years follow-up control exam, the exact relation between giant adenomas resection and psychotic disorder regression could not be established. Similar cases demand a multidisciplinary approach due to possible drug side effects and substitute therapy requirements.

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Literatura se obavezno citira po **Vankuverskim pravilima**.

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