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Original article

Magnetic resonance imaging of the heart as a method of long-term monitoring of right heart function after tetralogy of Fallot surgery

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Summary

Introduction. Cardiac magnetic resonance imaging (CMR) is considered the reference diagnostic method for quantifying right ventricular size and function, and pulmonary regurgitation in patients with tetralogy of Fallot surgery. The aim of this paper is to confirm the importance of magnetic resonance continuous postoperative monitoring of right and left heart function parameters as a diagnostic method that provides the most precise and accurate assessment.

Methods. The prospective observational study included subjects with TOF surgery who were diagnosed with residual morphological and/or functional disorders on control postoperative echocardiographic examinations. All subjects underwent magnetic resonance imaging of the heart on a 1.5 T scanner with dedicated coils for the heart surface according to the standard protocol for a period of one year from the beginning of the study. Criteria for exclusion from the study were: significant residual pulmonary stenosis, condition after pulmonary valve replacement, existence of residual shunt lesions, contraindications for cardiac magnetic resonance imaging (pacemaker, ICD, claustrophobia). Depending on the time elapsed since the tetralogy of Fallot surgery, the subjects were divided into groups: more than 15 years, 11–15 years, 6–10 years, less than 5 years.

Results. The study included 131 subjects with an average age of 24.18 ± 11.57 years with complete correction of TOF. Intergroup differences in values of right ventricular end-diastolic volume, right ventricular ejection fraction, and left ventricular ejection fraction were demonstrated, but there was no statistically significant intergroup difference in values of pulmonary regurgitation fraction. The negative interaction of the right and left ventricles intensifies during the years of follow-up of patients after TOF surgery, which is especially true fifteen years after surgery.

Conclusion. CMR has the most significant role in research efforts aimed at improving the outcomes of operated patients with tetralogy of Fallot.

Key words: tetralogy of Fallot, right ventricular dysfunction, cardiac magnetic resonance imaging

Introduction

In the longitudinal follow-up of patients operated for tetralogy of Fallot, the detection of morphological and hemodynamic residual disorders in asymptomatic and symptomatic patients is of great importance in order to decide on new therapeutic measures, such as pulmonary valve replacement, in order to improve the course and outcome of treatment [1]. Therefore, it

is important to identify risk factors for sudden cardiac death, as well as serious complications such as ventricular tachycardia and heart failure in patients with tetralogy of Fallot (TOF). Improved surgical procedures have reduced early mortality to less than 3%, but the annual mortality rate has multiplied 20–30 years after initial surgical remediation, mainly due to adverse cardiac events.

Pulmonary regurgitation (PR) is the most common complication in patients with TOF surgery, which is associated with progressive dilatation and impaired right ventricular systolic function (RV), and it adversely affects left heart function and geometry due to unfavorable ventriculo-ventricular interaction [5–11]. The ratio of right and left ventricular volume is a significant predictor of PR severity and right and left heart dysfunction [12–14]. Therefore, surgical replacement of the pulmonary valve is associated with a significant reduction in RV volume and an increase in right and left ventricular systolic function, shortening the duration of the QRS complex, improving symptoms, and NYHA functional class [15]. Other residual disorders after TOF surgery include tricuspid regurgitation, dysfunction, aortic root dilatation and ascending aorta, aortic regurgitation, residual atrial and ventricular septal defect, right ventricular outflow tract aneurysm, pulmonary artery branch stenosis.

Rhythm disorders are common in patients operated on for TOF: right-branch block with prolongation of the QRS complex is present in most patients; atrial flutter or fibrillation and ventricular tachycardia do not appear until the third or fourth decade of life. Cardiac magnetic resonance imaging (CMR) is considered a reference diagnostic method for quantifying right ventricular size and function and pulmonary regurgitation in patients with TOF surgery, as it provides a comprehensive accurate assessment of right and left heart morphology and physiology, and contributes to optimal types and times of reintervention [20–22]. The aim of this paper is to confirm the importance of magnetic resonance continuous postoperative monitoring of right and left heart function parameters as a diagnostic method that provides the most precise and accurate assessment.

Methods

The research included respondents with TOF surgery who in the period from 1 January 2012 to 30 September 2016 were diagnosed with residual morphological and/or functional disorders at postoperative control echocardiographic examinations. All subjects underwent magnetic resonance imaging of the heart within a period of one year from the beginning of the study.

Criteria for inclusion in the study were: asymptomatic subjects regardless of age who underwent complete correction of tetralogy of Fallot, and who were diagnosed with pulmonary regurgitation as the leading residual hemodynamic disorder at postoperative control echocardiographic examinations.

Criteria for exclusion from the study were: significant residual pulmonary stenosis, condition after pulmonary valve replacement, existence of residual shunt lesions, contraindications for cardiac magnetic resonance imaging (pacemaker, ICD, claustrophobia).

Depending on the time elapsed since the tetralogy of Fallot surgery, the subjects were divided into groups: more than 15 years, 11–15 years, 6–10 years, less than 5 years. The study was approved by the competent ethics committee.

Subjects underwent cardiovascular magnetic resonance imaging (CMR) according to a standard protocol. Magnetic resonance imaging of the heart was performed on a 1.5 T scanner with dedicated coils for the heart surface. Using two-dimensional high-speed shooting, steady-state acquisition sequences (steady-state free precession) in the short axis

direction were used. Recording parameters were as follows: flip angle 45°, echo time (TE) set to full minutes, repeat time (TR) 3.4–3.6 ms, cross-sectional thickness 8 to 9 mm, spacing 0 to 1 mm, 12 views/ segment, 111 KHz reading bandwidth, rectangular field of view (30–34 cm) and 160 scan matrix. Twenty-four phases per cardiac cycle were reconstructed retrospectively.

Pulmonary valve flow measurement was performed perpendicular to the flow using a standard two-dimensional retrospective-sensitized flow sequence. Thirty heart phases were reconstructed retrospectively. The recording parameters were as follows: two-dimensional fast faulty gradient echo, TR 6 to 7 ms, TE 3 ms, rotation angle 20°, reading bandwidth 90 KHz, 6 mm cross-sectional thickness, 6 views/segment, rectangular field of view (75% direction of infusion coding) and a scan matrix of 256 • 128. Recording was performed at rest and after administration of low doses (7.5 μg/kg-1/min-1) and high doses (20 μg/kg-1/min-1) dobutamine. Contraindications to the use of dobutamine were previous persistent ventricular tachycardia (often recurrent), supraventricular tachycardia, and obstruction of ventricular inflow or outflow. Available workstations were used for CMR analyzes. The volumetric data set of the ventricles was quantitatively analyzed using manual delineation of endocardial boundaries in end-systole and end-diastole excluding large trabeculae (visible at the next 3 cross-sections) and papillary muscles from blood volume. Biventricular end-diastolic volume, end-systolic volume, ejection fraction (EF) and valvular regurgitation fraction were calculated and compared with reference values.

The parameters of right ventricular dysfunction analyzed on CMR are: corrected right ventricular ejection fraction (cor RV-EF), regurgitation volume (RVol) and pulmonary regurgitation fraction (PRF).

The parameters of ventriculo-ventricular interaction analyzed on CMR are: the ratio of end-diastolic volumes of the right and left ventricles (RV/LV) and paradoxical movements of the interventricular septum.

Based on the severity of pulmonary insufficiency, i.e. gradation of the pulmonary regurgitation fraction (PRF) diagnosed with CMR, the subjects were divided into groups: mild (PRF <20%), moderate (PRF 21%–40%) and severe (PRF> 41%) regurgitation. The PRF value represents the retrograde-to-anterograde flow ratio on the pulmonary valve expressed as a percentage.

Based on the size of the right ventricle, i.e. RV-EDV (Right ventricle-End diastole volume) the subjects were divided into groups: mild dilatation RV (RV-EDV 110–140 mL/m2), moderate dilatation (RV-EDV 141–170 mL/m2) and severe dilatation (> 170 ml/m2).

Based on the values of the ejection fraction (EF) of the right ventricle, the subjects were divided into two groups: subjects with preserved (RV-EF ≥45%) and reduced ejection fraction (RV-EF <45%).

Statistical analysis of the data was done using the SPSS 24.0 statistical software package. Descriptive data are presented as absolute numbers, frequencies, percentages, average values +/- standard deviations, minimum and maximum values. The χ2-square test or Fisher's test of exact probability was used out of the nonparametric statistical tests, as well as the Mann-Whitney U test for ordinal data. Among the parametric tests, the independent samples t test and one-factor analysis of variance - ANOVA were used. Linear regression or Pearson/Spearman rank correlation was used to investigate the correlation.

Results

The study included 131 subjects with complete TOF correction who were diagnosed with residual hemodynamic and morphological disorders, primarily pulmonary regurgitation, at postoperative control echocardiographic

examinations. 52.7% of respondents were male and 47.3% were female. The mean age of the subjects was 24.18 ± 11.57 years. The group younger than 17 years consisted of 40 respondents (30.5%) with an average age of 12.95 ± 3.27 years. The group older than 17 years consisted of 91 respondents (69.5%) with an average age of 29.12 ± 10.4 years. 36 (27.5%) respondents had mild PRF, 45 of them had moderate PRF (34.4%) and 50 (38.2%) respondents had severe PRF.

Right ventricular dilatation was not found in 59 (45%) respondents, while 43 (32.8%) respondents had mild dilatation, 17 (13%) respondents had moderate dilatation, and 12 (9.2%) had severe dilatation of the right ventricle.

Preserved ejection fraction of the right ventricle was found in 100 (76.3%) respondents, while 31 (23.7%) respondents had reduced EF-RV. TOF surgery was performed more than 15 years ago in 72 (55%) subjects, 11–15 years ago in 35 (26.7%), 6–10 years ago in 17 (13%) respondents, while 7 (5.3%) of respondents were operated on in the last 5 years.

One-factor analysis of variance - ANOVA examined the dependence of the time elapsed on TOF surgery (less than 5 years, 6–10 years, 11–15 years, more than 15 years) and end-diastolic volume of the right ventricle. A high statistically significant difference was observed between the examined groups ($F = 4.105$, $p = 0.008$) (Table 1).

A statistically significant difference in the mean values of the ejection fraction of the right ventricle was observed between the group of subjects who had surgery less than 5 years ago and the group of subjects who had surgery 6–10 years ago, and between the group of subjects who had surgery 6–10 years ago and the group of subjects who had surgery 11–15 years ago. A high statistically significant difference ($p = 0.001$) was also observed between the group who were operated on 6–10 years ago and the group who were operated on more than 15 years ago. The obtained results are shown in Table 1.

A high statistically significant difference ($p = 0.001$) in the mean values of the ejection fraction of the left ventricle was observed between the group of subjects who underwent the surgery 6–10 years ago and the group of subjects who underwent the surgery 11–15 years ago. A high statistically significant difference ($p = 0.004$) was also observed between the group who underwent the surgery 11–15 years ago and the group who underwent the surgery more than 15 years ago. The results are shown in Table 1.

No statistically significant differences in the mean values of the pulmonary regurgitation fraction were observed between the groups of subjects divided on the basis of the time period from the operation (Table 1).

No statistically significant differences in the mean values of end-diastolic volume of the right and left ventricles were observed between the groups of subjects divided on the basis of the time period from the operation (Table 1).

No statistically significant differences in the mean values of the corrected ejection fraction of the right ventricle were observed between the groups of subjects divided on the basis of the time period from the operation (Table 1).

Linear regression showed that the EDV-RV/EDV-LV ratio has a higher beta coefficient ($\beta = 0.461$) and is a statistically significant ($p = 0.001$) predictor of the severity of pulmonary regurgitation compared to RV-EDV ($\beta = 0.047$, $p = 0.711$).

Discussion

The study included 131 subjects with an average age of 24.18 ± 11.57 years with complete correction of TOF who were diagnosed with residual hemodynamic and morphological disorders, primarily pulmonary regurgitation, on postoperative echocardiographic examinations.

Table 1. Statistical analysis of parameters of ventricular (dys)function on CMR

Parameter of ventricular (dys)function on CMR (SV ± SD)		F ip (between groups)		p (within groups)	
		F	p	Time elapsed from surgery	p
End-diastolic volume of the right ventricle (ml/ m2)					
<5 years				6–10 years	0.883
6–10 years	86.31 ± 28.48			11–15 years	0.470
11–15 years	99.01 ± 30.36			<5 years	0.263
> 15 years	115.50 ± 26.42	4.105	0.008	<5 years	0.048
6–10 years	126.20 ± 45.09			> 15 years	0.048
11–15 years				> 15 years	0.553
Right ventricular ejection fraction (%)					
<5 years				6–10 years	0.599
6–10 years	59.98 ± 8.64			11–15 years	0.986
11–15 years	55.94 ± 7.76			<5 years	0.383
> 15 years	55.20 ± 6.78	13.215	0.001	<5 years	0.001
6–10 years	48.25 ± 7.17			> 15 years	0.001
11–15 years				> 15 years	0.001
Left ventricular ejection fraction (%)					
<5 years				6–10 years	0.998
6–10 years	66.11 ± 7.85			11–15 years	0.656
11–15 years	66.65 ± 5.80			<5 years	0.919
> 15 years	64.22 ± 3.81	8.119	0.001	<5 years	0.071
6–10 years	59.17 ± 8.41			> 15 years	0.001
11–15 years				> 15 years	0.004
Pulmonary regurgitation fraction (%)					
<5 years				6–10 years	0.991
6–10 years	28.64 ± 13.54			11–15 years	0.884
11–15 years	31.00 ± 13.74			<5 years	0.831
> 15 years	34.80 ± 18.43	0.347	0.791	<5 years	0.944
6–10 years	32.53 ± 18.14			> 15 years	0.988
11–15 years				> 15 years	0.923
The ratio of end-diastolic volume of the right and left ventricles					
<5 years				6–10 years	0.999
6–10 years				11–15 years	0.842
11–15 years	1.45 ± 0.35			<5 years	0.892
> 15 years	1.47 ± 0.26	20.814	0.488	<5 years	0.739
6–10 years	1.61 ± 0.36			> 15 years	0.561
11–15 years	1.67 ± 0.68			> 15 years	0.953
Corrected right ventricular ejection fraction (%)					
<5 years				6–10 years	0.667
6–10 years	43.40 ± 13.30			11–15 years	0.882
11–15 years	37.81 ± 9.53	2,295	0.081	<5 years	0.297
> 15 years	35.42 ± 9.64			<5 years	0.100
6–10 years	33.38 ± 11.58			> 15 years	0.439
11–15 years				> 15 years	0.901

Surgical replacement of the pulmonary valve has been associated with a significant reduction in RV volume and an increase in right and left ventricular systolic function, shortening the duration of the QRS complex, improving symptoms, and NYHA functional class [15]. The ratio of right and left ventricular volume is a significant predictor of PR severity and right and left heart dysfunction [12–14]. As a relative indication for the replacement of the pulmonary valve, as in other congenital heart diseases, effort intolerance can be taken, i.e. reduced exercise capacity, but outcomes may be better if surgery is performed before the heart is dilated and before clinical status deteriorates [23].

In patients with symptoms of exercise intolerance, improvement in symptoms may be expected after pulmonary valve replacement, but no improvement in formal exercise testing parameters has yet been confirmed. In early childhood to the second decade of life, pulmonary regurgitation is well tolerated, and from the second decade of life it is associated with an increased risk of death due to ventricular arteries [23–26].

In order to determine the optimal time for lung valve replacement, a number of papers have analyzed preoperative RV volume limit values above which there is no postoperative reduction or normalization of RV size.

Villafañe et al. in their work published a "cut-off" value of 160 ml/m2 for normalization of RV end-diastolic volume and 82 ml/m2 for RV end-systolic volume [27].

Geva et al. in her study (multivariate cohort analysis) identified a preoperative RV-ESV index <90 ml/m2 and a QRS duration <140 ms, which would be associated with an optimal postoperative outcome (normal RV size and function), and an RV-EF <45% and QRS ≥160 ms were associated with suboptimal postoperative outcome (RV dilatation and dysfunction) [3, 4, 20].

Indications for any surgical intervention exist when the benefits outweigh the risks and when reinterventions can positively change the course of the disease. Indications for pulmonary valve replacement (PVR) can potentially include objective indications such as reduced mortality. Other acceptable indications would include alleviation of symptoms and improvement of quality of life [24, 25, 28].

In our study of 131 subjects, 76.3% of subjects had a preserved right ventricular ejection fraction, while 23.7% of subjects had reduced EF-RV.

Severe pulmonary regurgitation (PR) is usually associated with a regurgitation fraction of over 40%, which is generally well tolerated over a long period of time. However, PR worsens under conditions of increased pulmonary artery pressure, e.g. in pulmonary artery branch stenosis, acquired bronchopulmonary disease, left ventricular dysfunction, or pulmonary vascular disease. The adaptive RV response to the volume of load resulting from PR depends not only on the degree and duration of pulmonary regurgitation, but also on the characteristics of the right ventricle and pulmonary arteries. The volume load of the right ventricle causes an increase in EDV-RV, but with time also an increase in ESV-RV, which leads to a progressive deterioration of myocardial function. In adulthood, poor adaptation of the hypertrophied and noncompliant right ventricle to excessive volume load of significant PR leads to progressive deterioration and dysfunction of the right heart.

The time period elapsed from the operation to our research for the largest number of our respondents was longer than 15 years (45%), and the smallest number of our respondents was operated on in a period shorter than 5 years. This is explained by the fact that CMR examination is rarely performed in children in the relatively early postoperative period (up to 5 years), and when it is performed it means that there are significant sequelae after surgery. For this reason, this group of children is not similar to other age groups. One-way analysis of variance - ANOVA examined the influence of time elapsed since

TOF surgery (less than 5 years, 6–10 years, 11–15 years, more than 15 years) and end-diastolic volume of the right ventricle, as a parameter of size and global RV function. A high statistically significant difference was observed between the examined groups ($F = 4.105$, $p = 0.008$). This indicates the fact that EDV-RV worsens during the years of follow-up, especially 15 years after the surgery. Based on this, it can be concluded that more frequent controls and adherence to the algorithm of diagnostic procedures in the time after surgery, including cardiac magnetic resonance imaging, are needed, especially for subjects who underwent surgery 15 years ago [29].

Statistical analysis of the data showed intergroup differences in the values of the ejection fraction of the right ventricle and the ejection fraction of the left ventricle, but there was no statistically significant intergroup difference in the values of the fraction of pulmonary regurgitation.

As no statistically significant differences in mean PRF values were observed between groups of subjects divided by the time period elapsed from surgery, special caution should be exercised in routine follow-up EHO examinations during postoperative evaluation, as it may give the false impression that the disease is stagnant, and the condition is actually becoming worse and leads to global heart failure.

No statistically significant differences in the mean values of end-diastolic volume of the right and left ventricles, nor in the mean values of the corrected ejection fraction of the right ventricle were observed between the groups of subjects divided on the basis of the time period elapsed from the surgery. Linear regression showed that the EDV-RV / EDV-LV ratio has a higher beta coefficient ($\beta = 0.461$) and is a statistically more significant ($p = 0.001$) predictor of the severity of pulmonary regurgitation compared to RV-EDV ($\beta = 0.047$; $p = 0.711$).

Conclusion

By analyzing the elapsed time period from TOF surgery (less than 5 years, 6–10 years, 11–15 years, more than 15 years), intergroup differences in the values of right ventricular end-diastolic volume, right ventricular ejection fraction, and left ventricular ejection fraction were proven, but there was no statistically significant intergroup difference in the value of the pulmonary regurgitation fraction.

The negative interaction of the right and left ventricles intensifies during the years of follow-up of patients after TOF surgery, which is especially true fifteen years after surgery.

CMR is a key diagnostic method in a growing population of patients operated on for TOF, or the most significant role in research efforts aimed at improving the outcome of patients with tetralogy of Fallot.

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Ethical approval. The Ethics Committee of the Department of Cardiology of the University Children's Clinic (UDK) in Belgrade and the University Hospital (UB) Foca approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Magnetna rezonanca srca kao metod dugoročnog praćenja funkcije desnog srca nakon operacije tetralogije Fallot

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Uvod. Magnetna rezonanca srca (engl. Cardiac magnetic resonance - CMR) se smatra referentnom dijagnostičkom metodom za kvantifikaciju veličine i funkcije desne komore i pulmonalne regurgitacije kod pacijenata sa operisanom tetralogijom Fallot. Cilj ovog rada je da potvrdi važnost magnetno-rezonantnog kontinuiranog postoperativnog praćenja parametara funkcije desnog i lijevog srca kao dijagnostičke metode koja pruža najpreciznije i najtačniju procjenu.

Metode. Opservaciono-prospektivna studija uključila je ispitanike sa operisanom TOF kojima su na kontrolnim postoperativnim ehokardiografskim pregledima utvrđeni rezidualni morfološki i/ili funkcionalni poremećaji. Svim ispitanicima je urađena magnetna rezonanca srca na skeneru jačine 1.5 T sa namjenskim zavojnicama za srčanu površinu prema standardnom protokolu u periodu od godinu dana od početka istraživanja. Kriterijumi za isključenje iz studije bili su: značajna rezidualna pulmonalna stenoza, stanje poslije zamjene pulmonalne valvule, postojanje rezidualnih šant lezija; kontraindikacije za magnetnu rezonancu srca (pace-maker, ICD, klaustrofobija). U zavisnosti od vremena proteklog od operacije tetralogije Fallot, ispitanici su podijeljeni u grupe: više od 15 godina, 11–15 godina, 6–10 godina, manje od 5 godina.

Rezultati. Studijom je obuhvaćen 131 ispitanik prosječne starosti 24,18 ± 11,57 godina sa urađenom kompletnom korekcijom TOF. Dokazane međugrupne razlike u vrijednostima end-dijastolnog volumena desne komore, ejekcione frakcije desne komore, kao i ejekcione frakcije lijeve komore, ali nije bilo statistički značajne međugrupne razlike u vrijednosti frakcije pulmonalne regurgitacije. Negativna interreakcija desne i lijeve komore pojačava se u toku godina praćenja pacijenata nakon operacije TOF, što se posebno događa 15 godina nakon operacije.

Zaključak. CMR ima najznačajniju ulogu u istraživačkim naporima usmjerenim na poboljšanje ishoda operisanih pacijenata sa tetralogijom Fallot.

Ključne riječi: tetralogija Fallot, disfunkcija desne komore, magnetna rezonanca srca

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Original article

Effect of perioperative blood loss on cognitive function disorders after colon cancer surgery

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Summary

Introduction. Postoperative cognitive dysfunction (POCD) is very common in patients who are treated in intensive care units or in the surgery department after surgery. This increasingly present complication complicates and calls into question the recovery of the operated patient. We assumed that POCD was associated with blood loss in patients undergoing colorectal cancer surgery.

Methods. Our study included 60 patients older than 50 years who underwent elective open surgery for colon cancer. The same protocol was performed for each patient: preoperative preparation and anesthesia. All patients completed three psychometric tests (mini mental test - MMT, information test and Hooper test) the day before surgery, one day after surgery and the seventh day after surgery.

Results. Cognitive status examined on the basis of the MMT score showed a statistically significant difference in the number of received blood transfusions after surgery on the first day ($p = 0.016$) and the total number of received blood transfusions ($p = 0.026$). Cognitive status examined by the information test showed a statistically significant difference ($p = 0.025$) in the number of received blood transfusions after surgery on the first day. In patients whose cognitive status was examined by the Hooper test, a high statistically significant difference was observed in the number of received blood transfusions after surgery on the first day ($p = 0.001$). Cognitive status measured on the basis of MMT score showed that there was a statistically significant difference in the average values of the amount of blood given by transfusion after surgery ($p = 0.019$).

Conclusion. There was a statistically significant cognitive dysfunction in patients who had greater blood loss during surgery and the first day after surgery and who received more blood transfusions (more than 600 ml) during and after surgery. The introduction of psychometric tests in the assessment of cognitive functions as well as the choice of surgery may be important factors in the prevention of POCD.

Key words: cognitive dysfunction, blood loss, psychometric tests, colorectal cancer

Introduction

Cognitive functions include complex brain functions such as general intellectual functions, attention, memory, comprehension, thinking, executive functions, planning, verbal functions, graphomotor functions, etc., which allow a person to acquire knowledge, analyze and assess events around themselves, and adequately response to various stimuli, problem solving and future planning [1]. Postoperative cognitive dysfunction (POCD) is a transient disorder, and

yet a very significant complication that can occur after surgery, because memory impairment, ability to maintain concentration and information processing significantly affect the daily functioning of patients [2]. That is why it is very important to introduce psychometric tests for various cognitive functions in everyday work, which will enable easier detection, or recognition of cognitive dysfunction. Diagnosis requires preoperative and postoperative psychometric testing [3]. During extensive surgical interventions (resection of the colon) in the elderly, the probability of morbidity and mortality increases, and cognitive impairment has been reported very often [4, 5]. Observational studies have shown an association of postoperative hemoglobin concentration less than 10 g/L and an increased incidence of POCD [6, 7]. Some surgeries carry a higher risk of developing POCD than others, most often due to their complexity and large volume losses [8, 9]. Colorectal cancer is one of the most common cancers in modern man. Colon cancer is the third most common cancer in men, just behind lung and stomach cancer, and the third most common cancer in women, after breast and cervical cancer. It can occur at any age, but more than 90% of patients are older than 40 years, after which the risk doubles every ten years [10]. Surgery is the basic form of treatment for colorectal cancer, and the prognosis depends on the stage of the disease at the time of diagnosis. Between 80% and 90% of patients are cured if cancer is detected and treated at an early stage of cancer development. The aim of our study was to examine whether there is a relation between blood loss and POCD in colon cancer surgery.

Methods

Our study included 60 patients (35 men and 25 women) who underwent surgical resection of colon cancer, aged 50 to 84 years and educational level of 8 to 16 years of education. The diagnosis of the disease was made on the basis of a biopsy during a colonoscopy and histopathological findings. Patients were divided into two groups, depending on the type of anesthetic administered, group A - nesdonal (30 patients) and group B - propofol (30 patients), each other patient receiving the same anesthetic. Randomization was performed on the same principle. Every first subject received nesdonal and every second subject received propofol. The study included all patients who agreed to participate in the study and who signed an informative consent. Patients with stroke, psychiatric patients, patients with renal failure on dialysis and patients with severe systemic diseases were excluded from the study. Prior to inclusion in the study, each patient was diagnosed with cognitive status, i.e. the absence of severe cognitive dysfunction. We kept a separate card for each patient, designed only for this research. Upon admission to the hospital, we performed anesthesiological preparation of the patient for surgical treatment, which included anamnestic and physical examination of the patient, examination of medical documentation and decision on the type of anesthesia. We used the above standardized psychometric tests (mini mental test, information test and Hooper test) to verify and assess the state of cognitive functions in all patients. The state of cognitive functions was recorded immediately before the start of the surgery and after the first and seventh day after the completion of the surgery. All patients underwent the same anesthesia procedure at the secondary service level in the surgical operating room and intensive care unit. In premedication, patients received atropine 1 mg, midazolam 5 mg, and fentanyl 50 mcg I.M. (intramuscularly) half an hour before the start of surgery. Introduction to anesthesia was performed with nesdonal 5 mg/kg (group A) or propofol 2 mg/kg (group B) and leptosuccin 1.5 mg/kg. After intubation, anesthesia was maintained with fentanyl 5

mcg/kg, sevoran 0.2–5 minimum alveolar concentration (MAC) and pavulon (pancuronium bromide) 2 to 4 mg or tracrium (atracurium besilate) 0.3–0.6 mg/kg when needed muscle relaxation, in addition to sevoran as an inhalation anesthetic, air 1.5 L/min and O2 1.5 L/min were also included. At the beginning of the operation a central venous catheter was placed in the right internal jugular vein. All patients were monitored by prescribed standard monitoring (non-invasive measurement of arterial pressure, heart rate, saturation, ECG and central venous pressure). Half an hour before waking up each patient was administered a ketoprofen amp. 100 mg, metamizole sodium at a dose of 2.5 g I.V. (intravenous) and tramadol amp. 100 mg per infusion in the operating room. After the operation the patients were transferred to the ICU (intensive care unit) where they were connected to continuous monitoring of vital functions. Based on the value of CBC (complete blood count), and according to the obtained values (haemoglobin <100 g/L and haematocrit <0.25 L/L), transfusion of erythrocyte concentrate and FFP (fresh frozen plasma) was administered.

Results

All patients were divided into two age groups, one age group consisted of 32 patients, i.e. (53.3%), aged 50 to 68, and in the second age group there were 28 patients, aged 69 to 84, i.e. (47.7%). The average age of the patients was 68.51 ± 7.16. According to the gender structure, we had 35 men (58.3%) and 25 women (41.7%). Cognitive status examined on the basis of MMT score showed a statistically significant difference in the number of received blood transfusions after the operation on the first day (p = 0.016) and the total number of received blood transfusions (p = 0.026). Patients with cognitive impairment received significantly higher doses of blood transfusion after surgery on the first day (0.38 ± 0.49), and they had a higher number of total blood transfusions received (1.92 ± 1.23) compared to patients without cognitive impairment who received significantly fewer blood transfusions after surgery on the first day (0.11 ± 0.32) as well as the total number of blood transfusions received (1.16 ± 1.04). In the examined patients no statistically significant difference was observed in the number of administered blood transfusions during the operation and the number of received blood transfusions after the operation on the second day and more.

Table 1. Average values of the number of received blood transfusions during and after surgery of patients in relation to the cognitive status measured by MMT in patients after colon surgery

Received blood transfusions during and after surgery	Mini mental test (AS ± SD)		t	*p*
	Normal findings	Impairment of cognition		
Number of blood transfusions received during surgery	1.14 ± 0.71	0.38 ± 0.49	0.590	0.558
Number of blood transfusions received after surgery on the first day	**0.11 ± 0.32**	**0.38 ± 0.49**	**2.510**	**0.016**
Number of received blood transfusions after surgery on the second day and more	0.45 ± 0.80	0.16 ± 0.51	1.648	0.106
Total number of received blood transfusions	**1.16 ± 1.04**	**1.92 ± 1.23**	**2.285**	**0.026**

When the cognitive status of the patients (general intellectual ability) was examined by the information test a statistically significant difference (p = 0.025) was observed in the number of received blood transfusions after the operation on the first day. Patients who had below-average scores on the information test received a significantly higher number of blood transfusion on the first day (0,37 ± 0,48) compared to patients with above-average scores (0.11 ± 0.33). In the examined patients no statistically significant difference was observed in the number of received blood transfusions on the second day and more, as well as the total number of administered blood transfusions.

Patients whose cognitive status was examined on the basis of the Hooper test score showed a high statistically significant difference in the number of received blood transfusions after the first day of surgery (p = 0.001). Patients who were at high risk of cognitive impairment had a significantly higher number of administered blood transfusions after surgery on the first day (0.35 ± 0.48) compared to low-risk patients (0.11 ± 0.01). In the examined patients, no statistically significant difference was observed in the number of received blood transfusions during the operation, the number of received blood transfusions after the operation on the second day and more, as well as the total number of administered blood transfusions.

Table 2. Average values of the number of received blood transfusions during and after surgery of patients in relation to the cognitive status measured by the information test in patients after colon surgery

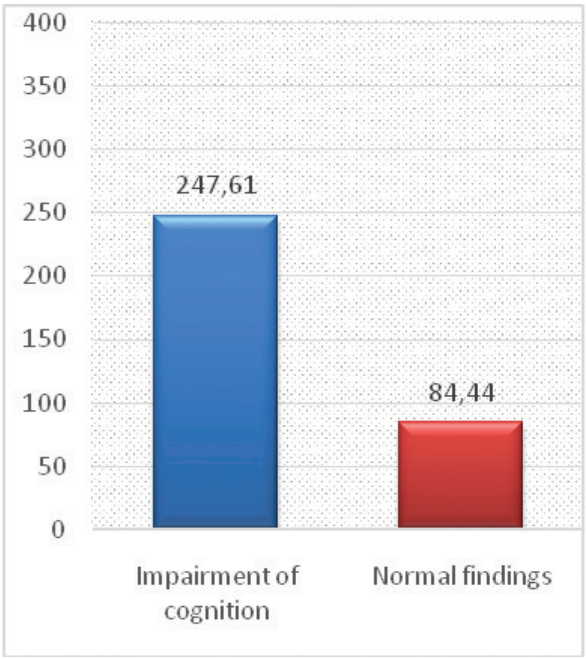
Received blood transfusions during and after surgery	Information test (AS ± SD)		t	*p*
	Above average	Below average		
Number of blood transfusions received during surgery	1.05 ± 0.74	1.13 ± 0.60	- 0.437	0.664
Number of blood transfusions received after surgery on the first day	**0.11 ± 0.33**	**0.37 ± 0.48**	**- 2.318**	**0.025**
Number of received blood transfusions after surgery on the second day and more	0.52 ± 0.71	0.30 ± 0.74	1.079	0.285
Total number of received blood transfusions	1.76 ± 0.90	1.67 ± 1.34	0.255	0.800

Table 3. Average values of the number of received blood transfusions during and after surgery of patients in relation to the cognitive status measured by the Hooper test in patients after colon surgery

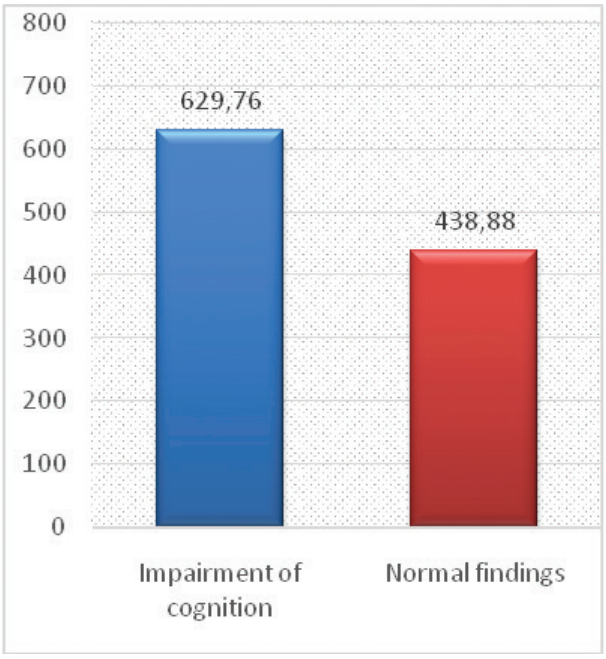
Received blood transfusions during and after surgery	Hooper test (AS ± SD)		t	*p*
	Low risk	High risk		
Number of blood transfusions received during surgery	1.44 ± 0.52	1.05 ± 0.64	1.692	0.096
Number of blood transfusions received after surgery on the first day	**0.11 ± 0.01**	**0.35 ± 0.48**	**- 5.222**	**0.001**
Number of received blood transfusions after surgery on the second day and more	0.66 ± 0.86	0.31 ± 0.70	1.336	0.187
Total number of received blood transfusions	1.77 ± 0.66	1.68 ± 1.30	0.205	0.838

When cognitive status was measured based on the MMT score a statistically significant difference was observed in the average values of the amount of blood given by transfusion after surgery (p = 0.019). Patients who had impaired cognition on MMT received a significantly higher amount of blood (247.61 ± 260.31 ml) after surgery compared to patients with normal findings (84.44 ± 225.52 ml). There was a statistically significant difference between the mentioned groups of patients in the average values of the total amount of blood given during and after the surgery, whereby patients with impaired cognition received significantly more blood during and after the surgery (629.76 ± 374.89 ml) in relation to patients without cognitive impairment (438.88 ± 297.02 ml).

Analysis of risk factors for cognitive impairment after anesthesia in colon cancer surgery revealed that a higher number of transfusions was given during surgery (OR = 1.597, [Cl = 1.098-5.951], p < 0.001) and a larger amount of blood was given during surgery (OR = 1,938, [Cl = 2,704-7,298], p < 0.001) represent statistically significant risk factors for the occurrence of cognitive impairment after colon cancer surgery. These factors are associated with a high risk of deteriorating cognitive function in these patients. The mean value of Hgb after surgery was 116.08 ± 19.59 g/L, and mean value of Hct after surgery was 0.34 ± 0.05 L/L. The significant difference between mean values of Hgb and Hct between groups of patients divided by number of administered transfusions on the first and second day after surgery was not observed (Figure 1).



Total amount of blood given after surgery



Total amount of blood given during and after surgery

Figure 1. Cognitive status after surgery - MMT

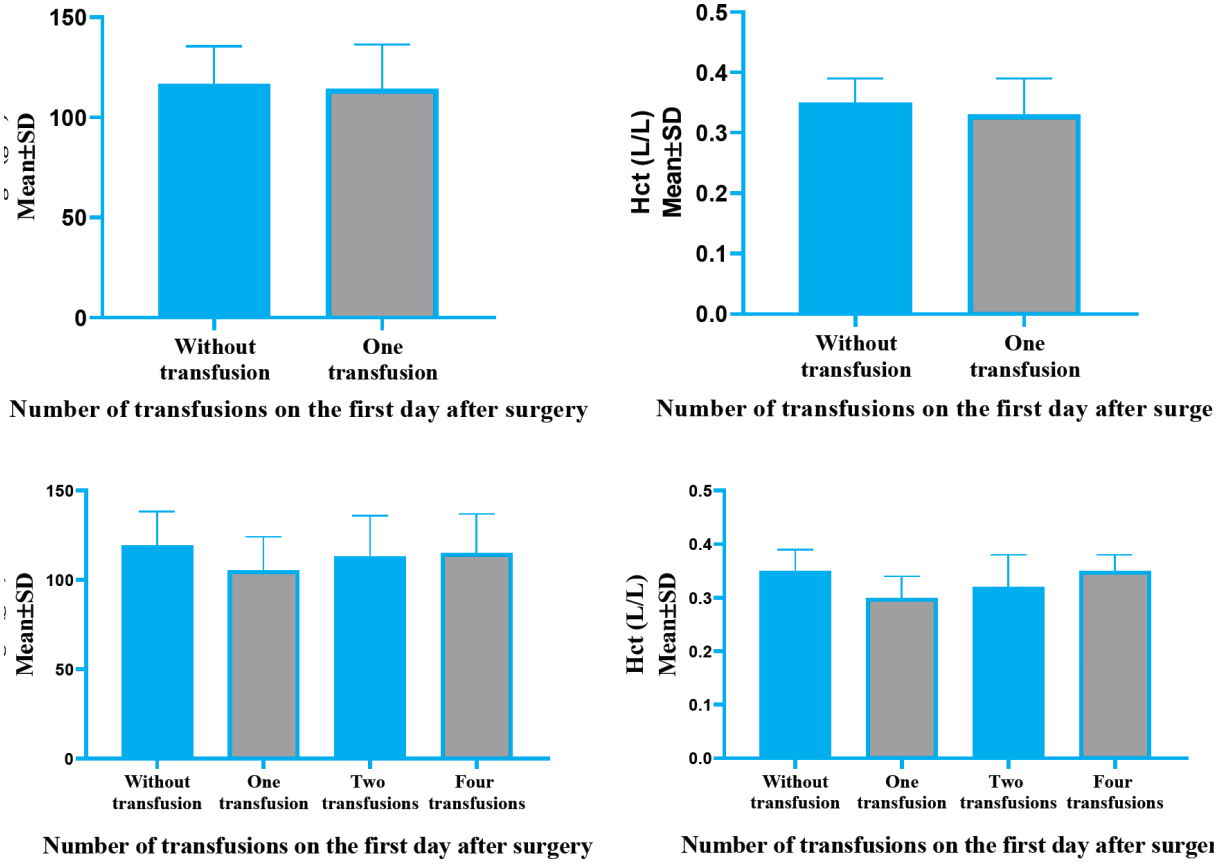


Figure 2. Mean concentrations of Hgb and Hct between groups of patients devided by number of administered transfusions on the first and second day after surgery

Hgb - haemoglobin, Hct - haematocrit; SD - standard deviation: ANOVA - univariate analyses of variance

Discussion

Blood viscosity affects cerebral blood flow and the value of haematocrit is the primary cause of viscosity. The decrease in haemoglobin due to dilution reduces the arterial oxygen content, so if there is no simultaneous increase in cerebral flow, there is a drop in oxygen supply. During colon surgery due to blood loss it comes to the hemodilution, so that blood flow through the brain and blood consumption in the brain fall at the same time. It is difficult to determine optimal haematocrit that will maintain normal oxygen supply, but also optimal blood flow through the brain, because it is involved in complex interaction with other parameters (temperature, depth of anaesthesia, etc.) that affect blood flow through the brain [11]. Nevertheless, some larger studies have found a trend towards increased morbidity and mortality in haematocrits lower than 22% [12, 13, 14]. It has been found that the lowest measured haematocrit value of 10% can be an independent stroke factor, and the risk increases for each percentage point of haematocrit decline [15]. Significant hemodilution (haematocrit between 15% and 17%) was related to a higher incidence of cognitive impairment six weeks after surgery [16]. In circumstances of excessive hemodilution, blood transfusion,

to increase haematocrit, carries a new risk. Namely, studies that found that a haematocrit lower than 22% causes an increase in cognitive impairment also showed that transfusion, with the aim of reversing the negative impact of hemodilution, can have an adverse effect on renal function and cause their stagnation. Therefore, it is safest to apply all methods to avoid excessive hemodilution during major surgical interventions. Due to the importance of prevention of cerebral ischemia, intraoperative monitoring of haematocrit levels, blood oxygen saturation (pulse oximetry) and monitoring of the operative field (volume of bleeding) are necessary [17]. Our results unambiguously show that a larger number of transfusions (more than two doses) as well as a larger amount of blood (more than 600 ml) administered during and the first day after surgery affect POCD. The methods currently available that identify cognitive impairment are neither specific nor sensitive enough. Current guidelines suggest the use of combined tests to improve the accuracy of predicting the occurrence of cognitive deficits. There is still a search for simple and effective methods, tests for early detection of mild cognitive changes, which is necessary for their more efficient treatment and prevention. Patients with severe cognitive impairment are usually excluded from the study and this results in the selection of subsamples of cognitively less impaired patients [18, 19]. Also, it should be taken into account that MMT is a neurocognitive instrument for measuring the global cognitive level with strict sensitivity to language deficit. The information test is a test of conceptual thinking and is a measure of general intellectual ability. This test is one of the most resistant tests to brain decline, so it can be used as a rough measure of premorbid intelligence. The Hooper test is the most well-known test of visual organization and is sensitive to the detection of brain pathology, as well as the detection of fragmentary perception. Postoperative cognitive impairment is defined as worsening of results in one or more tests. Based on these tests, we determined for each of the patients whether or not he had a cognitive disorder.

Conclusion

There was a statistically significant cognitive impairment in patients who had greater blood loss during surgery and the first day after surgery and received more blood transfusions (more than 600 ml) during and after surgery. The introduction of psychometric tests in the assessment of cognitive functions as well as the choice of surgery may be important factors in the prevention of POCD.

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Conflicts of interest. The authors declare no conflict of interest.

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Uticaj perioperativnog gubitka krvi na poremećaj kognitivnih funkcija poslije operacije karcinoma debelog crijeva

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Uvod. Postoperativni kognitivni deficit (POKD) se veoma često javlja kod bolesnika koji se poslije operacije liječe u jedinicama intenzivne njege ili na odjeljenju hirurgije. Ova sve češće prisutna komplikacija otežava i dovodi u pitanje oporavak operisanog pacijenta. Pretpostavili smo da je POKD povezan sa gubitkom krvi kod pacijenata koji su podvrgnuti operaciji kolorektalnog karcinoma.

Metode. U naš rad je bilo uključeno 60 pacijenata starijih od 50 godina koji su bili podvrgnuti elektivnoj otvorenoj operaciji karcinoma debelog crijeva. Za svakog pacijenta je bio sproveden isti protokol - preoperativna priprema i anestezija. Svi pacijenti su ispunili tri psihometrijska testa (mini mental test – MMT, test informisanosti i Huperov test) dan prije operacije, jedan dan poslije operacije i sedmog dana poslije operacije.

Rezultati. Kognitivni status ispitivan na osnovu skora MMT pokazao je statistički značajnu razliku u broju primljenih transfuzija krvi nakon operacije prvog dana ($p = 0,016$) i ukupnog broja primljenih transfuzija krvi ($p = 0,026$). Kognitivni status ispitivan testom informisanosti pokazao je statistički značajnu razliku ($p = 0,025$) u broju primljenih transfuzija krvi nakon operacije prvog dana. Kod pacijenata čiji je kognitivni status ispitivan Huperovim testom uočena je visoka statistički značajna razlika u broju primljenih transfuzija krvi nakon operacije prvog dana ($p = 0,001$). Kognitivni status izmjeren na osnovu skora MMT pokazao je da postoji statistički značajna razlika u prosječnim vrijednostima količine krvi date transfuzijom poslije operacije ($p = 0,019$).

Zaključak. Prisutan je statistički značajan poremećaj kognitivnih funkcija kod pacijenata koji su tokom operacije i prvog dana poslije operacije imali veći gubitak krvi i dobili veći broj transfuzija krvi (više od 600 ml) tokom i poslije operacije. Uvođenje psihometrijskih testova u procjenu kognitivnih funkcija, kao i izbor hirurške operacije mogu biti značajni faktori u prevenciji POKD.

Ključne riječi: kognitivni deficit, gubitak krvi, psihometrijski testovi, kolorektalni karcinom

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Influence of smoking on voice quality

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Summary

Introduction. During smoking, specific morphological changes occur within the larynx, which results in changes in voice quality. Given that voice is related to quality of life, it is necessary to identify the impact of smoking on voice quality.

Methods. A group of 85 respondents, aged 22 to 70 years (AS = 35.61; SD = 11.36), both sexes, categorized into two groups, smokers and non-smokers, were selected for this study. A recording of extended vocal A phonation was analyzed in the program for acoustic voice analysis - PRAAT. The research was realized at the Faculty of Medicine in Foca, during 2021.

Results. A statistically significant difference was found in four out of the five examined voice parameters. Namely, a statistically significant difference was observed in the mean value of the fundamental frequency (Fo) ($p = 0.042$), jitter ($p = 0.007$), shimmer ($p = 0.026$) and in the noise-to-harmonic ratio ($p = 0.018$) between smokers and non-smokers. Also, a statistically significant difference was found between two subgroups of subjects (those who smoked less than 10 years and those who smoked longer than 10 years) in the fundamental voice frequency Fo ($p = 0.011$), standard deviation of the fundamental frequency STD ($p = 0.047$) and amplitude perturbation expressed through shimmer in percentage (Shim) ($p = 0.017$). For other examined voice parameters, no statistically significant difference was noticed between these two subgroups of respondents.

Conclusion. Smoking affects most of the acoustic parameters of the voice, resulting in poorer voice quality. Also, the quality of the voice decreases as the smoking experience increases.

Key words: smoking, smoking experience, voice quality

Introduction

Despite the global anti-smoking campaign, most of the world's population still consumes nicotine. A study that aimed to investigate the prevalence of smokers in 12 European countries, find data that 42.4% of respondents had at least some experience with nicotine, in the way that 25.9% of respondents consume cigarettes, while 16.5% of them was with previous smoking experience [1].

The harmful effects of smoking on human health are well known. During smoking and prolonged exposure to the direct influence of nicotine, specific morphological changes occur within the larynx. Also influence of cigarette consumption on the physiology of the vocal tract is well documented [2] and includes pharyngeal diseases and disorders caused by prolonged

exposure to various harmful chemicals that are concentrated in cigarette smoke. Exposure to cigarette smoke can affect laryngeal tissue, causing inflammation of the vocal cords [3], as well as degradation of lung function resulting in reduced airflow through the vocal cords [4].

In addition to studies that have addressed structural and histological changes in the vocal cords, there are several studies that have examined changes in the acoustic parameters of the voice caused by cigarette smoking [5–8]. The results of these studies indicate a significant decrease in the fundamental frequency of the voice (Fo) in smokers as well as a significant increase in shimmer and jitter. All these parameters determine the quality of the voice [5]. The fundamental frequency of the voice (Fo) is an important acoustic characteristic of the speech signal. Fo is the lowest, and usually the strongest frequency produced by complex vocal cords, and it is expressed in hertz (Hz). Jitter as an acoustic parameter refers to the fundamental frequency perturbation, while the shimmer refers to the amplitude perturbation.

Smokers feel more tired when using their voice and are more likely to lose their voice, compared to non-smokers [9,10]. Voice can significantly affect social interaction [11] and quality of life in vocal professionals (people who use voice as one of the basic tools for work). Given that voice is related to quality of life in general, it is necessary to identify the impact of smoking on voice quality. Therefore, our study had two aims: 1) to examine the impact of smoking on selected acoustic voice parameters and 2) to examine the existence of differences in the quality of smokers' voices in relation to smoking experience.

Methods

A group of 85 healthy respondents, aged 22 to 70 years (M= 35.61; SD = 11.36), both sexes, were selected by the method of intentional sampling for this study. We divided the subjects into two groups, smokers (A) and non-smokers (B). The criterion for inclusion of the subjects in the first group was the consumption of cigarettes for a period of at least one year. This criterion was met by 42 respondents, 23 female and 19 male respondents. In the group of smokers, the respondents were aged 22 to 67 years, with an average age of M = 35.83 SD = 10.94. We further divided these respondents into two subgroups in relation to the smoking experience. Thus, the first subgroup consisted of respondents with a smoking experience of one to ten years, and the second subgroup consisted of those whose smoking experience was longer than 10 years. The control group consisted of 43 respondents, non-smokers, of whom 24 were female and 19 male. In the group of non-smokers, the respondents were aged 22 to 70 years, where the average age in this group was M = 35.39, SD = 11.89. Subjects of the A and B groups were matched by sex and age.

The voice recording was performed in an adequate room. The respondents were given the task of phonating vocal A for a long time, with optimal volume and pitch, for at least ten seconds. The recordings were recorded using the Voice Memos app. The recording was repeated three times, and the highest quality voice recording was used for acoustic analysis. The recorded material was converted to WAW format, so that it could be analyzed in the PRAAT program (Paul Boersma and David Weenink, Phonetic Sciences, University of Amsterdam) [12]. The voice quality was analyzed through the following five acoustic parameters: mean values of the fundamental frequency (Fo in Hz); standard deviation of the fundamental frequency (STD in Hz); jitter (Jitt in %); shimmer (Shimm in %) and noise-to-harmonic ratio (NHR in dB). Data were analyzed using the SPSS 20.0 statistical package.

Results

Table 1 shows the differences between smokers and non-smokers in terms of acoustic parameters of vocal A. We can observe that there is a statistically significant difference in four out of the five examined voice parameters. Namely, a statistically significant difference was observed in the mean value of the fundamental frequency (Fo) (p = 0.042), jitter (p = 0.007), shimmer (p = 0.026) and in the noise-to-harmonic ratio (p = 0.018).

By observing Table 2, we can see the acoustic structure of the voice in relation to the smoking experience. Namely, in the category of smokers, we categorized the two subgroups, smokers whose smoking experience is from one to ten years (smokers 1) and those whose smoking experience is more than 10 years (smokers 2). By testing the differences using the Mann-Whitney U test, a statistically significant difference was found in the fundamental frequency of the voice Fo (p = 0.011), in the standard deviation of the fundamental frequency STD (p = 0.047) and the amplitude perturbation expressed through shimmer in percentage (Shim) (p = 0.017). For other examined voice parameters, no statistically significant difference was noticed between these two subgroups of respondents.

Table 1. Differences between acoustic parameters of smokers and non-smokers

Vocal parameters	Group	N	Mdn	Min	Max	Mann-Whitney U	Z	P
Fo	smokers	42	142.54	92.60	221.44	672.000	-2.030	**0.042**
	non-smokers	43	142.54	95.23	230.68			
STD	smokers	42	2.02	1.06	63.08	740.500	-1.428	0.153
	non-smokers	43	1.76	0.73	50.85			
Jitt	smokers	42	0.40	0.15	0.96	597.500	-2.686	**0.007**
	non-smokers	43	0.31	0.13	0.92			
Shim	smokers	42	6.24	2.69	15.38	650.500	-2.219	**0.026**
	non-smokers	43	4.76	2.90	13.24			
NHR	smokers	42	16.37	7.21	24.00	634.000	-2.365	**0.018**
	non-smokers	43	14.17	5.26	22.64			

Fo - mean value of the fundamental frequency; STD - standard deviation of the fundamental frequency; Jitt - jitter; Shim - shimmer; NHR - noise-to-harmonic ratio in dB

Table 2. Acoustic parameters of voice in relation to the smoking experience

Vocal parameters	Group	N	Mdn	Min	Max	Mann-Whitney U	Z	P
Fo	smokers1	17	172.09	100.31	216.25	113.000	-2.550	**0.011**
	smokers2	25	132.59	92.60	221.44			
STD	smokers1	17	2.49	1.25	63.08	135.000	-1.986	**0.047**
	smokers2	25	1.95	1.06	42.22			
Jitt	smokers1	17	0.39	0.15	0.83	158.500	-1.385	0.166
	smokers2	25	0.44	0.20	0.96			
Shim	smokers1	17	7.25	3.60	14.13	119.000	-2.396	**0.017**
	smokers2	25	4.81	2.69	15.38			
NHR	smokers1	17	11.63	7.61	19.37	146.500	-1.691	0.091
	smokers2	25	15.40	5.26	22.64			

Fo - mean value of the fundamental frequency; STD - standard deviation of the fundamental frequency; Jitt - jitter; Shim - shimmer; NHR - noise-to-harmonic ratio in dB; smokers1 - smokers who smoke for less than 10 years; smokers2 - smokers who smoke for more than 10 years

Table 3 shows a regression analysis, where we examined predictive influence of sex and smoking experience. The model originally included age, sex, and smoking history, but by examining the preconditions for applying multiple regressions, we found that there was a collinearity between the variables of smoking experience and age ($r \geq 9$), so only sex and smoking were included in the regression model. Multiple standard linear regression showed that within the group of smokers, sex and smoking experience were statistically significant ($p < 0.001$) predictors of two out of the four examined voice parameters (Fo, Jitt). These predictors together as a model explain about 50% for Fo, i.e. 25% of the variance of Jitt values, and the most significant individual contribution in the model is given by sex (Fo = $\beta = 0.689$; $p < 0.001$; Jitt = $\beta = 0.448$; $p < 0.001$), which means that sex in relation to smoking experience best predicts the values of acoustic voice parameters.

Table 3. Predictors of acoustic voice parameters

	Model 1	β	t	p	F	p	Adjusted R^2
Fo	Sex	0.689	6.010	0.000	21.63	**0.000**	0.502
	Smoking experience	-0.106	-0.926	0.360			
Jitt	Sex	0.448	3.198	0.003	8.04	**0.001**	0.256
	Smoking experience	-0.203	1.450	0.155			
Shimm	Sex	0.251	1.629	0.111	3.32	0.046	0.102
	Smoking experience	-0.227	-1.477	0.148			
NHR	Sex	0.124	0.768	0.447	1.21	0.308	0.010
	Smoking experience	1.77	1.093	0.281			

Fo - mean value of the fundamental frequency; Jitt - jitter; Shim - shimmer; NHR - noise-to-harmonic ratio

Discussion

The fact is that the larynx is only part of the system of organs involved in the formation of voice and speech, however, as the larynx is responsible for phonation, we examined only how smoking affects the phonation of vocal A, or how it affects acoustic parameters (Fo, STD, Jitt, Shimm, NHR).

Fundamental frequency values obtained in speech signals are usually less than 300 Hz for children and greater than 100 Hz for adults, or 120 Hz for men and 210 Hz for women [13–15]. The results of our study showed that the fundamental frequency of voice (Fo) is significantly lower than the frequency of voice in non-smokers, which is an indicator of poorer voice quality. The obtained results are consistent with the results of other studies that found that smoking reduces the values of the fundamental frequency of the voice [16, 17].

Both parameters have elevated values in smokers compared to non-smokers and this difference is statistically significant (jittter ($p = 0.007$); shimmer ($p = 0.026$)). Increased jitter value is an indicator of poorer voice quality, while at the same time higher shimmer values in the spoken voice are perceived as hoarseness [18]. NHR as an acoustic parameter estimates the presence of noise in the analyzed speech signal, and higher NHR indicates the presence of more noise in the signal and poorer voice quality. In our study, smokers had higher NHR values compared to non-smokers,

and the difference between the groups was statistically significant (p= 0.018). Research examining the isolated and multifactorial effect of smoking on voice quality has yielded similar results, that smoking affects the presence or occurrence of noise in the fundamental voice [16]. The literature shows that cigarette smoking changes the quality of the voice, causing a reduced amount of harmonics and an increased presence of noise in the voice [19].

When it comes to differences in voice quality in relation to the smoking experience, statistically significant differences were shown on the following acoustic parameters: Fo (p = 0.011), STD (p = 0.047) and shimmer (0.017). Namely, the smoking experience has had the effect of reducing the fundamental frequency of voice in people who smoke for more than 10 years, compared to those who consume cigarettes for a shorter period of time. Our results showed that the values of Fo decrease more, if the smoking experience of the respondents is longer, which is again a clear indication that the smoking duration negatively affects the values of Fo. Regarding the frequency perturbation expressed through jitter, we did not find a statistically significant difference between the group of smokers1 and smokers2, however, respondents from the subgroup smokers2 had higher minimum and maximum values for this acoustic parameter. Shimmer was significantly higher in subjects from the subgroup smokers2 compared to subjects from the subgroup smokers1, and this difference was statistically significant (p = 0.017). Results similar to ours, which suggest that this type of acoustic change is associated with long-term smoking, are found in a study by Vincent and Gilbert [19]. When it comes to the acoustic parameter related to the presence of noise in the analyzed signal - NHR, no statistically significant difference was found. The absence of a significant difference between the groups is somewhat unexpected, since NHR reflects the presence of noise in the signal acoustics, and among other components, it includes frequency and amplitude perturbations. From the above results, we can conclude that some other factors besides smoking affect the presence of noise in the signal. It is also possible that acoustic parameters whose values remain unchanged when viewed in relation to the smoking experience, may be less sensitive to prolonged and continuous nicotine intake.

To further analyze the predictive influence of certain variables, we performed regression analysis, where sex and smoking experience were included into the model as predictors, while the dependent variables were acoustic voice parameters. This model explained 50% of the variance for Fo and about 25% for Jitt, while this model did not show a significant effect for other parameters ($p \geq 0.01$).

Conclusion

The acoustic analysis of the voice in smokers showed a statistically significant deviation on four out of the five examined parameters: Fo, shimmer, jitter and NHR. Decreased Fo and NHR values, as well as increased jitter and shimmer values, indicate poorer voice quality in smokers compared to non-smokers. Also, certain parameters, Fo, STD and Shimmer are significantly worse in smokers whose smoking experience is longer than 10 years compared to those who have shorter experience, which means that the quality of the voice is worse, if the smoking experience is longer.

The limitation of this research is that we did not use the number of cigarettes smoked per day, which would also contribute to a more detailed insight into the effects of nicotine on the voice of smokers. Also, comparing the objective assessment and clinical findings with the VHI index, we would get data on whether smokers subjectively feel worsening of the voice and how long after consuming cigarettes.

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Conflicts of interest. The authors declare no conflict of interest.

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Uticaj pušenja na kvalitet glasa

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Uvod. Prilikom pušenja javljaju se specifične morfološke promjene unutar grkljana, što za posljedicu ima promjene u kvalitetu glasa. Imajući u vidu da je glas povezan sa kvalitetom života, neophodno je identifikovati uticaj pušenja na kvalitet glasa.

Metode. Za ovu studiju odabrano je 85 ispitanika, starosti od 22 do 70 godina (AS = 35,61; SD = 11,36), oba pola, kategorisanih u dvije grupe, pušači i nepušači. Analiziran je snimak produženog foniranja vokala A u programu za akustičku analizu glasa PRAAT. Istraživanje je realizovano na Medicinskom fakultetu u Foči, tokom 2021. godine.

Rezultati. Nađena je statistički značajna razlika na četiri od pet ispitivanih parametara glasa. Naime, statistički značajna razlika uočena je kod srednje vrijednosti osnovne frekvencije (Fo) (p = 0,042), jittera (p = 0,007), shimmera (p = 0,026) i u odnosu šuma i harmonika (p = 0,018) između pušača i nepušača. Takođe, utvrđena je statistički značajna razlika između dvije podgrupe ispitanika (oni koji puše manje od 10 godina i oni koji puše duže od toga) u osnovnoj frekvenciji glasa Fo (p = 0,011), standardnoj devijaciji osnovne frekvencije STD (p = 0,047) i perturbaciji amplitude koja je izražena kroz shimmer u procentima Shim (p = 0,017). Za druge ispitivane parametre glasa nije evidentirana statistički značajna razlika između ove dvije podgrupe ispitanika.

Zaključak. Pušenje utiče na većinu akustičkih parametara glasa, rezultirajući lošijim kvalitetom glasa. Takođe, kvalitet glasa opada kako se pušački staž povećava.

Ključne riječi: pušenje, pušački staž, kvalitet glasa

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Original article

Reading ability of young school-age children

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Summary

Introduction. Reading is a complex linguistic and cognitive ability, acquired through learning. Children of typical development in the first four years of school completely master the reading skill. However, some children may have difficulty learning to read despite their preserved intellectual abilities and adequate training. The aim of this paper is to determine the reading ability and to identify reading disorder in children of younger school age.

Methods. The sample consisted of 123 students of third, fourth and fifth grade of elementary school. The three-dimensional reading test - the text "One Snowy Day" was used. Reading speed, reading accuracy and reading comprehension were assessed.

Results. Slow reading was identified in 35.3% of third graders and 22.2% of fourth graders. Deficits in reading accuracy were observed in 8.8% of third grade students. Delays in the development of reading comprehension were identified in most of the examined students. On the whole, our results showed that there is no statistically significant difference in reading ability between boys and girls.

Conclusion. A significant number of children is late in mastering reading skills. Given that reading speed increases significantly with age, and the number of errors decreases, we expect that many slow readers will reach an appropriate reading speed, and that most of the children who showed unexpected number of errors will master accurate word decoding. Since comprehension deficits were identified in the majority of respondents, we conclude that a significant number of children did not reach the developmental stage in which reading becomes a means of learning.

Keywords: reading, reading speed, accuracy in reading, reading comprehension, young school age

Introduction

Reading is a complex language activity acquired through active learning. At the same time, it is a cognitive activity that we learned the most about by studying acquired reading disorders in adults with brain damage. Thanks to empirical data on reading disorders in people with acquired dyslexia and aphasia, several theoretical models of reading have been proposed [1]. A common feature of these models is the distinction of different reading pathways.

Analyzing different models of reading, Vuković [1] stated that the visual characteristics of a written word are processed through two readings pathways: phonological (indirect) and lexical (direct). When using the phonological path, the visual forms of the written word are connected with the corresponding image in the mental lexicon after the grapheme-phonemic conversion, i.e. indirectly. On the other hand, when using the lexical path of reading, visual forms of words are connected with the corresponding image in lexical memory through meaning, or the written word is recognized immediately after connecting with the visual image in orthographic lexicon, without relying on its meaning [1]. Differences in the ability to read different types of words, as well as the appearance of different types of reading errors in people with acquired dyslexia and aphasia, speak in favour of the two distinct pathways of processing written language symbols [2, 3].

Reading is a demanding cognitive ability, whose adoption process takes a relatively long time. One of the key preconditions for the development of reading is having a developed spoken language. Metalinguistic awareness, or the ability to think about language and manipulate its structural characteristics, is especially important [4]. Phonological awareness, i.e. general knowledge about the phonetic structure of language, is crucial for reading – in particular, phonemic awareness (knowledge that spoken words are composed of individual phonemes that can be analyzed and manipulated) [5]. This is supported by numerous empirical studies, which established the connection between different aspects of phonological awareness and early reading development [6, 7, 8, 9, 10]. In addition to phonological awareness, Čolić and Vuković [11] found that the awareness of grammatical structure of a sentence (syntactic awareness) is also an important early reading predictor.

Children are gradually and systematically taught to read, beginning with the first grade of elementary school. However, there are some indicators of reading skills development even in the preschool period. From the developmental point of view, mastering the skill of reading goes through three phases: logographic, alphabetical and orthographic [12]. In the *logographic* phase, which is characteristic of preschool age, the so-called pseudo-reading occurs [13]. During this period, the child pretends to read picture books, the text of which he usually knows by heart. One gets the impression that a child at that age has some level of awareness of the text. Preschool children process words as wholes, or as any other visual symbol, although they recognize some letters. Furthermore, in this phase, there is an awareness of parts of language; prerequisite skills for reading such as phonological awareness develop. The *alphabetic* phase begins in the first year of school and it is a characteristic of early reading. It implies the development of phonological decoding through learning graphemes and their connection with phonemes, i.e. the child's ability to connect the right speech sound with a particular letter. The next phase in the development of reading is *orthographic* phase, where the ability to directly recognize words appears. At this stage, the child no longer processes the word segments, but the word as a whole. Thus, the orthographic phase is characterized by fluent reading, which usually occurs after two or three years of systematic training. Fluent reading is achieved by improving word decoding, through frequent repeating of words from text to text. It should be borne in mind, however, that in this period, learning by listening is still more effective than learning by reading. Therefore, it is recommended that at this stage, adults read material which is above the level of children's reading competence. It is usually considered that children at the age of nine go to the next stage when they become able to use reading as a means of learning.

In this phase, the children successfully master new words and syntactic forms; they are able to answer questions and discuss the content which was read [13]. In other words, a nine-year-old child of typical development, who has undergone systematic training, can understand texts from textbooks and other books corresponding to their age. This level of development is expected after four years of learning to read.

Having in mind the stated facts about reading and the importance of reading for learning, as well as the fact that there is little data on the children reading ability in the Republic of Srpska, this paper aims to examine reading skills of children in lower grades of elementary school. Our goal was to determine the speed of reading, accuracy in reading and reading comprehension. We also wanted to identify difficulties in reading.

Method

The sample included 123 respondents (55 boys and 68 girls), aged 8–10, of the third, fourth and fifth grade of the elementary school "Jovan Dučić" in Šekovići, the Republic of Srpska.

The criteria for inclusion were: the respondent has to attend third, fourth or fifth grade; they have undergone systematic, conventional reading training; they have average or above-average intellectual abilities. The criteria for exclusion were: presence of evident neurological, sensory and bodily impairments. The research was realized in the first semester of the school year 2020-21, after obtaining the consent of the school administration, parents and students.

The three-dimensional reading test - the text "One Snowy Day" [14], which is adapted to the Ijekavian dialect of the Serbian language, was used to assess reading. The test was conducted individually. Prior to testing, the purpose of the test was explained to each subject. The respondents were first asked to read the given text aloud. The examiner measured the reading time (this was used to assess reading speed) and recorded errors (to assess reading accuracy). Afterwards, the respondents were asked to retell the text. During the retelling, the examiner recorded the facts that the respondents managed to reproduce (which was used to assess reading comprehension).

Statistical Package for Social Sciences for Windows, version 23.0, 2015 (SPPS) was used in the analysis and data processing. Firstly, descriptive statistical methods were used to obtain central measure and variance. Kolmogorov-Smirnov test showed that sample does not follow normal distribution (K-S, $Z = 2.98$, $Z1 = 1.60$, $Z2 = 3.86$, $p < .001$, $p1 = 0.01$, $p2 < .001$), therefore nonparametric χ^2 test and Mann-Whitney U test were used. Pearson's coefficient was used to determine the correlation between the examined variables. Values less than $p < 0.05$ were considered statistically significant.

Results

Table 1 presents the results of reading speed in third, fourth and fifth grade students. The number and percentage (in brackets) of the respondents who were within the minimum, maximum and average reading time are shown [15].

The data in Table 1 show that, as expected, third-grade students needed the most time to read, while fifth-grade students read the given text the fastest. It was also shown that a significant percentage of third and fourth grade children did not reach the appropriate reading speed. We determined that there is a statistically significant difference in reading speed between students of the examined school age ($\chi^2 = 21.835$; $df = 6$; $p = 0.001$).

Table 1. Distribution of respondents according to reading speed

Grade	Minimum	Average	Maximum	Disorder	Total of respondents
3rd	2 (5.9)	10 (29.4)	10 (29.4)	12 (35.3)	34
4th	12 (27.3)	10 (22.7)	12 (27.3)	10 (22.7)	44
5th	14 (31.1)	15 (33.3)	16 (35.6)	0 (0.0)	45
Total	28 (22.8)	35 (28.5)	38 (30.9)	22 (17.9)	123
$\chi^2 = 21.835$; df = 6; p = 0.001					

Number and percentage of respondents are shown (% in brackets)

The results in Table 2 show that the respondents from all three grades made reading errors. However, only in the third grade we found students who, according to the number of errors, could be classified as having reading disorder.

We also found a statistically significant difference in terms of the number of reading errors between students of the examined school age ($\chi^2 = 32.954$; df = 8; $p < 0.001$). Thus, our findings show that the number of reading errors decreases significantly with age.

Table 2. Distribution of respondents according to the number of errors

Grade	Minimum	Average	Maximum	Disorder	Total of respondents
3rd	12 (35,3)	14 (41,2)	3 (5,3)	2 (8,8)	34
4th	37 (84,1)	3 (6,8)	4 (9,1)	0 (0,0)	44
5th	28 (62,2)	9 (20)	8 (17,8)	0 (0,0)	45
Total	77	26	15	2	123
$\chi^2 = 32.954$; df = 8; $p < 0.001$					

Number and percentage of respondents are shown (% in brackets)

The data in Table 3 show that the majority of our respondents reproduced a minimal number of facts, which clearly indicated difficulties in reading comprehension. There was no statistically significant difference in reading comprehension between students of the examined school age ($\chi^2 = 0.777$; df = 2; p = 678). Thus, in statistical terms, reading comprehension did not improve significantly from the third to the fifth grade.

Tables 4, 5 and 6 show the results of reading in male and female subjects of the third, fourth and fifth grade, obtained using the Mann-Whitney U test.

The test results showed that there was no statistically significant difference between boys and girls in the third grade in reading speed (U = 140.00; p = .89), reading comprehension (U = 110.00; p = .25) and the number of errors (U = 120.00; p = .39).

The test results showed that there was no statistically significant difference between boys and girls in the fourth grade in reading speed (U = 237.00, p = .99), reading comprehension (U = 187.50, p = .22) and the number of errors (U = 237.00, p = .99).

The test results showed that there was no statistically significant difference between

boys and girls in the fifth grade in reading speed (U = 171.00, p = .08), reading comprehension (U = 199.00, p = .26) and the number of errors (U = 210.00, p = .33).

The results of the correlation analysis showed that in all students of the examined age there is a statistically significant (p < 0.001) moderate positive correlation between reading comprehension and reading speed for the third (r = 0.588), fourth (r = 0.536) and the fifth grade (r = 0.662) respondents.

Table 3. Distribution of respondents according to reading comprehension

Grade	Minimum	Average	Total of respondents
3rd	34 (100)	0 (0,0)	34
4th	43 (97,8)	1 (2,3)	44
5th	44 (97,8)	1 (2,2)	45
Total	121	2	123
χ^2 = 0.777; df = 2; p = .678			

Number and percentage of respondents are shown (% in brackets)

Table 4. Reading, third grade

GENDER	N	READING SPEED		READING COMPREHENSION		READING ERRORS	
		Mdn	IQR	Mdn	IQR	Mdn	IQR
male	16	81.00	92	3.00	2	1.50	5
female	18	90.00	54	2.00	2	2.50	9
Mann-Whitney U Test		U = 140.00; p = .89		U = 110.00; p = .25		U = 120.00; p = .39	

Table 5. Reading, fourth grade

GENDER	N	READING SPEED		READING COMPREHENSION		READING ERRORS	
		Mdn	IQR	Mdn	IQR	Mdn	IQR
male	19	52.00	23	4.00	3	0	0
female	25	50.00	41	3.00	2	0	0
Mann-Whitney U Test		U = 237.00, p = .99		U = 187.50, p = .22		U = 237.00, p = .98	

Table 6. Reading, fifth grade

GENDER	N	READING SPEED		READING COMPREHENSION		READING ERRORS	
		Mdn	IQR	Mdn	IQR	Mdn	IQR
male	19	48.00	20	4.00	1	0	5
female	26	41.00	21	4.00	2	0	3
Mann-Whitney U Test		U = 171.00, p = .08		U = 199.00, p = .26		U = 210.00, p = .33	

Discussion

In this study, reading was examined in the third, fourth and fifth grade elementary school students. Our intention was to determine reading ability and identify reading disorders. With this aim, reading speed, reading accuracy, and reading comprehension were assessed. The results showed that 35.3% of the third and 22.2% of the fourth graders read slowly, or below the level expected for their age. When it comes to the number of errors, or the accuracy of reading, the deviation was determined only in the third grade students (8.8%), while the fourth and fifth grade students were within the expected norms. In terms of reading comprehension, respondents in all three grades were able to reproduce only a minimal number of test-predicted facts. According to our findings, there is a significant positive correlation between reading speed and reading comprehension.

Further analysis of the obtained results showed that the reading speed significantly increased with school age, and the number of reading errors decreased. These findings speak in favour of the typical development of reading skills in most of our respondents, viewed from the perspective of decoding written texts. This is supported by the fact that none among the fifth-grade children had reading speed and accuracy below the expected level. In other words, our findings show that after three years of learning children can fully master the reading skill. The results support the author's finding that learning to read takes at most four years [16, 17], after which a new phase begins where reading becomes a learning tool. According to this, the fifth grade students included in our study were expected to show good results in reading comprehension. However, this was where our fifth-grade respondents demonstrated very poor achievement. In addition to the poor result, we must point out that, in terms of reading comprehension, the fifth grade respondents did not significantly differ from the third and fourth grade respondents. As to the cause of the poor development of reading comprehension among our respondents, we cannot give a precise answer at this time. However, we can conclude that the majority of the fifth-grade respondents have not reached the expected stage in the development of reading, or they do not use reading as a learning tool. This is in agreement with the results of previous research, which has also found that most children at the end of the first cycle of education still do not use their reading skill as a learning tool [18, 19, 20].

From the point of view of reading development, phonological and orthographic decoding abilities lead to the recognition of words which, in typical development, is manifested in fluent reading. However, to understand the text, processes that connect semantic, syntactic and reference relations between words, phrases and sentences are necessary [21]. In other words, reading comprehension results from the development and coordinated use of language skills (translation of the written word into phonological code - decoding, vocabulary and knowledge of grammar) and cognitive functions (working and short-term memory, reasoning and monitoring) [21, 22]. The connection between cognitive abilities and reading comprehension is also shown in results of studies that found deficits in executive functions [23], as well as working memory deficits in children and adults with developmental reading disorder [24, 25]. Considering this relationship, the assessment of reading comprehension should be made in relation to the quality of working memory and executive functions, which is left as a challenge for future research.

According to the findings of some authors, the reason for poorer achievements in reading comprehension and insufficient use of reading competence for learning, partly lies in inadequate educational system [20]. Examining the development of reading liter-

acy in the first four grades of primary school, the authors of the study found that most children at the end of the fourth grade are not fully ready to use reading as a learning tool. Therefore, we believe that in the mentioned period, much more attention should be paid to enabling children to use the acquired reading skill as a learning tool.

When it comes to the prevalence of developmental reading disorder, the data differ depending on the school age. Previous studies have shown that 12.96% of the second, third and fourth grade students have reading difficulties [26]. Similar data are found in a recent study of the second and third grade children, where the presence of dyslexia was found in 13.7% of respondents [27]. By comparing the results of these two researches, it could be concluded that there was a slight increase in reading disorders in children who speak Serbian. On the other hand, the results of other research indicate the presence of reading disorder in a significantly smaller percentage of children. Specifically, Čolić [28] determined the presence of dyslexia in 5.3% of fourth grade students. These results suggest that age is a very important variable when considering the presence of a developmental dyslexia.

According to the traditional point of view, the children should go through at least two years of systematic training before any reading difficulties found can be characterized as a disorder. It should be borne in mind that in languages with "shallow" (transparent) orthography – such as Serbian, in which the phonemes and graphemes have a very regular and consistent relationship, and the rules of writing are clear – developmental disorder of reading occur in a smaller percentage of cases than in languages with "deep" (non-transparent) orthography (English or French for example) in which the relationship between grapheme and phoneme is complex and inconsistent. When determining the presence of reading disabilities of the children whose mother tongue is Serbian, a good starting point can be the fact that developmental dyslexia occurs in about 5% of Slavic children.

The results of our study showed that a number of lower primary school respondents are late in mastering the reading skill. Bearing in mind the results of the fifth grade students, we expect most of our lower grade respondents to successfully master this skill. However, they can also be expected to have problems in the transition to the phase of using reading as a learning tool.

The presence of difficulties and poorer development of reading comprehension in the respondents of our sample cannot be attributed to the developmental reading disorder. Since almost all children included in the sample had poor achievement in reading comprehension, these results may be related to a number of diverse factors. On the one hand, it is possible that insufficient attention is paid to the development of reading literacy in the education system. On the other hand, weaker lexical-semantic abilities as well as minor deviations in the development of cognitive functions related to reading are possible.

It needs to be mentioned that our research was conducted during the COVID-19 pandemic, when most of the classes with students involved in the study were conducted online. This has led to a lack of interactive teaching in which students would be more often encouraged to retell and answer questions related to the texts. It is possible that such learning circumstances have also contributed to the weaker development of reading literacy. Negative impact of COVID-19 was also noticed by other authors [29].

On the whole, our results showed that there is no statistically significant difference in reading ability between boys and girls. This finding is in line with the findings of authors who state that gender does not have a significant impact on the occurrence of developmental dyslexia [27, 30].

Conclusion

We identified a number of the third and fourth grade children who were late in the development of reading. In the third grade, this delay is manifested in slow reading and the appearance of a large number of errors. Fourth graders showed poorer results only in reading speed. In the fifth grade, no difficulties were recorded in either of these two reading characteristics. These data suggest the possibility that most of our third and fourth grade respondents will reach the expected reading speed and accuracy in reading. However, the possibility that a small number of respondents will develop reading disorder cannot be excluded.

Our results showed the presence of difficulties in reading comprehension in most of the respondents included in the study. It was also shown that in the span between the third and fifth grade there was no significant improvement in reading comprehension. This finding suggests that children after four years of training have not reached the stage of development in which reading becomes a learning tool.

Finally, our results showed that, on the whole, there is no statistically significant difference in reading ability between boys and girls.

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Ethical approval. The Teacher's Council of the Primary school "Jovan Dučić" in Šekovići, the Republic of Srpska, approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Sposobnost čitanja kod dece mlađeg školskog uzrasta

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Uvod. Čitanje je složena jezička i kognitivna sposobnost, koja se stiče učenjem. Deca tipičnog razvoja u prve četiri godine školovanja u potpunosti ovladavaju veštinom čitanja. Međutim, kod neke dece mogu da se ispolje teškoće u učenju čitanja uprkos očuvanim intelektualnim sposobnostima i adekvatnoj obuci. Cilj ovog rada je utvrđivanje sposobnosti čitanja i identifikovanje smetnji u čitanju kod dece mlađeg školskog uzrasta.

Metode. Uzorak su činila 123 učenika trećeg, četvrtog i petog razreda osnovne škole. U istraživanju je korišćen Trodimenzionalni test čitanja – tekst „Jedan snežni dan". Procenjivani su brzina čitanja, tačnost u čitanju i razumevanje pročitanog.

Rezultati. Sporo čitanje identifikovano je kod 35,3% učenika trećeg i 22,2% učenika četvrtog razreda. Odstupanja u tačnosti čitanja uočena su kod 8,8% učenika trećeg razreda. Kašnjenje u razvoju razumevanja pročitanog identifikovano je kod većine ispitanih učenika. U celini gledano, nisu utvrđene značajne razlike u sposobnosti čitanja između dečaka i devojčica.

Zaključak. Na osnovu rezultata istraživanja može se zaključiti da značajan broj dece kasni u savladavanju tehnike čitanja. S obzirom da se brzina čitanja sa uzrastom značajno povećava, a broj grešaka smanjuje, očekujemo da će veći broj učenika koji su sporo čitali dostići brzinu čitanja koja odgovara njihovom uzrastu, kao i da će određen broj dece koja su ispoljila neočekivan broj grešaka ovladati tačnim dekodiranjem reči. Budući da su smetnje razumevanja identifikovane kod većine ispitanika, možemo zaključiti da znatan broj dece nakon četvorogodišnje obuke nije dostigao fazu u razvoju u kojoj čitanje postaje sredstvo učenja.

Ključne reči: čitanje, brzina čitanja, tačnost u čitanju, razumevanje pročitanog, mlađi školski uzrast

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Original article

Voice condition assessment and the effect of rehabilitation in vocal professionals

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Summary

Introduction. The human voice is an important characteristic that enables the distinction of human from other living beings. Otherwise, it represents a picture of a person´s personality, his health, mental and emotional state. The research aims are to determine the voice characteristics of vocal professionals with diagnosed vocal cord nodules by subjective voice assessment and objective voice measurement before and after vocal rehabilitation.

Methods. This study has involved 25 examinees, aged 23 to 56. The subjective voice assessment was conducted with the Voice Handicap Index - VHI questionnaire and the objective voice measurement by a computerized laboratory for voice analysis "Kay Elemetrics". The obtained data were processed using descriptive and analytical statistics.

Results. Before the vocal rehabilitation and the subjective and objective voice measurements, the examinees had greater psychosocial difficulties associated with their voice quality. After two months of vocal rehabilitation, there has been a significant improvement in the voice of all subjects on the VHI scale. A statistically significant and highly statistically significant improvement have been noticed in six out of seven analyzed parameters of vocal A, by the objective measurement of voice. Namely, the obtained values - the percentage of jitter Jitt (%), the percentage of shimmer Shim (%), the relative average perturbation value RAP (%) and the coefficient of fundamental frequency variation - vFo were highly statistically significant ($p < 0.01$). The VTI - voice turbulence index and the SPI - soft phonation index also improved, the observed difference was statistically significant ($p < 0.05$), while the observed difference in the FTRI parameter was not statistically significant ($p > 0.05$).

Conclusion. Vocal rehabilitation has influenced the improvement of the voice quality, which means that the results obtained by objective voice measurements were more in accordance with the results of the subjective voice assessment.

Key words: voice, vocal rehabilitation, measurement, acoustic voice analysis, perceptual voice evaluation

Introduction

Vocal professionals are individuals who use voice as the basic means of their professional activity. They use it on a much larger scale, longer duration, higher intensity and under various professional and microclimate conditions [1].

The voice of a human involves a variety of sounds produced in a human phonatory organ. A human voice is a portrayal of one's personality, their health, psychological and emotional

state [2]. The term vocal professional includes a range of occupations that require the successful use of voice and speech, such as singers, actors, teachers, radio and television presenters, priests, commanders, lawyers, street vendors and many others. For the vocal professionals, a healthy and pleasant voice is important, because with a disrupted speech and voice they would not be able to do their job successfully [3].

According to the recommendation of the Center for Voice Disorders at Wake Forest University, there are four levels of vocal use depending on the importance of the voice for the profession:

Level I - Elite vocal professionals (actors and singers) where even the slightest damage to the voice affects their professional activity.

Level II - Vocal professionals (educators, leaders, priests, lawyers, politicians…) where moderate voice impairment affects their profession.

Level III - Non-vocal professionals (doctors, judges, command staff in the army and politics…) where only severe voice impairment affects their profession.

Level IV - Non-vocal nonprofessionals (all other occupations) where voice quality does not affect a profession which is important for everyday communication [2].

Causes of voice damage in vocal professionals are the same as for nonprofessionals, although vocal professionals are more exposed to damage due to specific working conditions, vocal load and special psychological conditions. Vocal fatigue leads to a change in vocal quality and a reduction in voice control, which results in reduced durability. In such situations, vocal professionals have an unpleasant sensation in the throat and neck, feel pain when swallowing, and avoid talking due to consistent tiredness [4]. The most common problems of the vocal professionals are hoarseness, murmured voice, voice tension, weak voice and ultimately loss of voice [5]. Dysphonia is a voice disorder that denotes any deviation from its normal features of pitch, intensity, and quality [6]. Vocal difficulties can also affect the psychological state of a patient and cause concern if and when the voice will function normally [5]. Hoarseness can affect communication and social integration, thereby deteriorating the quality of life of every human being [7].

The vocal cord nodules are limited calluses occurring on the free edge of the vocal cord, between the anterior and the middle third (the so-called Frenkel point) of both vocal cords and they are most often benign changes on the vocal cords.

The nodules may interfere with the professional activities of the patient and they should be treated, because any further strain on the voice organ of the patient with vocal cord nodules additionally damages the vocal cords [6].

The vocal rehabilitation is an effective method that applies to voice disorders and tends to change the way of vocal production. It reduces the unnecessary tension of the larynx and neck muscles and the proper flow of air through the glottis. In addition to the techniques of correct vocal production, vocal hygiene is also performed [8, 9].

The research aim is to determine the voice characteristics of vocal professionals with diagnosed vocal cord nodules by the subjective voice assessment and objective voice measurement before and after vocal rehabilitation.

Methods

In this study, 25 examinees participated, aged 23 to 56, with mean age 40.05. All the subjects were first examined by an otorhinolaryngologist, by indirect laryngoscopy, and after the diagnosis was established, they were referred to a logopedic outpatient clinic where vocal rehabilitation was performed, twice a week for 30 to 45 minutes.

In this research, the subjective voice assessment and objective voice measurement have been performed.

The subjective voice assessment has been performed using the Voice Handicap Index – VHI [10] questionnaire, which covers three areas: functional, emotional and physical. Each area contains ten questions. This questionnaire demonstrates the effectiveness of vocal rehabilitation and evaluates the extent of the voice problem experienced by a patient. All examinees filled out the VHI questionnaire for the first time they reported to the logopedic outpatient clinic and after two months they filled it for the second time. There was no time limit for completing the questionnaire.

The objective voice measurement has been conducted by the computerized laboratory for the voice analysis of the company ''Kay Elemetrics". In all examinees, the vocal A was recorded and analyzed. The acoustic structure of vocal A was analyzed for at least three seconds, from three attempts, in a room isolated from the noise, in a comfortable sitting position, with the usual voice pitch and intensity of the speaking voice. Seven parameters of multidimensional voice analysis were analyzed: the parametric signal (percentage of jitter (%)), the relative average perturbation value - RAP (%), the coefficient of fundamental frequency variation - vFo, the percentage of shimmer Shim (%), the voice turbulence index - VTI, the soft phonation index – SPI and the tremor analysis (frequency tremor intensity index- FTRI %). This method of assessment (acoustic analysis) is non-invasive and gives objective data on voice quality and allows monitoring of changes in voice over a longer period [11].

The subjective voice assessment and objective voice measurement were performed twice - before the beginning of vocal rehabilitation and two months later, after its completion.

Methods of descriptive and analytical statistics have been used in describing and analyzing the obtained data. From the methods of descriptive statistics, the arithmetic mean with the corresponding standard deviation was used, as well as the minimum and maximum frequency and percentage were used, and everything was presented in tabular form. In analytical statistics, the Student's t-test for parametric data and the Wilcoxon test of equivalent pairs for non-parametric data were used to assess the significance of the difference. Since the sample size was 25 subjects, the significance of the difference in the Wilcoxon test was determined by the Zed-Z test, because the data behaved according to the normal distribution. Statistical processing and analysis were done in the computer program SPSS ver. 20 (Statistical Package for the Social Sciences).

Results

Structure of the examinees in relation to gender, shown in Table 1.

Table 1. Sample structure with respect to gender

Gender	Frequency	Percentage
Female	16	82.0
Male	9	18.0
Total	25	100

f - frequency; p - percentage

The average age of the examinees is 40.05 years. Vocal professionals, whose voice use causes vocal strain, were represented in the study (Table 2).

Table 2. Sample structure with respect to occupation

Occupation	Frequency	Percentage
Teachers	10	49.0
Professors	7	35.0
Singers	4	8.0
Educators	4	8.0
Total	25	100

f - frequency; p - percentage

Table 3 shows the results on the VHI scale before vocal rehabilitation. Based on the results obtained before vocal rehabilitation, the examinees had greater psychosocial difficulties related to their voice quality. Since they were not able to use their voice adequately for professional and social needs, it also had a negative effect on their emotional state.

Table 4 shows the results obtained by the VHI scale after vocal rehabilitation. After vocal rehabilitation, there has been an improvement in the voice of all examinees (100%) on all the subscales, which has positively affected their voice as well as the quality of life.

Table 3. Results on the VHI scale before vocal rehabilitation

VHI subscale		Frequency	Percentage
Physical subscale	Mild	0	0
	Moderate	0	0
	Heavy	25	100.0
Emotional subscale	Mild	4	20.0
	Moderate	2	10.0
	Heavy	19	70.0
Functional subscale	Mild	0	0
	Moderate	6	30.0
	Heavy	19	70.0
Total score	Mild	0	0
	Moderate	1	5.0
	Heavy	24	95.5

Table 4. Results on the VHI scale after vocal rehabilitation

VHI subscale		Frequency	Percentage
Physical subscale	Mild	25	100.0
	Moderate	0	0
	Heavy	0	0
Emotional subscale	Mild	25	100.0
	Moderate	0	0
	Heavy	0	0
Functional subscale	Mild	25	100.0
	Moderate	0	0
	Heavy	0	0
Total score	Mild	25	100.0
	Moderate	0	0
	Heavy	0	0

f - frequency; p - percentage

Table 5. Values of vocal parameters before and after vocal rehabilitation

Vocal parameters	Middle value (MV) Before vocal rehabilitation	After vocal rehabilitation	p
Jitter (%)	2.396±1.053	0.200±0.100	p<0.01
Shimmer (%)	5.056±1.657	1.896±0.122	p<0.01
RAP	1.890±1.602	0.200±0.114	p<0.01
vFo	2.810±1.430	0.579±0.268	p<0.01
VTI	0.179±0.227	0.089±0.151	p<0.05
SPI	20.822±11.009	4.901±1.767	p<0.05
FTRI	1.006±0.461	0.671±0.658	p>0.05

The data are presented as an arithmetic mean ± standard deviation and as range (min - max). Jitt (%) - jitter percentage; Shim (%) - shimmer percentage; RAP - relative mean perturbation value; vFo - coefficient of variation of the fundamental frequency; VTI - voice turbulence index; SPI - attenuated phonation index; FTRI - frequency tremor intensity index

Table 5 shows the values of acoustic parameters before and after vocal rehabilitation. The results of acoustic parameters of the vocal A before and after vocal rehabilitation differed significantly. The observed difference in the parameters: Percentage of jitter Jitt (%), percentage of shimmer Shim (%), the relative average perturbation value RAP (%) and the coefficient of fundamental frequency variation - vFo were highly statistically significant. The obtained values of the parameters were as follows: Jitter (%) $W = 456$, $Z = -4.761$, $p < 0.01$; Shimmer (%) $W = 440$, $Z = -4.871$, $p < 0.01$; RAP $W = 389$, $Z = -4.461$, $p < 0.01$; vFo $W = 424$, $Z = -4.661$, $p < 0.01$.

The voice turbulence index - VTI and the soft phonation index - SPI have also improved, the observed difference was statistically significant ($W = 129.4$, $Z = -2.158$, $p < 0.05$, $W = 465$, $Z = -4.781$, $p < 0.01$). Tremor analysed by the frequency tremor intensity index - FTRI did not show significant improvement, the observed difference was not statistically significant ($W = 168$, $Z = -1.263$, $p > 0.05$).

Discussion

Vocal cord nodules most often occur in vocal professionals, individuals whose primary occupation is based on their voice, but also in children. They cause the hoarseness of voice of varying intensity. The hoarseness of the voice caused by vocal cord nodules in vocal professionals can affect physiological functioning, social adaptability and emotional state and cause psychological and emotional problems and thus impact their quality of life [7, 11, 12, 13].

The goal of vocal rehabilitation is to restore the voice of patients so that they will be able to use it adequately for their professional and social needs, which will improve their quality of life.

Before the beginning of vocal rehabilitation, an objective voice measurement showed that all the analyzed parameters were distorted, which inadequately reflected on their professional activity and thus the quality of life. After the completion of the vocal rehabilitation, a statistically significant and highly statistically significant improvement has been observed in six out of seven analyzed parameters of the vocal A: Jitter - Jitt (%), the relative average perturbation value - RAP, the coefficient of fundamental frequency variation - vFo, the percentage of shimmer Shim (%), the voice turbulence index – VTI, the soft phonation index - SPI, which is in accordance with other studies [13, 14, 15, 16, 17]. There was no significant improvement in the frequency tremor intensity index - FTRI, which can be explained by the short duration of vocal rehabilitation, which lasted two months. A large number of examinees in this study simultaneously attended vocal rehabilitation and completed their professional duties, not preserving their voice, which further slowed down their recovery.

The results obtained by the subjective voice assessment before vocal rehabilitation indicated a severe voice disorder. These results are in accordance with previous studies where it has been confirmed that dysphonia can cause psychological and emotional problems, which negatively affected their social integration [7, 9, 12, 14, 18, 19].

After the vocal rehabilitation, the voice of each examinee has improved, which means that the vocal rehabilitation produced positive results. Mathur et al. [20] had a positive outcome of vocal therapy on voice quality in vocal professionals. Other authors had a positive impact on the implementation of educational guidelines for vocal hygiene and vocal rehabilitation in patients with dysphonia in their studies [21, 22]. Many studies have shown that vocal rehabilitation can lead to improved voice quality [13, 14, 23].

Conclusion

Vocal professionals are people who are most susceptible to the development of all types of laryngeal pathology, but also functional pathologies that occur mainly due to improper and excessive use of voice. Vocal cord nodules represent one of the most serious laryngeal problems for vocal professionals. Vocal rehabilitation based on giving guidelines on voice hygiene, mastering the technique of proper breathing, eliminating hard attacks and tension in the neck and shoulders has a significant role in the treatment of vocal cord nodules. Vocal rehabilitation is of great importance for vocal professionals, primarily by achieving aesthetically high quality and good voice, and at the same time it is strongly focused on improving their quality of life.

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Ethical approval. The Ethics Committee of the Public Health Hospital "Sveti Vračevi" in Bijeljina approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Procena stanja glasa i efekat rehabilitacije kod vokalnih profesionalaca

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Uvod. Ljudski glas je važna karakteristika koja omogućava razlikovanje čoveka od drugih živih bića. Inače, predstavlja sliku ličnosti jedne osobe, njenog zdravstvenog, psihičkog i emotivnog stanja. Cilj istraživanja je da se subjektivnom procenom i objektivnim merenjem utvrde glasovne karakteristike vokalnih profesionalaca sa čvorićima na glasnicama pre i nakon vokalne rehabilitacije.

Metod. Ova studija obuhvatila je 25 ispitanika starosne dobi od 23 do 56 godina. Subjektivna procena glasa sprovedena je pomoću Indeksa glasovnog oštećenja (Voice Handicap Index - VHI scale) i objektivnog merenja glasa kompjuterizovanom laboratorijom za analizu glasa „Kay Elemetrics". U opisivanju i analiziranju dobijenih podataka korišćene su metode deskriptivne i analitičke statistike.

Rezultati. Pre vokalne rehabilitacije subjektivnim i objektivnim merenjem ispitanici su imali izražene psihosocijalne poteškoće koje su se odražavale na kvalitet glasa. Nakon dvomesečne vokalne rehabilitacije na VHI skali došlo je do značajnog poboljšanja glasa kod svih ispitanika. Objektivnom analizom glasa, visoko statistički značajno i statistički značajno poboljšanje primećeno je kod šest od sedam analiziranih parametara vokala A. Odnosno, dobijene vrednosti - procenat jitter-a Jitt (%), procenata shimmer-a Shimm (%), relativna srednja vrednost perturbacije RAP (%) i koeficijent varijacije osnovne frekvencije - vFo su bile veoma statistički značajne ($p < 0,01$). Poboljšali su se i indeks turbulencije glasa VTI i indeks prigušene fonacije SPI, uočena razlika je bila statistički značajna ($p < 0,05$), dok uočena razlika parametra FTRI nije bila statistički značajna ($p > 0,05$).

Zaključak. Vokalna rehabilitacija je značajno uticala na poboljšanje kvaliteta glasa, odnosno rezultati dobijeni objektivnim merenjem bili su u skladu sa rezultatima subjektivne procene glasa.

Ključne reči: glas, vokalna rehabilitacija, merenje, akustička analiza glasa, perceptivna analiza glasa

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Original article

Analysis of clinical parameters of white spots on young permanent teeth after their treatment with different dental varnishes

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Summary

Introduction. Detection of early carious lesion and its remineralization is the most effective way for caries treatment. The aim of this study is to compare effectiveness of remineralization of the early carious lesions with different fluoride varnishes.

Method. The research included 30 children, girls and boys, aged 12 and 13, in whom the presence of white lesions on at least two vestibular surfaces was detected on 60 permanent teeth during a clinical examination by visual method. Gingival status was determined based on bleeding or non-bleeding after probing, activity of the white lesion was visually examined and the size of the lesion was measured. After the measurement, the application of varnishes was performed by the procedure that two different dental varnishes were applied to two different teeth with white lesion in the same person: group I – fluoride varnish with 1.5% non-organic ammonium fluoride, group II – fluoride varnish enriched with minerals with 5% sodium fluoride. Activity, lesion dimensions and gingival status were examined after four, eight and twelve weeks when new varnishes were also applied.

Results. Inactivation of white lesions was recorded in the eighth week, but statistically significant difference was recorded after twelve weeks with 56.2% inactive lesions in the group I and 57.5% in the group II. There was no recorded difference in the lesion activity of the varnishes. Changes in the gingivo-incisal diameter during the visits amounted to: 3.47 mm/3.59 mm/3.53 mm/3.46 mm for the group I and 3.21 mm/3.19 mm/3.18 mm/3.20 mm for the group II. Changes in mesio-distal diameter amounted to: group I: 2.94 mm/2.81 mm/2.84 mm/2.4 mm; group II: 2.94 mm/2.87 mm/2.89 mm/2.90 mm. Statistically significant difference in both diameters was recorded between the first and second visit in the group I ($p = 0.0046$). There was no statistically significant difference recorded in the group I during other visits. In the group II statistically significant differences in the changes of lesion dimension were not recorded. Statistically significant differences $p < 0.001$ were recorded in the presence of gingival bleeding between the examined groups at the first visit, where significantly more lesions with healthy gingiva were observed in group I (84.4%).

Conclusion. Dental fluoride varnishes cause remineralization of early carious lesion after twelve weeks without significant difference between classic and enriched varnishes.

Key words: caries, white lesion, fluoride, remineralization

Introduction

Caries, as one of the most frequent chronical diseases, remains a very significant public health problem in our country as well as in the world. In the previous decades new scientific knowledge was developed and it influenced the paradigm shift in caries prevention and treatment. Modern principle of minimum intervention dentistry is focused on the early prevention and diagnosis of caries in order to restore the tooth integrity by secondary prevention measures, enabling thus significant savings in comparison to classic restoration treatment [1]. This principle implies: determination of the caries risk, dental plaque control, application of a certain hygiene and diet regime, as well as remineralization of the early carious lesions. The early carious lesion or white spot (white spot lesion - WSL) represents the earliest clinical stage of disease which manifests itself in histopathological changes within crystal bar of the surface intact enamel where ''ad integrum'' recovery can still be used. Clinically the lesion manifests itself as a white matte surface and in this stage of disease it has reversible character. At this stage it is possible to stop further demineralization and cavity formation process by using certain preparations and stimulate remineralization eliminating thus the necessity for preparation and restoration [2]. The existing evidence clearly shows that caries is the consequence of the disturbed balance between permanently present remineralization and demineralization processes caused by the presence of active cariogenic biofilm and continuous presence of dissolvable carbohydrates. Longer enamel exposure to acids produced by cariogenic bacteria leads to more extensive mineral extraction from hydroxyapatite crystal with increase in the volume of intercrystal areas. In case of further demineralization this phenomenon becomes clinically visible as turbidity of the bright enamel surface already around the fourteenth day and this is marked as the early carious lesion, or "white spot" [1, 3]. The possibility to control caries by stimulating remineralization process is a significant achievement of modern dentistry. Fluorides have been used for a longer period of time as a standard procedure not only in prevention, but also in remineralization of early lesions. It is recommended to use preparation with high fluoride concentration, whereby application of dental varnishes has proved to be most efficient and secure choice in children of school and preschool age [4]. Besides the high prevention effects achieved by fluoride varnishes recent research increasingly point to the necessity of the presence of the building elements for restoration of the crystal apatite [5]. One of those - very popular one is dental fluoride varnish enriched by amorphous calcium phosphate, stabilized by milk protein casein phosphopeptide (CPP-ACP) [6].

There are few studies that followed dynamics of the clinical changes of the white spot. The aim of the research was to determine to what extent it is possible to track by visual-tactile method clinical recovery of the white spot on enamel and whether the type of varnish influences changes in clinical parameters of the remineralization process.

Method

Research was conducted with 30 children (12 boys and 18 girls), ages 12 and 13. Out of each respondent two permanent teeth were chosen which, during clinical examination by visual method, showed white spots on at least two vestibular surfaces. The research included only healthy children without local or common diseases and/or allergies.

After professional removal of the soft tooth deposits, the tooth was air-dried for 5 seconds. First the gingival status of the examined teeth was determined using WHO periodontal probe with the rounded tip, whereby after probing sulcus in the white spot area it was monitored whether there would be

bleeding. We decided to use gingival bleeding as a parameter of oral hygiene practice, because determination of plaque index is often not a reliable sign, as children are used to brush their teeth immediately before the dental check-up. Then the lesion size was determined in millimeters using graded periodontal probe, whereby gingivo-incisal and mesio-distal diameters were measured. Visual lesion examination implied observation of the lesion, which depending on whether it was rough and matte or smooth and shiny could be characterized as active or inactive. After the gingival status had been determined, the lesion was measured and visual examination was conducted, varnish was applied so that two different varnishes were used with the same person and on two different teeth:

Group I (classic varnish) – fluoride varnish (Fluor Protector S®, Vivadent, Lichenstein) with 1.5% non-organic ammonium fluoride (7700 ppmF u 1 ml) in base with water and alcohol and with alcohol as a solvent which has 4 times higher concentration after bonding,

Group II (enriched varnish) – fluoride varnish enriched with minerals (MI varnish®, GC, Tokyo, Japan) with 5% sodium fluoride (22.600 ppmF u 1 ml) containing also a bioavailable calcium phosphate in from of casein-phosphopeptide RECALDENT™ (ACP-CPP).

Application of varnish was conducted by special applicators (brushes) according to standard procedure and strictly adhering to producer's instruction. After both treated teeth had been painted from all sides, respondents and their parents were advised not to drink and eat for the next 60 minutes and not to brush teeth until the evening. All participants were educated how to brush their teeth properly (with a toothpaste containing 1450 ppm fluoride). During the next two visits, after four weeks (second visit) and eight weeks (third visit) from the first application of varnish, soft teeth deposits were removed with the rotating brush and toothpaste without fluoride. Gingival status, lesion activity, diameter in mesio-distale and gingival-incisal direction were recorded in the monitored teeth and varnishes were applied again. After twelve weeks (fourth visit), all measurements were conducted again.

The results regarding changes in white spots dimensions were shown in form of average value of all individual measures and by determining median and standard deviation. Regression, stagnation or progression of the initial lesion were recorded and the results from the visits and treatment groups were compared. Statistical processing of results was done by the program SPSS 16.0 Windows and by using the program MS Office Word and MS Office Excel. Test for independent samples or non-parameter Mann-Whitney U test was used depending on the normality of characteristic. Normal distribution of the observed characteristics was tested by Kolmogorov–Smirnov test and Pearson's chi-Squared test. For changes in related samples Wilcoxon signed-rank test was used with the significance limit of at least $p = 0.05$.

Results

During the first visit the examined lesions were active. Clinical inactivation of lesions was noticed during the third visit, after eight weeks (group I 15.6%; group II 15.2%). Half of the observed lesions were characterized as inactive after twelve (12) weeks during the fourth visit (56.2% group I and 57.5% group II; $p< 0.0001$). No significant lesion activities were recorded between the examined varnishes (Table 1).

Regarding changes in the lesion dimension in the group I, a statistically significant change was noticed in both directions: mesio-distale and gingival-incisale between the first and second visit ($p = 0.046$) (Table 2 and Table 3). During other visits (third and fourth visit) no statistically significant differences in change of

Table 1. Lesion activity in the examined groups during visit

	Group I N=32 N (%)		Group II N=33 N (%)		p
	A	I	A	I	
1 visit	32 (100.0)	0 (0.0)	33 (100.0)	0 (0)	p=0.03
2 visit	32 (100.0)	0 (0.0)	33 (100.0)	0 (0)	p=0.03
3 visit	27 (84.4)	5 (15.6)	28 (84.8)	5 (15.2)	p=0.03
4 visit	14 (43.8)	18 (56.2)	14 (42.4)	19 (57.5)	p=0.03
p (result for related sample)	p<0.0001		p<0.0001		

A = active lesion; I = inactive lesion

mesio-distale and gingivo-incisal lesion diameter were recorded in the group I (Table 2 and Table 3). There were no statistically significant changes in lesion dimension in both directions mesio-distale and gingivo-incisal in the group II. The value of gingivo-incisal changes in dimension between visits in the group I amounted to 3.47 mm/3.59 mm/3.53 mm/3.46 mm, and in the group II 3.21 mm/3.19 mm/3.18mm/3.20 mm. Regarding mesio-distal diameter the values were 2.94 mm/2.81 mm/2.84 mm/2.91 mm for the group I and 3.21 mm/3.19 mm/3.18 mm/3.20 mm for the group II.

Determination of gingival health by presence or absence of bleeding through probing points out to the level of hygiene routine. During the first check-up of the group I, a significantly greater number of surfaces with healthy gingiva was noticed (84.4%), whereas the condition of the group II was much worse (48.5%). During the second visit there was a mild decrease in healthy segments in the group I (there was no statistical significance) and increase in healthy segments in the group II, so that both groups were getting equal. This continued during further monitoring until the check-up after twelve weeks when there was no difference (93.8% group I; 87.9% group II, p> 0.05). The treated lesions were surrounded with healthy gingiva (Table 4).

Table 2. Changes in the size of lesion in mesio-distal direction in the examined groups during visits

	Group I N=32 X±SD (mm)	Group II N=33 X±SD (mm)	p
1 visit	2.94±0.98	2.94±0.99	p=0.971/ NS
2 visit	2.81±0.97	2.87±0.92	p=0.622/ NS
3 visit	2.84±0.95	2.89±0.93	p=0.736/ NS
4 visit	2.91±0.97	2.90±1.1	p=0.736/ NS
2 vs 1 visit 3 vs 1 visit 4 vs 1 visit	**p=0.046** p=0.083/ NS p=0.180/ NS	p=1.000/ NS p=1.000/ NS p=1.000/ NS	

Table 3. Changes in the size of lesion in gingivo-incisal direction in the examined groups during visits

	Group I N=32 X±SD (mm)	Group II N=33 X±SD (mm)	p
1 visit	3.47±1.08	3.21±1,013	p=0.455 / NS
2 visit	3.59±1.01	3.19±1,01	p=0.150 / NS
3 visit	3.53±1.09	3.18±1,0	p=0.239 / NS
4 visit	3.46±1.07	3.20±1,01	p=0.338 / NS
2 vs 1 visit 3 vs 1 visit 4 vs 1 visit	**p=0.046** p=0.157 / NS p=1.000/ NS	p=0.157/ NS p=0.157/ NS p=0.157/ NS	

Table 4. Presence of gingival bleeding around the treated lesions in the examined groups during visits

	Group I N=32 N (%)		Group II N=33 N (%)		p
	Bleeding	Without bleeding	Bleeding	Without bleeding	
1 visit	5 (15.6)	27 (84.4)	17 (51.5)	16 (48.5)	p=0.001
2 visit	8 (25.0)	24 (75.0)	5 (15.2)	28 (84.8)	p=0.26
3 visit	1 (3.1)	31 (96.9)	5 (15.2)	28 (84.8)	p=0.26
4 visit	2 (6.2)	30 (93.8)	4 (12.1)	29 (87.9)	p=0.26
p (result for ralared sample)	p=0.001		p=0.001		

Discussion

Fluoride treatment is a usual prevention method used in order to reduce enamel demineralization by Fluoride concentration in saliva and plaques efficient in preventing the process of demineralization and activating the one of remineralization. Organic acids produced by cariogenic bacteria cause reduction in the plaque pH value, which consequently leads to fluoride diffusion from plaque and saliva into enamel and formation of fluoridated hydroxyapatite. This new crystal form is more resistant to acids [7]. The work group formed in 2018 by the American Dental Association (ADA) and Center for Dentistry based on evidence recommends the use of 5% varnish based on fluoride for either blocking or recovery of the inactivated carious lesion on smooth surfaces of permanent teeth [8]. In the systematic analysis of the published studies, Urquhart et al. point out that by application of 5% fluoride varnish

chances for either blocking or recovery of lesion on milk or permanent teeth are 2 to 3 times higher when compared to diseased enamel surfaces treated only by oral hygiene [9]. Researches show prolonged fluoride release from 5% varnishes (contain 22.000 ppmF) in the first six months after application and with the highest release in the first three months [10].

We decided for gingival bleeding as a parameter for defining the level of hygiene practice as determination of the plaque index is often not a reliable marker due to the fact that children brush their teeth immediately before dental check-up. Alavi and Yagarhi found out that the teeth treated by fluorine showed decrease in plaque index and reduced gingival inflammation and that fluorine treatment prevented development of white spots in children wearing fixed braces [11].

Although there was a statistically significant difference in gingival bleeding around treated lesions between the examined groups before the research (15.6% group I and 51.5% group II), it disappeared already during the subsequent visits, which points out to unevenness of the examined groups before the application of varnishes. However, the initial differences did not impact the remineralization process. Decrease in gingival reaction was gradual and started occurring only after two months (third visit), which points out to the significance of frequent remotivation for the establishment of healthy habits [12]. Wiegand et al. emphasize that application of varnishes can maintain balance on enamel surface even in patients who do not follow advice regarding anticariogenic nutrition and regular hygiene practice with fluoride toothpaste [13].

For our research we used specimen of classic and enriched fluoride dental varnish being among the rare ones registered in B&H, which points out to low dentists' interest in profilactic and secondary prevention intervention. Certain researches show a slightly higher effectiveness of combination of fluoride and remineralised biovelent ions [14, 15]. There was no significant difference between classical and enriched dental varnish in our research, which is in accordance with other studies [16, 17].

The most interesting aspect of the research was the result of statistically significant dimensional changes in both directions: mesio-distal and gingivo-incisal between the first and second visit in the examined teeth of the group I. It is confusing that there was a decrease in mesio-distal diameter and that there was even an increase in lesion dimension in gingivo-incisal. Possible explanation for higher decrease in mesio-distal diameter could lie in more aggressive teeth brushing after given instruction or demineralization level was more expressed with respondents showing gingivitis, so that oral hygiene and varnish effect led to an intensified remineralization in the first run. There is so far no adequate explanation for significant increase in gingivo-incisae lesion diameter, although it was minimum and there are also no requests for research using different methodology for monitoring remineralization process. Some studies which recorded mineral density using DIAGOdent apparatus have not discovered such variations [18, 19], so that this finding could be ascribed to inaccuracy in measurement.

The results demonstrate that in the period of three months there was no significant reduction in white spots dimensions in both groups where we applied varnish two times, which at first sight could point out to low effectiveness of dental varnishes. However, by further monitoring of the activity after three months, significant increase in clinically inactive lesions was noticed as a clear sign of recovery. Statistically significant decrease in the number of active lesions in the twelveth week from the beginning of the research is still only partial, which indicates that this period is insufficient for recovery. Rahmi et al. showed that a more significant level of clinical reduction of the "white spot" was to be expected only after six months, and that even afterwards there could remain a whitish ''scar" [20, 21].

Deficiency of this study was the fact that the analysis did not include other important parameters for demineralization reduction different from mere oral hygiene, such as presence of free sugars, whose effect, when consumed frequently, cannot be neutralised by fluoride. [22]. No significant difference in effectiveness of the examined dental varnishes was noticed. Certain researches published results about more favourable reminalisation features of varnishes containing kazein phosphopeptide-amorphium calcium phosphate (CPP-ACP), whereas other prioritized solely classic varnishes [23–25].

Conclusion

Fluoride-based varnishes lead to remineralization of the early carious lesions, but a period longer than three months is necessary to clinically visible reduction of the "white spots" size. This makes it a very unreliable parameter for monitoring the recovery. Lesion inactivity, i.e. its transition from the stage in which it is rough and matte to the one in which it is smooth and bright is the first visible remineralization sign which precedes reduction in lesion dimension. There is no significant difference in remineralization effectiveness between classic and enriched dental varnishes.

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Ethical approval. The Ethics Committee of the Public Health Institution Dental Institute of the Republic of Srpska approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

*The Ethics Committee of the Public Health Institution Dental Institute of the Republic of Srpska gave its consent no: 01-343-3/17 on 15.2.2017. Ministry of Education and Culture of the Republic of Srpska gave its consent no: 07.041/052-7273/17 on 05.10.2017. For each child parents signed their consent which is a part of the medical documentation.

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Analiza kliničkih parametara kod bijelih mrlja mladih stalnih zuba nakon izloženosti različitim dentalnim lakovima

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Uvod. Detekcija početne kariozne lezije i njena remineralizacija je najefikasniji način liječenja karijesa. Cilj rada je upoređivanje efikasnosti remineralizacije početne kariozne lezije različitim fluoridnim lakovima.

Metod. U ispitivanje je bilo uključeno 30 djece oba pola, uzrasta 12 i 13 godina, kod kojih je na 60 stalnih zuba tokom kliničkog pregleda vizuelnom metodom otkriveno prisustvo bijelih mrlja na najmanje dvije vestibularne površine. Utvrđivalo se stanje gingive na osnovu prisustva ili odsustva krvarenja poslije sondiranja, vizuelno se ispitivao aktivitet bijele mrlje i mjerena je veličina lezije. Nakon mjerenja vršena je aplikacija lakova postupkom da su kod iste osobe na dva različita zuba sa bijelom mrljom aplikovana dva različita dentalna laka: I grupa – fluoridni lak sa 1,5% neorganskog amonijum fluorida, II grupa - fluoridni lak obogaćen mineralima sa 5% sodium fluorida. Aktivitet, dimenzije lezije i stanje gingive provjeravani su nakon četiri, osam i dvanaest nedjelja kada su vršene i nove aplikacije lakova.

Rezultati. Inaktivacija bijelih mrlja bilježi se u osmoj nedjelji, ali statistički značajna razlika evidentirana je nakon dvanaest nedjelja sa 56,2% inaktivnih lezija u I grupi i 57,5% u II grupi. Nije zabilježena razlika u aktivitetu lezija između lakova. Promjene gingivo-incizalnog promjera tokom posjeta su iznosile: 3,47 mm/3,59 mm/3,53 mm/3,46 mm za I grupu i 3,21 mm/3,19 mm/3,18 mm/3,20 mm za II grupu. Promjene mezo-distalnog promjera su iznosile: I grupa: 2,94 mm/2,81 mm/,2,84 mm/2,4 mm; II grupa: 2,94 mm/2,87 mm/2,89 mm/2,90 mm. Uočena je statistički značajna razlika oba promjera između prve i druge posjete u I grupi ($p = 0,0046$). Pri ostalim posjetama u I grupi nije evidentirana statistički značajna razlika. U II grupi nisu uočene statistički značajne razlike promjene promjera dimenzija lezije. Evidentirane su statistički značajne razlike $p< 0,001$ u prisustvu gingivalnog krvarenja između ispitivanih grupa pri prvoj posjeti, gdje je kod I grupe uočeno značajno više lezija sa zdravom gingivom (84,4%).

Zaključak. Dentalni fluoridni lakovi dovode do remineralizacije početnih karioznih lezija nakon dvanaest nedjelja, bez značajnih razlika između klasičnih i obogaćenih lakova.

Ključne riječi: karijes, bijela mrlja, fluor, remineralizacija

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Original article

Attitudes and factors associated with adverse patient outcomes as perceived by nurses and medical doctors

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Summary

Introduction. The patient and his safety should be at the center of quality health care, which is a challenge for every health system. Adverse patient outcomes (APO) are defined as damage caused by a drug or other intervention in a primary, secondary or tertiary health care facility, which results in a complication of the primary or the emergence of a new disease or injury. The aim of our study was to determine how frequent the APO are, and to determine the differences between nurses and doctors in the frequency, causes and attitudes towards APO.

Methods. This cross-sectional study included 100 health professionals, nurses and medical doctors employed at the primary and secondary level of health care. The research was conducted in the period from May to October 2020. The questionnaire was partially taken from a general questionnaire offered on the website of the Agency for Healthcare Research and Quality and the standardized Perceived stress scale was used to measure the degree of subjective stress.

Results. Forty-four health professionals (44%) experienced adverse patient outcomes in their career, doctors (52%) significantly more often than nurses (36%) ($p = 0.039$). More than a half of respondents (52.3%) declared that APO happens few times a month. Seventy percent of the respondents blame their own stress burden as the main factor associated with APO. Doctors more often than nurses (69.2%) blame problems in communication between health professionals as the main cause of APO (27.8%) ($p = 0.046$).

Conclusion. For doctors, the main cause of APO is problem in communication, while nurses more often think that patient safety is priority when compared to doctors. Almost two thirds of respondents blame their own stress burden as a factor associated with APO.

Key words: frequency, attitudes, adverse patient outcomes

Introduction

Adverse patient outcomes (APO) in the provision of health care have been happening since the beginning of medicine. As early as the 4th century BC, the preventive measure "primum non nocere", or "first, do no harm", is mentioned in Greece. As at that time, so now it is just

as important not to harm as it is to help those in need. The patient and his safety should be at the center of quality health care, which is a challenge and a priority of every health system [1, 2]. The adverse patient outcomes are defined as damage caused by a drug or other intervention in a primary, secondary or tertiary health care facility, which results in a complication of the primary or the emergence of a new disease, illness or injury. Adverse outcomes can also be called iatrogenic conditions and it is necessary to distinguish them from complications, which are also undesirable, but can also occur during proper treatment [3, 4]. Patient safety implies the effort and activities undertaken by the healthcare team to ensure that the application of all procedures and the environment around the patient allow the provision of health care with the aim to enable the desired outcome of treatment of patients [5]. Patient safety is known to be the most reliable indicator of the quality of the health system in all countries that provide health care in the public or private sector [6–8].

Despite the rapid development of medicine, the sophistication of medical equipment, as well as the increasing adoption of modern and effective risk control techniques, there is a growing possibility of errors in health care. According to data from the most of European Union countries, about 8–12% of patients suffer some damage as a result of treatment errors [9, 10]. One of the reports of the American Medical Institute says that every year over a million people suffer the consequences caused by mistakes in health care. An average of 44,000 to 98,000 people die each year from mistakes made by doctors or nurses, while the tax burden on taxpayers is $ 37.6 billion [11, 12].

According to the definition of the World Health Organization (WHO), work in a health team is defined as the cooperation of several experts in achieving a common goal, which is the treatment and provision of health care to patients, and work in a health team must not be divided but well-coordinated by the health team leader [13]. In order for the organization in the health team to be of high quality and professional, it is necessary for each member of the health team to take responsibility for the part of the work they perform. This is the only way for the health team to achieve good results in patient care through coordinated action, because a larger number of members of the healthcare team, compared to an individual, can achieve greater efficiency and scope of work, and the number of errors in this case is significantly lower [14]. The basic task of all members of the healthcare team is to ensure patient safety that is directly correlated with the occurrence of expected or unexpected adverse events. It has long been thought that a patient's safety depends most on the doctor-patient relationship. However, with the development of the nursing profession and the technology applied in nursing procedures, the provision of health care takes on another dimension, which largely depends on nurses who are also a significant part of the healthcare team. Therefore, we should strive to make the healthcare system as safe as possible at all levels [15–17]. There is a public opinion that nurses are most responsible for patient safety. The reason for this is that nurses play a central role in patient safety, which is why there is a danger that all medical errors are attributed to nurses, instead of errors to other members of the healthcare team or errors in the healthcare system. In contrast, research shows that thanks to nurses, a large number of unwanted mistakes and events have been prevented and that they protect patients from insecurity and certain omissions in clinical practice. It is therefore important to mention that almost every procedure in patient care requires and involves a certain degree of potential risk [18].

The most common APO associated with the healthcare process are nosocomial infections, poor hand hygiene that can cause infections, adverse drug side effects, pressure ulcers, and patient falls [19]. The consequences

of medical errors can be fatal, severe physical or mental damage, as well as minor damage [20–22]. After mistakes occur, members of the healthcare team (nurses and doctors) become demoralized and dissatisfied, in addition, the consequence of APO can be a direct material or criminal liability for healthcare workers, with possibility to lose licence for clinical practice [23–25].

The occurrence of APO in the healthcare system is a global problem. However, there is not much data in the literature on the difference in frequency, attitudes, and factors associated with APO between nurses and doctors. That is why in our research we paid special attention to determine how frequent the adverse patient outcomes are, and to determine the differences between nurses and doctors in the frequency, causes and attitudes towards APO.

Methods

The research was conducted as a cross-sectional study in the population of health professionals, medical doctors and nurses employed at the primary and secondary level of health care. The sample consisted of health professionals from the "University Hospital Foca" and the "Health Center Foca". The study included 100 subjects (50 nurses and 50 medical doctors) of both genders, aged 20 to 65 years. Prior to the start of the research, the written consent of the competent institutions was obtained. Participation in the study was voluntary, and the survey was anonymous.

Data were collected by survey. To obtain the data, a questionnaire was used which was composed of questions for collecting socio-demographic data, as well as the frequency of perceived APO, causes and types of APO, as well as attitudes about APO. The questionnaire was consisted of twenty questions that were partially taken from a general questionnaire offered on the website of the United States of America (USA) Agency for Healthcare Research and Quality [26]. The questions are tailored to the needs of this research, and a number have been designed and intended specifically for this topic.

An integral part of the questionnaire was a standardized Perceived stress scale (PSS). This scale measures the degree to which respondents experience their lives as unpredictable, uncontrolled, and overburdened, the three basic components of experiencing stress. The PSS measures the degree of subjective stress through assessments of lack of control, feelings of satiety and unpredictability of life. The scale is consisted of 10 particles that are like: How confident are you that you can deal with your problems in the last month? Respondents rate their experience of a particular stressor on a Likert scale with scores from 0 to 4 (0 never, 1 almost never, 2 sometimes, 3 quite often and 4 very often). The total score is obtained by summing the responses where a higher score indicates a higher level of perceived stress.

The methods of descriptive and analytical statistics were used in the paper. Among the methods of descriptive statistics, measures of central tendency and measures of variability were used, namely: arithmetic mean with standard deviation and relative numbers for categorical variables. Among the methods of analytical statistics Student's t test was used for bound samples. Of the nonparametric tests, the chi-squared test was used to assess the difference between the groups. The usual value of $p< 0.05$ was taken as the level of statistical significance of differences, while the values of $p< 0.01$ were considered highly statistically significant. Results were statistically analyzed in GraphPad Prism software (GraphPad, La Jolla, CA, USA) and SPSS software package version 21.0 (Statistical Package for Social Sciences SPSS 21.0 Inc, USA).

Results

Our sample was consisted of 100 health professionals divided by profession in two groups, the first group was consisted of 50 nurses (50%) and the second group was consisted of 50 (50%) doctors. The mean age of the subjects was 45.53 ± 12.64 years. Respondents were divided into two categories in relation to age, the category of younger respondents, from 20 to 40 years (34%) and the category of older respondents (from 41 to 65 years) (66%). There was no significant difference between the groups of respondents divided by profession in relation to age. Fifty-four percent of respondents had more than 21 years of work experience. Fifty percent of respondents work in primary health care, i.e. in the health center, while the remaining 50% of respondents work in secondary health care, i.e. in the hospital. Statistical analysis showed that there was a high statistically significant gender difference between the groups of respondents divided by profession (p = 0.001), with significantly more women (88%) in the group of nurses than in the group of doctors (54%). Also, nurses significantly (p = 0.001) more often had a longer work experience (74%) compared to doctors (34%). According to the PSS, prevalence of stress among respondents was 57% and there was significantly (p< 0.001) higher number of doctors who had a high level of stress (76%) compared to nurses (38%) (Table 1). Also, Figure 1 shows that doctors had significantly (p< 0.001) higher level of PSS total score (19.04 ± 4.65) when compared to nurses (14.72 ± 2.53) (Figure 1).

Table 1. Differences in age, gender, level of health care, years of work experience and level of stress between nurses and doctors

Variables	Nurses (n=50)		Doctors (n=50)		Total (n=100)		P (χ^2)
	n	%	n	%	N	%	
Age							
20 to 40 years	16	31	18	36	34	34	0.673
41 to 65 years	34	68	32	64	66	66	
Gender							
Male	6	12	23	46	29	29	0.001
Female	44	88	27	54	71	71	
Level of health care							
Primary	24	48	26	52	50	50	0.841
Secondary	26	52	24	48	50	50	
Years of work experience							
1 to 20 years	13	26	33	66	46	46	<0.001
21 do 42 years	37	74	17	34	54	54	
Perceived stress scale							
Average level of stress	31	62	12	24	43	43	<0.001
High level of stress	19	38	38	76	57	57	

χ2 - Chi-squared test

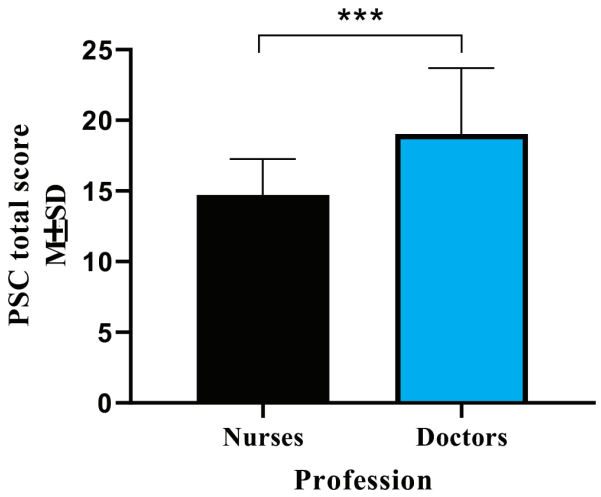

Figure 1. Mean values of Perceived stress scale total score between respondents divided by profession. PSS - Perceived stress scale; M - mean, SD - standard deviation; *p< 0.05; **p<0.010; ***p< 0.001

Table 2 shows differences in experience and cause of APO between nurses and doctors. Forty-four health professionals (44%) experienced adverse patient outcomes in their career, doctors (52%) statistically more often than nurses (36%) (p = 0.039). More than a half of respondents (52.3%) declared that APO happens few times a month, 31.8% stated that APO happens annually and 15.9% respondents stated that it happens every day. Between nurses and doctors significant difference in frequency of APO was not observed. Fifty-two percent (52.4%) of respondents stated that the main cause of APO is problem in communication between healthcare professionals, 38.6% said that the main cause is problem in organization at workplace, while only 9% of respondents said that the cause of their experience of APO was personal problem. Doctors significantly more often (69.2%) blame problems in communication as main cause of APO than nurses (27.8%), while nurses more often (22.3%) than doctors (0%) declare that the cause of APO is on personal level (p = 0.046). More than a half of respondents (54.5%) stated that the fall of a patient was their experience with APO, 29.5% stated that the mistake was related to medication error, and 15.9% said that the APO arose as consequence of identity replacement. Nurses (63%) significantly more often than doctors (41.2%) declare that falls are the type of APO according to their experience (p = 0.031). When they are asked to express their opinion whether a COVID-19 pandemic affects a more often occurrence of APO, 44% of respondents agreed with this statement, 39% of them did not know, while 17% of respondents declared that they do not think that pandemic could affect more frequent occurrence of APO. Doctors significantly more often (54%) stated that pandemic could affect more frequent occurrence of APO than nurses (34%) (p = 0.021). Seventy percent of health professionals declared that their own stress burden is a main cause of APO, but between groups of respondents the statistical significance was not observed (Table 2).

Seventy-three percent of respondents stated that patient safety is priority in the work of healthcare staff. However, significantly more doctors (38%) did not agree with this statements when compared to nurses (16%) (p = 0.013). Eighty percent of health professionals stated that they are actively working to improve patient safety and 89% of respondents stated that the protocols are followed and because of that the possibility of APO is reduced,

Table 2. Differences in experience, frequency and causes of adverse patient outcomes between nurses and doctors

Variables	Nurses (n=50)		Doctors (n=50)		Total (n=100)		P (χ^2)
	n	%	n	%	n	%	
The expirience of APO							
No	32	64	24	48	56	56	0.039
Yes	18	36	26	52	44	44	
Frequency of APO (n=44)							
Annually	7	38.9	7	26.9	14	31.8	0.655
Few times a month	8	44.4	15	57.7	23	52.3	
Every day	3	16.7	4	15.4	7	15.9	
The main cause of APO (n=44)							
Organizational	9	50	8	30.8	17	38.6	0.046
Personal	4	22.3	0	0	4	9	
Communication between health professionals	5	27.8	18	69.2	23	52.4	
Type of AOP (n=44)							
Medication errors	7	25.9	6	35.3	13	29.5	0.031
Falls	17	63.0	7	41.2	24	54.5	
Identity replacement	3	11.1	4	23.5	7	15.9	
A COVID-19 pandemic affects a more frequent occurrence of APO							
No	12	24	5	10	17	17	0.021
I don't know	21	42	18	36	39	39	
Yes	17	34	27	54	44	44	
Stress at work is the main cause of APO							
No	13	26	17	34	30	30	0.762
Yes	37	74	33	66	70	70	

APO - adverse patient outcomes; χ2 - Chi-squared test

Table 3. Differences in attitudes of nurses and doctors about the safety of patients and occurrence of adverse patients outcomes

Variables	Nurses (n=50)		Doctors (n=50)		Total (n=100)		P (χ^2)
	n	%	n	%	n	%	
Patient safety is a priority in the work of healthcare staff							
I agree	42	84	31	62	73	73	0.013
I don't agree	8	16	19	38	27	27	
We are actively working to improve patient safety							
I agree	39	78	41	82	80	80	0.617
I don't agree	11	22	9	18	20	20	
The protocols are followed and thus the possibility of APO is reduced							
I agree	46	92	43	86	89	89	0.338
I don't agree	4	8	7	14	11	11	
APO prevention is discussed in the department							
Never	13	26	12	24	25	25	0.048
Frequently	23	46	33	66	56	56	
Allways	14	28	5	10	19	19	
Information about APO is available to healthcare professionals							
I agree	36	72	36	72	72	72	1.000
I don't agree	14	28	14	28	28	28	
Patient safety always comes first							
I agree	46	92	48	96	94	94	0.400
I don't agree	4	8	2	4	6	6	
The frequency of reporting APO							
Allways	14	28	2	4	16	16	0.003
Frequently	14	28	21	42	35	35	
Rarely	7	14	15	30	22	22	
Never	15	30	12	24	27	27	

APO - adverse patient outcome; χ^2 - Chi-squared test

94% of them stated that patient safety comes first and 72% stated that information about APO is available to healthcare professionals, but the difference between nurses and doctors was not observed. However, significantly more nurses (28%) stated that APO prevention is always discussed in the department when compared to doctors (10%) ($p = 0.048$). Also, nurses more often (28%) stated that they always report APO when compared to doctors (4%) (Table 3).

Discussion

Our research was conducted on a sample of 100 health professionals (50% of nurses and 50% of medical doctors) and aimed to identify the most common causes, types and frequency of adverse events in clinical practice. Also, the aim of the study was to determine the factors that affect the occurrence of APO in the workplace and whether there is a difference in these parameters and attitudes between nurses and doctors. The observed population is mostly female (70%), aged 41 to 63 years (66%) in direct contact with patients in healthcare facilities of primary (50%) or secondary level (50%).

In the most developed countries of the world, despite the use of the most modern technologies, the frequency of APO ranges from 10% to 12%, and more than half of the cases can be prevented if the health service is well organized and coordinated [27]. However, the results of the frequency of APO in our country and in the world vary, and this especially depends on whether studies have been done on patients or based on assessment of health professionals. According to a research by Hodak et al. [19] conducted in Osijek in March 2016, on a sample of 100 nurses, it was found that 45% of the surveyed health professionals had workplace experience in the form of APO [19]. Our results are similar to this study, out of the total number of respondents, 44% of our respondents had an APO at workplace by the time of the survey, and doctors (52%) statistically more often than nurses (36%) ($p = 0.039$). Almost third of our respondents (31.8%) stated that the APO happens once a year, 52.3% stated that APO occurs several times a month, while 15.9% of respondents report that adverse events occur every day. However, there are studies with a much higher frequency of APO. In the research by Jušić et al. [28] from 2015, performed on the sample of 90 nurses working at the General Hospital Šibenik, 67.8% of health professionals state that they have had an APO in their practice, 1.1% state that APO occurs once a week, up to 66.7% of respondents report that APO occurs several times a year [28]. Cross-sectional study by Chakravarty et al. [29] performed on a sample of 175 doctors and 60 nurses reported that 72% of doctors and 80% of nurses have experienced an APO at least five times a year, but there was no significant difference between nurses and doctors [29].

Studies not based on perception of health professionals, but instead done on patients, show different results. A study by Cho et al. [30] performed in 232 hospitals in California on 124,204 patients showed that APO were quite rare and that in this patient population APO occurred in 6.8% of cases, while the remaining 93.2% of patients were without APO [30]. However, it should be borne in mind that this study was performed only in the surgery departments with 20 groups of patients with surgical diagnoses. The results of this study also showed that this number is not negligible and that it is crucial to reduce the number of APO in the health system. The authors have also concluded that adequate health care by nurses is key to addressing the frequency of APO [30]. These results of lower frequency of APO are supported by many multi-centric studies. According to a study by Baker et al. [31] conducted in Canada in 2004 on a sample of 3745 patients, it was found that the frequency of APO was 7.5%. According to a systematic review article by Vrijes et al. [32]

from 2008, in which eight studies with 74,485 patients were analyzed, the frequency of APO was 9.2%, with an estimate that 43.5% of them were preventable [32]. These results of a much lower frequency of APO could be explained by the fact that in these countries the health system is better organized. The same authors [32] state that about 39.6% of APO are caused by surgery, 15.1% are caused by drugs, 7% are caused by diagnostic procedures, 5.5% are caused by the application of therapeutic procedures, 3.4% are caused by decline, 1.6% was caused postpartum, 1.1% occurred as a result of anesthesia, while 3% occurred as a result of neonatal birth injury. While, in our study more than a half of respondents (54.5%) stated that the fall of a patient was their experience with APO and 29.5% stated that the mistake was related to medication error, where nurses (63%) significantly more often than doctors (41.2%) had experience of APO in the form of falls ($p = 0.031$).

Communication in the field of health care is of great importance because the way of communication of health professionals affects the course and manner of treatment of patients, their satisfaction, and consequently their health condition. It is very important that healthcare professionals have experience in the field of communication and are able to patiently and actively listen to and observe the patient. Also, in order for the treatment of the patient to be effective, it is necessary for the members of the health team to have good and positive communication with each other. Although communication is very important in healthcare. Unfortunately, very little attention is paid to it and it is neglected, and heavy workload of healthcare workers, lack of time and fatigue could be the reasons for being neglected [33]. In our study more than a half (52.4%) of respondents stated that the main cause of their experience of APO was a problem in communication (52.4%), 38.6% of respondents said that the challenges in organization at workplace were the main cause of their experience of APO, while only 9% of them said that the cause of their experience of APO was personal problem. Doctors significantly more often (69.2%) blame problems in communication as the main cause of APO than nurses (27.8%), while nurses more often (22.3%) than doctors (0%) declare that the cause of APO is on personal level. Our results coincides to a study by Chakravarty et al. [29], where doctors significantly more often blame the communication problems as a main factor associated with APO ($p< 0.05$) [29]. In the study of Holton et al. [34] the psychological well-being of Australian clinical staff during the corona virus infection (COVID-19) was assessed. The authors concluded that one-quarter of respondents reported symptoms of psychological distress, with significantly higher scores of stress ($p< 0.001$), anxiety ($p< 0.001$) and depression ($p< 0.001$) in comparison to doctors [34]. This is the reason why we examined the perception of health professionals related to COVID-19 pandemic as possible contributing factor of more frequent occurrences of APO and 44% of respondents confirmed that during pandemic APO were more common, where significantly more doctors (54%) than nurses (34%) had this opinion ($p = 0.021$). While, even 70% of our respondents state that stress is the major factor associated with APO, the difference between nurses and doctors was not observed. However, our results showed that prevalence of stress measured by PSS was 57%, and doctors (19.04 ± 4.65) had significantly higher levels of PSS total score when compared to nurses (14.72 ± 2.53) ($p< 0.001$). Stress is a feeling of pressure that people experience when demands placed on them exceed the resources they have to meet these demands [35]. In the cross-sectional study of Sathiya et al. [35] among 84 doctors and 116 nursing staff prevalence of stress measured by PSS was found to be 39.5%, with higher levels of PSS score in doctors (18.35 ± 4.7) when compared to nurses (17.16 ± 5.5), but without significant difference in mean scores [35]. Higher mean values of PSS total score in our doctors could be associated with higher prevalence of APO in doctors when compared to nurses. According to a study

by Kakemam et al. [36] from 2019, performed in 115 hospitals in Iran, on a sample of 2895 nurses and technicians, it was determined that 29.1% of nurses and technicians experienced an adverse event in the last 6 months, and logistic regression analysis found that workplace stress was one of the statistically significant predictors of more frequent occurrence of adverse events [36].

Even though the patient safety is the first aim of every health professional and it should be in the center of every health system, despite intense advances in technology, the prevalence of APO is still very high [9, 10, 30]. However, there is a very little data in literature about perception from front-line nurses and doctors, who are working in health centers and hospitals, even though any possible success in error reduction depends on full support from these workers only [29]. With the aim to elucidate the attitudes of front-line nurses and doctors towards APO we found out that for 73% of them patient safety is priority, 80% are actively working to improve patient safety, for 94% patient safety comes first, 89% strictly follow protocols in aim to reduce occurrence of APO and 75% discuss about APO prevention in their departments. The study by Jušić et al. [28] also examined the attitudes of nurses about patient safety as a priority in the workplace, and it was found that only 35.6% of respondents agree with this statement, which is a significantly lower percentage when compared to our research. Possible explanation is that in our study significantly more doctors (38%) do not agree with this statements when compared to nurses (16%) ($p = 0.013$). In the same study [28] 70% of respondents believe that they are actively working to improve patient safety, while 64% state that patient safety always comes first regardless of the amount of work in the ward. Also, 92% of respondents state that they follow protocols in their daily work and 85% state that they discuss the prevention of APO that occur in the departments [28]. According to the study of American Agency for Healthcare Research and Quality Patient Safety Indicators (AHRQ) from 2014, which was performed in 653 hospitals, which involved 405,281 patients, of which 35% were nurses, 81% of respondents rated patient safety as excellent or very good, but only 38% of nurses reported regularly occurrence of APO [37], while in our study 73% of respondents reported occurrence of APO on regular basis.

Conclusion

Our research has shown that 44% of healthcare professionals experienced APO, doctors significantly more often than nurses. For more than a half of respondents, significantly more often doctors, the main cause of APO is a problem in communication. Also, more than 50% of respondents, mainly nurses, stated that the fall of a patient was their experience of APO. Doctors significantly more often blame COVID-19 pandemic as a contributing factor of APO. Almost two thirds of respondents blame their own stress burden as a factor associated with APO, and perceived stress level was significantly higher in doctors when compared to nurses. More than a two thirds of respondents share attitude that patient safety comes first, as well as that they are actively working to improve patient safety and that they would report APO regularly. Nurses more often think that patient safety is priority and they more often report APO when compared to doctors.

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Ethical approval. The Ethics Committee of the "University Hospital Foca" approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Učestalost, stavovi i faktori povezani sa pojavom neželjenih događaja kod pacijenata iz perspektive medicinskih sestara i doktora medicine

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Uvod. Sigurnost pacijenta bi trebalo da bude na prvom mjestu svakom zdravstvenom radniku, što je izazov svakog zdravstvenog sistema. Neželjeni događaji pacijenata se definišu kao šteta uzrokovana lijekom ili drugom intervencijom na primarnom, sekundarnom ili tercijarnom nivou zdravstvene zaštite, što dovodi do nastanka komplikacije primarne bolesti ili pojave nove bolesti ili povrede. Cilj naše studije je bio da utvrdimo učestalost neželjenih događaja i da utvrdimo razlike između medicinskih sestara i doktora medicine u učestalosti, uzrocima i stavovima prema neželjenim događajima.

Metode. U ovoj studiji presjeka je učestvovalo 100 zdravstvenih radnika, medicinskih sestara i doktora medicine zaposlenih u primarnom i sekundarnom nivou zdravstvene zaštite. Istraživanje je sprovedeno od maja do oktobra 2020. godine. Upitnik je djelimično preuzet sa vebsajta Istraživačke Agencije za istraživanje zdravstvene njege i njenog kvaliteta, a standardizovana skala doživljenog stresa je korišćena za mjerenje nivoa subjektivnog stresa.

Rezultati. Četrdeset četiri zdravstvena radnika (44%) su tokom svog radnog staža doživjeli pojavu neželjenog događaja kod pacijenata, doktori (52%) značajno češće u odnosu na medicinske sestre (36%) (p = 0,039). Više od polovine ispitanika (52,3%) je izjavilo da se neželjeni događaji dešavaju nekoliko puta mjesečno. Sedamdeset posto ispitanika navode da je njihov sopstveni stres povezan sa pojavom neželjenog događaja. Doktori značajno češće (69,2%) navode da je problem u komunikaciji između zdravstvenih radnika glavni uzrok pojave neželjenih događaja u odnosu na medicinske sestre (27,8%) (p = 0,046).

Zaključak. Za doktore, glavni uzrok nastanka neželjenih događaja je problem u komunikaciji između zdravstvenih radnika, dok medicinske sestre češće navode da je sigurnost pacijenata prioritet u odnosu na doktore medicine. Dvije trećine ispitanika navode sopstveni stres kao faktor koji je udružen sa pojavom neželjenog događaja.

Ključne riječi: učestalost, stavovi, neželjeni događaji kod pacijenata

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Original article

Attitudes of nurses and nursing students towards patients with mental illness

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Summary

Introduction. According to the data of the World Health Organization (WHO), mental illnesses are on the rise. The World Health Report estimates that today about 1 billion people suffer from mental and behavioral disorders or psychosocial problems such as those related to alcohol and drug abuse. Stigmatization of the mentally ill is one of the burning social problems of those people, and the attitudes and behavior of nurses/technicians significantly affect the self-stigmatization of patients, and thus their condition and recovery. The main aim of this study was to assess attitudes of nurses and nursing students towards patients with mental illnesses.

Method. The research conducted is a cross-sectional study. The study covered two countries, Bosnia and Herzegovina and Serbia. In June and July 2018, 200 nurses and nursing students from the second to the fourth year of study were surveyed. Data were collected with original anonymous questionnaires, which was made for the purpose of this research.

Results. Seventy percent of nurses believe that people with mental illness are discriminated against in our society, while there are statistically significant differences between respondents in relation to demographic characteristics ($\chi 2 = 10.217$; $p = 0.037$). Nurses working in psychiatric wards show a lower level of stigmatization compared to nurses working in other wards ($\chi 2 = 25.553$; $p = 0.001$). Nursing students have more negative attitudes towards mentally ill people compared to nurses ($\chi 2 = 13.471$; $p = 0.009$). Nurses from Serbia show a higher level of tolerance towards people with mental disabilities compared to nurses from Bosnia and Herzegovina ($\chi 2 = 16.115$; $p = 0.003$).

Conclusion. The results of the research show that stigmatization of patients with mental illness still exists among health professionals. Undergraduate and continuing medical education of nurses should include more content related to access to the patient with mental disorders, communication skills in psychiatry, mental health promotion and prevention of stigmatization.

Key words: stigma, nurses, mental illness

Introduction

According to the World Health Organization (WHO), mental illness is on the rise. The World Health Report estimates that today about 1 billion people suffer from mental and behavioral disorders or psychosocial problems such as those related to alcohol and drug abuse. Over 120 million people worldwide suffer from depression, twice as many women (WHO 2002).

In 1996, depression was the fourth health problem, and in 2020, depression is expected to be the second world health problem. Depressive disorders are the biggest cause of disability and disability pensions in Europe in the last 10 years [1].

Psychiatric diseases are divided into several groups: organic mental disorders (dementia, delirium), mental disorders caused by the use of psychoactive substances, schizophrenia, mood disorders (mania, depression and bipolar disorder), personality disorders, intellectual disabilities, mental psychological disorders and unspecific mental disorders. It is estimated that about 70 million people in the world are addicted to alcohol, that about 50 million people have epilepsy, and 24 million people suffer from schizophrenia (in all parts of the world, about 1% of the population suffers from schizophrenia). One million people commit suicide each year, and 10 to 20 million try to kill themselves. It is estimated that one in four people will be affected by a mental problem or disorder at some point in their lives. Therefore, the prevention of mental disorders and the promotion of mental health are crucial for any society. The attitudes of mental health service users emphasize the fact that their subjective and intersubjective experiences of mental disorder and the psychiatric system are as important and valid as the attitudes of professionals, especially nurses who work with and are in daily contact with mentally ill people [1, 2].

To understand the social exclusion of people with mental health difficulties, we need to understand the concept and meaning of stigma. Stigma generally refers to labeling a person as different from "normal" resulting in a lack of acceptance or exclusion from society. Global indicators on the stigmatization of people with mental health problems indicate that in most countries, people with mental disabilities are considered less valuable than people without mental health problems. All people with mental disorders are stigmatized, but patients with schizophrenia and similar disorders are much more stigmatized than those with depression and anxiety disorders. To reduce stigma, it is important to talk openly about mental illnesses, just as we do with other serious physical illnesses [3].

The aim of this research is to examine the attitudes and level of social distance towards patients with mental illness by nurses/technicians in order to plan activities aimed at reducing stigma and social distance. This is extremely important because the attitudes and behavior of nurses/technicians significantly affect the self-stigmatization of patients, and thus their condition and recovery. The specific objectives of this research were to examine the attitudes of nurses towards patients with mental illness and determine whether there are differences in their attitudes in relation to demographic characteristics, between nurses employed in psychiatry and those employed in other wards, between nursing students and working nurses and between nurses from Bosnia and Herzegovina and nurses from the Republic of Serbia.

Method

This cross-sectional study was conducted in two countries, Bosnia and Herzegovina and the Republic of Serbia.

The study included 150 nurses and 50 nursing students from the second to the fourth year of study of different sex, place of residence, work experience, level of health care, aged 20 to 60 years. Prior to the start of the research, the consent of the director of all the above constitutions was required to conduct the study, in accordance with the certification procedures, and it was obtained in written form. The research was conducted during the period of one month, from June 2018 to July 2018.

Data about socio-demographic cahracteristics were obtained by questionnaire made by authors. Data about attitudes of nurses and nursing students towards patients with mental illness were collected with Mental Illness: Clinicians'

Attitudes Scale, MICA-2 used to determine and measure clinicians' attitudes towards mental disorders. The MICA-2 questionnaire contains 16 statements and for each statement answers from "I completely agree" (with the stated statement) to "I do not agree at all" were offered. The participation in the study was voluntary.

Statistical analysis of the data was done with the help of the SPSS software system (version 20). The X2 test was used as a statistical test. The data are presented in tables. The usual value of $p < 0.05$ was taken as the level of statistical significance of the differences.

Results

The study included 200 respondents aged 20 to 60 years, of which a larger number of respondents (50.5%) belonged to the age group of 20–39 years, while the remaining 49.5% of respondents belonged to the older age group of 40–60 years, and the average age of the respondents was 38.88 (13.16) years. Among the respondents there were 39 (19.5%) men and 161 (80.5%) women. Out of the total number of respondents, 150 (75%) of them work as nurses or technicians, while the remaining 50 (25%) are the students of the second, third and fourth year of the study program Nursing. The largest number of respondents (71) graduated from high school, 2% have a college degree, while only four respondents have a university degree (Table 1).

Thirty-four percent of nurses and technicians work in primary health care while the remaining 66% work in secondary health care. Fifty-two (52.6%) of respondents have a length of service of up to 20 years, while 47.4% of respondents have a longer length of service (from 21-40 years), the average length of service is 19.53 (11.12) years. 16.7% of respondents were examined in the Health Center in Foca, the same percentage was examined in Visegrad, and in the hospitals in Foca and Jagodina, 24% of respondents were examined in the Special Psychiatric Hospital in Sokolac, while 9.3% of nurses were examined in the Care Home for Persons with Disabilities in Visegrad (Table 2).

Table 1. Socio-demographic characteristics of respondents

Socio-demographic characteristics of respondents	Number (%)
Age	
20-39 years	101 (50.5)
40-60 years	99 (49.5)
Gender	
Male	39 (19.5)
Female	161 (80.5)
Workplace	
Nurses/technicians	150 (75)
Nursing students	50 (25)
Education	
High school	142 (71)
College	4 (2)
Faculty	4 (2)
Students	50 (25)

Table 2. Data obtained by the survey on health care and length of service of respondents (nurses and technicians)

Socio-demographic characteristics of respondents	Number (%)
Health care	
Primary	51 (34)
Secondary	99 (66)
Work experience	
0-20 years	79 (52.6)
21-40 years	71 (47.4)
Place of work of nurses	
- Health center in Foca	25 (16.7)
- Health center in Visegrad	25 (16.7)
- University Hospital in Foca	25 (16.7)
- Special Psychiatric hospital in Sokolac	36 (24)
- Jagodina General Hospital	25 (16.7)
- Care home for persons with disabilities in Visegrad	14 (9.3)
Year of study of nursing students at the Faculty of Medicine in Foca	
Second year	16 (32)
Third year	17 (34)
Fourth year	17 (34)

Table 3 shows that out of the total number of surveyed nurses and nursing students, 37.4% of respondents agree largely or completely with the statement that they learn about mental health only as much as they have to. Forty-three (43.4%) percent of respondents partially or fully agree with the statement that people with mental disorders can never recover so much to have a good quality of life. Out of the total number of respondents, 15.3% would never tell their friends if they suffer from mental disorder, because of fear of changing their opinion about them. No statistically significant difference was observed between the age groups and the groups of respondents in relation to the length of service in terms of the mentioned claims (Table 3).

The largest percentage of respondents (81.4%) would never use the terms "crazy" to describe psychiatric patients they met in their work to other colleagues and the largest number of respondents (67.3%) would continue to work with their colleague if they told him they had a mental disorder. Seventy percent of respondents believe that people with mental illness are discriminated against in our society. There was a statistically significant difference between the groups of respondents, both in relation to age ($\chi^2 = 10.217$; $p = 0.037$) and in relation to length of service ($\chi^2 = 9.890$; $p = 0.042$). Older respondents and respondents with a longer length of service believe that people with mental illness are discriminated against in our society compared to the younger group of respondents and the group with a shorter length of service. There was no statistically significant difference between the groups of respondents in relation to age or length of service when it comes to the attitudes of health workers towards mentally ill persons (Table 4).

Table 3. Learning about mental health, quality of life of sick people and confiding to friends about their own diagnosis, in relation to the age and work experience of the respondents (nurses / technicians)

Variables	Socio - demographic characteristics (age and length of service)	The answer that best reflects the degree of agreement with the claims offered Number (%)					χ^2	p
		I do not agree at all	Mostly I disagree	I'm not sure	Mostly I agree	I totally agree		
I only learn about mental health as much as I have to, but I don't want to burden myself with extra learning either	**Age**						8.891	0.064
	20-39 years	10 (6.7)	11 (7.3)	14 (9.3)	15 (10)	1 (0.7)		
	40-60 years	31 (20.7)	17 (11.3)	11 (7.3)	34 (22.7)	6 (4)		
	Work experience						2.556	0.635
	0-20 years	19 (12.7)	13 (8.7)	16 (10.7)	27 (18)	4 (2.7)		
	21-40 years	22 (14.7)	15 (10)	9 (6)	22 (14.7)	3 (2)		
People with mental disorders can never recover enough to have a good quality of life	**Age**						3.208	0.524
	20-39 years	6 (4)	14 (9.3)	12 (8)	15 (10)	4 (2.7)		
	40-60 years	12 (8)	21 (14)	20 (13.3)	28 (18.7)	18 (12)		
	Work experience						4.015	0.404
	0-20 years	10 (6.7)	23 (15.3)	16 (10.7)	21 (14)	9 (6)		
	21-40 years	8 (5.3)	12 (8)	16 (10.7)	22 (14.7)	13 (8.7)		
If I were suffering from a mental disorder, I would never tell my friends, for fear of changing their opinion of me	**Age**						5.224	0.265
	20-39 years	19 (12.7)	19 (12.7)	6 (4)	5 (3.3)	2 (1.3)		
	40-60 years	41 (27.3)	21 (14)	21 (14)	12 (8)	4 (2.7)		
	Work experience						3.208	0.524
	0-20 years	29 (19.3)	25 (16.7)	12 (8)	9 (6)	4 (2.7)		
	21-40 years	31 (20.7)	15 (10)	15 (10)	8 (5.3)	2 (1.3)		

Table 4. Attitude of health workers towards psychiatric patients (fear, discrimination) and attitude towards discrimination of mental patients in relation to age and length of service

Variables	Socio - demographic characteristics (age and length of service)	The answer that best reflects the degree of agreement with the claims offered Number (%)					χ^2	p
		I do not agree at all	Mostly I disagree	I'm not sure	Mostly I agree	I totally agree		
I would use the terms "crazy", "wander", "go crazy" to describe to other colleagues psych. patients I have met in my work	**Age** 20-39 years 40-60 years	37 (24.7) 63 (42)	7(4.7) 15 (10)	3 (2) 14 (9.3)	1 (0.7) 3 (2)	3 (2) 4 (2.7)	2.863	0.581
	Work experience 0-20 years 21-40 years	53 (35.3) 47 (31.3)	12 (8) 10 (6.7)	9 (6) 8 (5.3)	1 (0.7) 3 (2)	4 (2.7) 3 (2)	1.321	0.858
If a colleague told me he had a mental disorder I would continue to work with him	**Age** 20-39 years 40-60 years	0 (0) 4 (2.7)	0 (0) 6 (4)	13 (8.7) 26 (17.3)	11 (7.3) 31 (20.7)	27 (18) 32 (21.3)	9.939	0.051
	Work experience 0-20 years 21-40 years	0 (0) 4 (2.7)	2 (1.3) 4 (2.7)	22 (14.7) 17 (11.3)	19 (12.7) 23 (15.3)	36 (24) 23 (15.3)	8.150	0.086
People with mental illness are discriminated against in our society	**Age** 20-39 years 40-60 years	1 (0.7) 6 (4)	0 (0) 6 (4)	10 (6.7) 21 (14)	31 (20.7) 37 (24.7)	9 (6) 29 (19.3)	10.217	0.037
	Work experience 0-20 years 21-40 years	2 (1.3) 5 (3.3)	1 (0.7) 5 (3.3)	15 (10) 16 (10.7)	44 (29.3) 24 (16)	17 (11.3) 21 (14)	9.890	0.042

More than half of the respondents (51.3%) said that they were just as comfortable talking to people with psychiatric illnesses as they were to those with somatic illnesses and thirty-five percent of respondents agreed with the statement that patients with schizophrenia and similar diseases should not be confused with other patients in the waiting room. Twelve percent of nurses/technicians would complain of somatic disturbances in the event of a person suffering from a mental disorder, e.g. mid-chest pain, attributed to mental illness. There was no statistically significant difference between age groups and groups of respondents with different work experience in terms of any of the mentioned claims (Table 5).

Out of all the nurses working in the psychiatric ward, only 3.3% agree with the statement that they learn about mental health only as much as they have to, while that percentage is significantly higher in the group of nurses working in other wards (34%) (χ^2 = 36.008; p = 0.001). Also, a statistically significant difference (χ^2 = 25,553; p = 0.001) was observed in the attitude of nurses regarding the avoidance of an acquaintance who would find out that he is mentally ill, with only 1.3% of nurses working on psychiatric ward agreeing with this statement, while this view is supported by 6.7% of nurses working in other wards. The difference between the two groups of respondents (χ^2 = 23.505; p = 0.001) was also observed in terms of whether patients with schizophrenia should or should not be mixed with other patients in the waiting room, where 18% of nurses working in the

Table 5. Communication and care of health workers towards mentally ill persons in relation to age and work experience

Variables	Socio - demographic characteristics (age and length of service)	The answer that best reflects the degree of agreement with the claims offered Number (%)					χ^2	p
		I do not agree at all	Mostly I disagree	I'm not sure	Mostly I agree	I totally agree		
I am just as comfortable talking to people with psychiatric disorders as I am to those with somatic disorders	**Age**							
	20-39 years	3 (2)	9 (6)	16 (10.7)	15 (10)	8 (5.3)	2.317	0.678
	40-60 years	8 (5.3)	14 (9.3)	23 (15.3)	31 (20.7)	23 (15.3)		
	Work experience							
	0-20 years	5 (3.3)	14 (9.3)	19 (12.7)	24 (16)	17 (11.3)	1.157	0.885
	21-40 years	6 (4)	9 (6)	20 (13.3)	22 (14.7)	14 (19.3)		
Patients with schizophrenia and related diseases should not be mixed with other patients in the waiting room	**Age**							
	20-39 years	14 (9.3)	9 (6)	11 (7.3)	16 (10,7)	1 (0.7)	8.175	0.085
	40-60 years	23 (15.3)	23 (15.3)	18 (12)	20 (13.3)	15 (10)		
	Work experience							
	0-20 years	18 (12)	12 (18)	18 (12)	27 (18)	4 (2.7)		
	21-40 years	19 (12.7)	20 (13.3)	11 (7.3)	9 (6)	12 (8)	16.336	0.067
If a person with a mental disorder complains of somatic disorders, such as mid-chest pain, I will attribute it to mental illness	**Age**							
	20-39 years	29 (19.3)	7 (4.7)	5 (3.3)	7 (4.7)	3 (2)	5.618	0.230
	40-60 years	55 (36.7)	22 (14.7)	14 (9.3)	5 (3.3)	3 (2)		
	Work experience							
	0-20 years	43 (28.7)	13 (8.7)	10 (6.7)	9 (6)	4 (2.7)	3.661	0.454
	21-40 years	41 (27.3)	16 (10.7)	9 (6)	3 (2)	2 (1.3)		

psychiatric wards agreed with this statement, compared to the nurses working in other departments, of which 34% are of the opinion that patients with schizophrenia should not be mixed with other patients in the waiting room (Table 6).

A statistically significant difference was observed in terms of whether respondents would listen to the suggestion of older colleagues to behave incorrectly towards mentally ill patients ($\chi^2 = 10.588$; $p = 0.041$), with a significantly higher number of nurses (53.5%) holding of this attitude that they would not listen to an older colleague, in comparison to students (13%). A high statistically significant difference ($\chi^2 = 13{,}471$; $p = 0.009$) between groups of respondents (nurses and nursing students) was also observed in terms of providing opportunities for the mentally ill to be employed in the institution where the respondents work, with only 3% of nursing students who agree with this statement, while the percentage of nurses (17.5%) with this attitude is significantly higher (Table 7).

Table 8 shows that there is a statistically significant difference ($\chi^2 = 12{,}006$; $p = 0{,}017$) between the groups of respondents (nurses/technicians) working in different countries (Bosnia and Herzegovina and Serbia), in terms of the attitude that people with mental disorders can never be so good at having a good quality of life, where 32% of nurses from Bosnia and Herzegovina agreed with this statement, while the percentage of respondents from Serbia that supported this statement was significantly lower (11.4%). Also, a statistically significant difference ($\chi^2 = 16.115$; $p = 0.003$) was observed in terms of the view that anyone with a history of mental disorders should be excluded from public office, with 9.3% of respondents from Serbia who agree with this statement, and 17.4% of respondents from Bosnia and Herzegovina who agree with this statement as well (Table 8).

Table 6. Statistically significant differences in the attitudes of nurses in relation to the workplace

Variables	Workplace	The answer that best reflects the degree of agreement with the claims offered Number (%)					χ^2	p
		I do not agree at all	Mostly I disagree	I'm not sure	Mostly I agree	I totally agree		
I only learn about mental health as much as I have to, but I don't want to burden myself with extra learning either	Psychiatric ward	22 (14.7)	9 (6)	0 (0)	5 (3,3)	0 (0)	36.008	0.001
	Other wards	19 (12.7)	19 (12.7)	25 (16.7)	44 (29.3)	7 (4.7)		
If I found out about an acquaintance that he had become mentally ill, I would start avoiding him	Psychiatric ward	11 (7.3)	5 (3.3)	18 (12)	2 (1.3)	0 (0)	25.553	0.001
	Other wards	66 (44)	25 (16.7)	13 (8.7)	7 (4.7)	3 (2)		
Patients with schizophrenia and related diseases should not be mixed with other patients in the waiting room	Psychiatric ward	13 (8.7)	14 (9.3)	8 (5,3)	1 (0.7)	0 (0)	23.505	0.001
	Other wards	24 (16)	18 (12)	21 (14)	35 (23.3)	16 (10.7)		

Table 7. Differences in attitudes between nurses and nursing students

Variables	Level of education	The answer that best reflects the degree of agreement with the claims offered Number (%)					χ^2	p
		I do not agree at all	Mostly I disagree	I'm not sure	Mostly I agree	I totally agree		
If an older colleague told me that I should treat a psychiatric patient incorrectly, I would not listen.	Nurses/ technicians	19 (9.5)	11 (5.5)	13 (6.5)	27 (13.5)	80 (40)	10.588	0.041
	Nursing students	9 (4.5)	3 (1.5)	12 (6)	16 (8)	10 (5)		
I would employ a mentally ill person in my institution	Nurses/ technicians	44 (22)	18 (9)	53 (26.5)	23 (11.5)	12 (6)	13.471	0.009
	Nursing students	13 (6.5)	17 (8.5)	14 (7)	4 (2)	2 (1)		

Table 8. Differences in the attitudes of nurses in relation to the country in which the respondents work

Variables	State	The answer that best reflects the degree of agreement with the claims offered Number (%)					χ^2	p
		I do not agree at all	Mostly I disagree	I'm not sure	Mostly I agree	I totally agree		
People with mental disorders can never recover enough to have a good quality of life	Bosnia and Herzegovina	15 (10)	35 (23.3)	27 (18)	33 (22)	15 (10)	12.006	0.017
	Serbia	3 (2)	0 (0)	5 (3.3)	10 (6.7)	7 (4.7)		
Anyone with a history of mental disorders should be excluded from performing any public duty	Bosnia and Herzegovina	36 (24)	29 (19.3)	34 (22.7)	16 (10.7)	10 (6.7)	16.115	0.003
	Serbia	6 (4)	0 (0)	5 (3.3)	9 (6)	5 (3.3)		

Discussion

Quality interaction between psychiatric patients and nurses/technicians is very important. It affects the patient's self-image and self-esteem. It also has an impact on cooperation with the patient, acceptance of treatment and the hospital environment (if the patient is hospitalized). The nurse-patient interaction can have a beneficial effect on the patient and his treatment, but it can also have an adverse effect and have a negative impact on the patient, his health and treatment. In order for the interaction to be of good quality and to have a therapeutic effect, a positive attitude is important, which implies the absence of prejudice and discrimination. Nurses/technicians, as well as other health professionals, are very important in programs to combat stigma (prejudice against psychiatric patients) because as professionals they have a certain degree of credibility. Although health professionals should play a key role in establishing respect and rights for patients. Many patients report the presence of stigma within the health system. This is confirmed by research on the stigmatization of psychiatric patients by health professionals. One of the foreign surveys of the attitudes of health workers has shown that they may have less optimistic expectations regarding the recovery of the mentally ill than the general population [4].

A study conducted in China on the attitudes of medical staff working with community psychiatric patients shows a "relatively high level of stigma" towards the mentally ill (Mentally Ill Chemical Abusers, MICA = 51.69) [5], and in our study the level of stigma is high, as many as thirty-five percent of respondents agree with the statement that "patients with schizophrenia and similar diseases should not be confused with other patients in the waiting room", while 45.9% of respondents disagree with this statement, and 19.3% are unsure of their attitude.

On the other hand, a study conducted in Denmark [6] showed a "relatively low level of stigmatizing attitudes" by medical staff working in psychiatry for people with schizophrenia (MICA = 32 for doctors, MICA = 38.13 for nurses / technicians). It is stated that this result is not accompanied by other international research that shows a higher level of negative attitudes. This is interpreted as the result

of a recovery-oriented treatment approach. The least negative attitudes were shown by females who work in community psychiatry, with many years of experience and who participate in the educational recovery programs. Such differences may be due to cultural differences in the level of stigmatization of psychiatric patients by health professionals. Members of Asian cultures may express a greater degree of stigmatization than their Western counterparts, probably because of their cultural orientation toward the well-being and needs of society rather than the needs of the individual [7].

In a study conducted in Croatia on the population of high school students, students, general population and health workers, health staff states that they would not form a friendly relationship with a patient at the ward, because they would lose their professional relationship [8]. The results of our research are very similar, out of the total number of nurses/technicians and health care students surveyed, forty-six percent believe that people with mental illness are dangerous and unpredictable, 32.6% are unsure of their position, while the remaining 21.3% generally or completely disagree with this statement. Also, eight percent of respondents said that if they found out about an acquaintance that he had become mentally ill, they would avoid him, 20.7% of respondents are not sure of their position, while the majority of respondents (71.3%) disagree with this claim.

When it comes to the occurrence of a mental disorder in a colleague, the largest number of respondents (67.3%) in our study would continue to work with their colleague in case they tell him that he has a mental disorder, 26% are unsure of their position, while 6.7% would not continue to work with his colleague in the mentioned situation.

Very few health professionals are willing to have an emotional relationship with a mentally ill person if that relationship was not established before the onset of the illness. It is recommended that nurses working in psychiatry should seek to help people who have entered into an emotional relationship with a person who has developed a mental illness, whether a child, partner or friend, in order to maintain that relationship [4, 8, 9]. In our study, 39.3% of surveyed nurses/technicians believe that a woman would be reckless to marry a man suffering from a mental disorder, even though she seems to have fully recovered, which sufficiently shows that awareness and knowledge of mental disorders is not high enough.

According to a research conducted in Croatia in 2015, which surveyed 170 nursing students and nurses/technicians employed in psychiatric and non-psychiatric departments, it was found that more than 60% of respondents agree that psychiatric patients are dangerous, and more than 65% believe that people with mental disorders can never recover enough to establish a good quality of life [9]. In our study, 46% of nurses believe that psychiatric patients are dangerous, while 43.4% state that people with mental disorders can never recover enough.

According to the same research from Croatia, more than 70% of respondents state that if a colleague told them he had a psychiatric disorder, they would still want to work with him. Seventy percent of the respondents in the Croatian study state that in their own case, they would never tell their friends that they suffer from a mental disorder [9].

When it comes to continuing to work with a colleague who has been diagnosed with a mental disorder, the results of our research are similar. The largest number of respondents (67.3%) would continue to work with their colleague if he told them that he had a mental disorder. However, our results show that out of the total number of respondents, 15.3% would never say that to their friends, for fear of changing their opinion about them, unlike a survey in Croatia where more than 55% of respondents would never tell their

colleagues because of fear of changing their attitude towards them [9].

Only 22.6% of respondents state that they are not as comfortable talking to people with mental disorders as they are to those with a somatic diagnosis. This result may be due to experience working with psychiatric patients, as 24% of respondents work in psychiatric wards. The result can also be related to the fact that most respondents have more than 10 years of experience in the profession. The length of clinical experience can reduce the discomfort of talking to people with psychiatric disorders. Our results are similar to the research from Croatia where 17% of respondents state that talking to a person with mental or somatic illness is not equally pleasant [9].

It is worrying that a significant percentage of respondents believe that if a person suffering from a mental disorder complains of somatic disorders (e.g. chest pain), they will attribute it to a mental illness. In a study in Croatia, the percentage of respondents who would attribute somatic symptoms to psychological ones is significantly higher and amounts to 70% [9]. This can be related to research which concluded that stigma leads to discrimination in the provision of health care for physical illness in psychiatric patients [10], as well as less use of diagnostic procedures for physical illness in mentally ill [11].

It is also interesting to note that 37.4% of respondents agree with the statement that "they learn about mental health only as much as they have to and do not want to be burdened with additional learning, while in research in Croatia this percentage is significantly higher (60%) [9]. This result could be justified by the difficulties encountered in the work of staff working with the mentally ill, such as inability to relax, psychological stress and the amount of responsibility, which is why staff do not want to be burdened with additional learning in their spare time.

Conclusion

Based on our results we concluded that a significantly higher percentage of nurses/technicians with a longer length of service believe that people with mental illness are discriminated against in our society compared to the younger group of respondents and the group with a shorter length of service. Nurses working in non-psychiatric wards are willing to learn about mental health only as much as they have to, which is significantly more, compared to the nurses working in psychiatric wards. Nursing students have more negative attitudes toward patients with mental disorders compared to nurses. Nurses working in Bosnia and Herzegovina in significantly higher numbers believe that people with mental disorders can never recover so much to have a good quality of life and that patients with a history of mental disorders should be excluded from public duty, compared to nurses working in Serbia. Research results show that stigmatization of patients with mental disorders still exists among health professionals. Undergraduate and continuing medical education of nurses should include more content related to access to patients with mental disorders, communication skills in psychiatry, mental health promotion and prevention of stigma.

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Conflicts of interest. The authors declare no conflict of interest.

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Stavovi medicinskih sestara i studenata zdravstvene njege prema pacijentima sa mentalnim oboljenjima

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Uvod. Prema podacima Svjetske zdravstvene organizacije mentalne bolesti su u velikom porastu. U Izvještaju o svjetskom zdravlju SZO procjenjuje se da danas oko milijardu ljudi pati od mentalnih poremećaja i poremećaja ponašanja ili od psihosocijalnih problema poput onih koji su vezani za zloupotrebu alkohola i droga. Stigmatizacija mentalno oboljelih je jedan od gorućih socijalnih problema tih osoba, a stavovi i ponašanje medicinskih sestara/tehničara značajno utiču na samostigmatizaciju pacijenata, a time i na njihovo stanje i oporavak.

Metod. Sprovedeno istraživanje je tipa studije presjeka. Studija je obuhvatila dvije države, Bosnu i Hercegovinu i Srbiju. U junu i julu mjesecu 2018. godine anketirano je 200 medicinskih sestara i studenata zdravstvne njege od druge do četvrte godine studija. Podaci su prikupljeni originalnim upitnicima anonimnog karaktera, koji su napravljeni za potrebe ovog istraživanja.

Rezultati. Sedamdeset posto medicinskih sestara smatra da su osobe oboljele od mentalnih bolesti diskriminisane u našem društvu, dok između ispitanika postoje značajne statističke razlike u odnosu na demografske karakteristike ($\chi^2 = 10,217$; $p = 0,037$). Medicinske sestre koje rade na psihijatrijskim odjeljenjima pokazuju manji nivo stigmatizacije u odnosu na sestre koje rade na drugim odjeljenjima ($\chi^2 = 25,553$; $p = 0,001$). Studenti zdravstve njege imaju negativnije stavove prema mentalno poremećenim osobama u odnosu na medicinske sestre ($\chi^2 = 13,471$; $p = 0,009$). Medicinske sestre u Srbiji pokazuju veći nivo tolerancije prema osobama sa mentalnim poteškoćama u odnosu na medicinske sestre u Bosni i Hercegovini ($\chi^2 = 16,115$; $p = 0,003$).

Zaključak. Rezultati istraživanja pokazuju da stigmatizacija pacijenata sa mentalnim poremećajima i dalje postoji među zdravstvenim radnicima. Dodiplomsko obrazovanje i kontinuirana medicinska edukacija medicinskih sestara treba da uključi više sadržaja vezanih za pristup bolesniku sa mentalnim poremećajima, komunikacijskim vještinama u psihijatriji, promociji mentalnog zdravlja i prevenciji stigmatizacije.

Ključne riječi: stigma, mentalni poremećaj, tolerancija, antistigma

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Case report

Fibrous epulis - case report

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Summary

Introduction. Epulis is a change in gingival tissue that occurs under the influence of chronic irritation. Histologically, there are several different types of epulis. Fibrous epulis is benign tumor of gingiva that most often occurs in interdental papilla area as a result of local irritation (inadequate restorative fillings, carious teeth, subgingival deposits or the combination of them). The aim of this paper is to present a clinical case of fibrous epulis.

Case report. A 25-year-old girl reported to the Specialist Center for Dentistry in Foca. Clinical examination revealed a gingival tissue enlargement in the area of the upper jaw central incisors with speech and chewing function disturbances. Intraoral examination revealed a change above the level of gingiva, reddish-pink in color with smooth surface texture and soft consistency. The size of the change was 1 x 1.5 cm. It was connected to the interdental gingiva between teeth 12 and 21 by a narrower base. Clinically, a significant amount of soft and hard dental deposits surrounded the remaining teeth. Remaining gingiva was swollen, red, bleeding on provocation. The anamnesis did not confirm the presence of other acute and chronic diseases. The patient was not pregnant. She was informed about clinical condition assessment, as well as possible therapeutic procedures. Our patient was treated with non-surgical periodontal therapy and surgical excision of the enlargement. After histopathological examination of the removed tissue, the diagnosis was made: *"Fibrous epulis cum ulceration"*.

Conclusion. Clinical examination is insufficient for definite diagnosis. Therefore, a histopathological examination of the tissue is mandatory for fibrous epulis definite diagnosis. Treatment of choice is surgical excision of the enlargement and removal of predisposing factors to avoid recurrence.

Key words: gingiva, epulis, central incisors

Introduction

The most common mechanisms in the development of a soft tissue tumor-like lesion in the oral cavity are reactive hyperplasia and neoplasia, and most localized growths are thought to be reactive rather than neoplastic in nature [1]. Epulis is a relatively common tumor of gingival tissue and can be defined as a massive lesion that develops in response to chronic and recurrent tissue irritations that stimulate an excessive response of the organism. Most pathological

changes in gingival tissue are thought to be due to the reactive nature of the tissue [2].

Although epulis is classically categorized into different subtypes, the current literature has identified three main types: fibrous epulis, granulomatous epulis, and giant cell epulis [3]. Fibrous epulis is a common benign change (enlargement) of the gingiva that most often occurs in the area of the interdental papilla as a result of local irritation (calculus, bacterial plaque, caries, inadequate restoration) [4].

Case report

A 25-year-old girl reported to the Periodontology Clinic - Specialist Center for Dentistry in Foca. The patient gave anamnestic data in which she reported the swelling of gingival tissue in the last year, which has increased since last month. The enlargement of the tissue caused her difficulties in performing the functions of chewing and speech, which is why she sought medical advice. On intraoral examination, a reddish-pink, soft tissue change was observed on the upper alveolar arch on the vestibular side in the area of the central incisors. Enlargement of the tissue, 1 x 1.5 cm in size, was attached with a narrower base in the region of the interdental space of teeth 12 and 21. Clinically, a significant amount of soft and hard dental deposits was present surrounding the remaining teeth (Figure 1). The gingiva of the remaining teeth was swollen, red, bleeding on provocation. The anamnesis did not confirm the presence of other acute and chronic diseases. The patient was not pregnant. She was introduced to the clinical condition assessment, as well as possible therapeutic procedures. After giving her written consent to accept the offered therapeutic procedures, our patient was treated with conservative therapy of periodontium. After that, the enlargement was removed with a surgical scalpel under local anesthesia without tooth extraction. A sample of gingival tissue was sent for histopathological analysis (Figure 2). At the follow-up examination, the surgical sutures were removed and the patient was advised to correct inadequate restorative fillings.

Figure 1. Fibrous enlargement of gingival tissue in the area of the upper central incisors

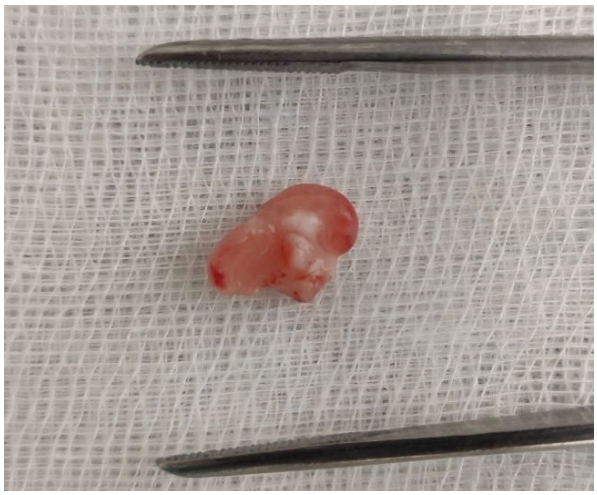

Figure 2. Gingival tissue sample sent for histopathological analysis

After pathohistological examination of the removed tissue, the diagnosis was made: "*Fibrous epulis cum ulceration*".

- **Radiological examination**. Orthopantomography revealed resorption of alveolar bone in the area of upper jaw central incisors interdental region and numerous restorative fillings (Figure 3).
- **Histopathological finding.** The mass of the excised tissue was 1.5 × 1 × 0.5 cm in size. It

had a grayish-white appearance and a firm consistency (Figure 3). Sections stained with hematoxylin and eosin revealed coatings of hyperplastic layered squamous epithelium and mild chronic inflammation consisting of lymphocytes and plasma cells. After a detailed histopathological examination, the diagnosis was made: *Fibrous epulis cum ulceration*.

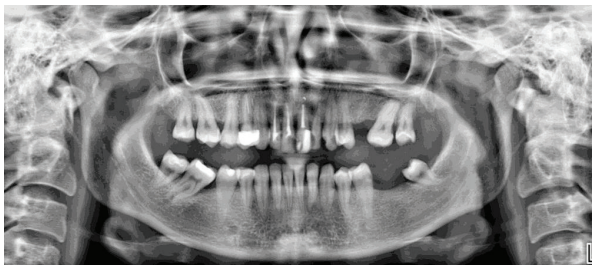

Figure 3. Orthopantomographic image - before the interventions

Figure 4. Postoperative results

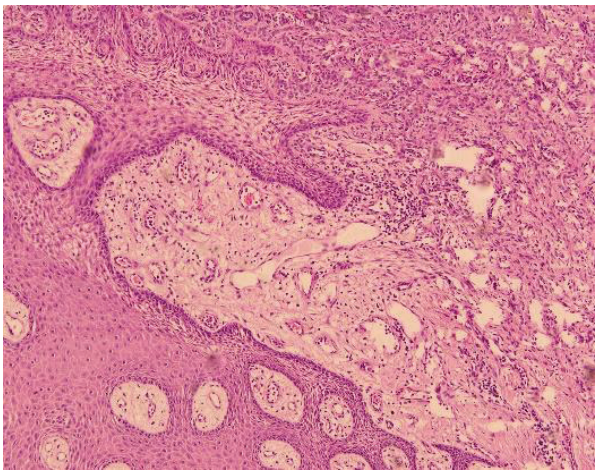

Figure 5. Histopathological image

- **Postoperative finding**. Clinical examination revealed proper healing of gingival tissue and sutures were removed. The patient was monitored postoperatively at regular intervals and three months after the operation, minimal scar tissue and healthy tissue were present around the site of the previous lesion (Figure 4).

Discussion

Epulis is fibrous inflammatory hyperplasia that usually occurs as a result of gingival enlargement due to local irritation of the gums. Epulis is a lesion that does not respond to pain, but its presence causes difficulties in performing functions. In the oral cavity, most local irritants are physical and stimulate submucosal connective tissue, periodontal ligament, or periosteum [5]. Fibrous epulis occurs in response to local irritation with sharp edges (inadequate restorative fillings, carious tooth, or the presence of subgingival calculus). This common type of epulis often results from interdental papillae. The etiology of fibrous epulis, in this case, may be inadequate restorations and subgingival calculus, as chronic factors of irritation. As suggested by Peralles et al., another possible etiology of this lesion is local tissue irritation by bacterial agents and cellular products that induce tissue hyperplasia [6]. Most previous studies have shown that the frontal region, as seen in our case, of the oral cavity was more affected by gingival hyperplasia, ranging from 57% to 71% of cases [7], and this can be explained by the fact that these regions are drier, less exposed to oral moisture and therefore less exposed to saliva with all its positive characteristics. Fibrous epulis in the current case appeared in 25-year-old female patient. And according to most reports the epulis is more common in women [8]. This is probably caused by the high concentration of estrogen, which is considered a favorable factor for their formation and affects their growth. A study by Bataineh and Al-Dvairi [9]

showed that epulis often appeared in people between the ages of 21 and 60. The obtained results are in accordance with our case report where the change occurred in a patient in her twenties. In addition to aforementioned, the other study from Brazil had reported that females on their third to fourth decades of life were the predominant group affected by inflammatory gingival hyperplasia and that the most cases affected the anterior portion of the oral cavity [10]. Literature data indicates that females have greater knowledge about oral health, a more positive attitude toward dental visits, a healthier lifestyle and higher level of oral health behavior than males [11]. However, due to COVID-19 pandemic concerns, it took a year for our female patient to seek dental care when difficulties in performing the functions of chewing and speech became far too obvious for a month prior to a dental visit.

Epulis treatment involves excision of the gingiva, reconstruction, and removal of the source of irritation to prevent a recurrence. Our patient was treated with non-surgical periodontal therapy (identification of dental deposits, motivation and education of proper oral hygiene maintenance, removal of dental deposits), surgical excision of the epulis and instructed to correct inadequate restorative fillings that contribute to chronic irritation and cause hyperplasia of gingival tissue.

Conclusion

Although the etiology of gingival epulis has not been determined, continuous trauma due to the presence of soft and hard dental deposits as well as inadequate restorative fillings seem to be the main factor for the development of fibrous epulis in this case. Only clinical examination makes it difficult to diagnose, so histopathological examination of the tumor is mandatory to confirm the definitive diagnosis of fibrous epulis. The treatment of choice is surgical excision of the enlargement with its base and removal of predisposing factors to avoid recurrence.

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Ethical approval. The Ethics Committee of the Faculty of Medicine Foca approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflict of interest. The authors declare no conflict of interest.

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Fibrozni epulis - prikaz slučaja

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Uvod. Epulis je promjena na gingivi koja nastaje pod dejstvom hronične iritacije. Histološki postoji više različitih vrsta epulisa. Fibrozni epulis predstavlja benigni tumor gingive koja se najčešće pojavljuje u predjelu interdentalne papile kao rezultat lokalne iritacije (neadekvatni konzervativni radovi, kariozni zubi, subgingivalne naslage ili njihova kombinacija). Cilj rada je prikazati klinički slučaj fibroznog epulisa.

Prikaz bolesnika. Djevojka starosti 25 godina se javila u Specijalistički centar za stomatologiju u Foči. Kliničkim pregledom ustanovljeno je uvećanje gingivalnog tkiva u predjelu centralnih sjekutića gornje vilice sa smetnjama u obavljanju funkcija govora i žvakanja. Intraoralnim pregledom uočava se promjena iznad nivoa gingive, crveno-ružičaste boje, glatke površinske teksture i mekane konzistencije. Veličina promjene je bila 1 x 1,5 cm. Užom bazom je bila vezana za interdentalnu gingivu između zuba 12 i 21. Klinički je bila prisutna znatna količina mekih i čvrstih zubnih naslaga u predjelu preostalih zuba. Gingiva preostalih zuba je bila otečena, crvena, krvarila na provokaciju. Anamnezom nije potvrđeno prisustvo drugih akutnih i hroničnih oboljenja. Pacijentkinja nije bila u drugom stanju. Upoznata je sa procjenom kliničkog stanja, kao i mogućim terapijskim procedurama. Naša pacijentkinja je liječena nehirurškom terapijom oboljelog parodoncijuma i hirurškom ekscizijom promjene. Nakon patohistološkog pregleda odstranjenog tkiva, postavljena je dijagnoza: "*Fibrous epulis cum ulceration*".

Zaključak. Samo kliničkim pregledom je teško postaviti dijagnozu; zbog toga je histopatološki pregled tumora obavezan za potvrđivanje definitivne dijagnoze fibroznog epulisa. Izbor tretmana je hirurška ekscizija izrasline sa njegovom bazom i uklanjanje predisponirajućih faktora da bi se izbjegao recidiv.

Ključne riječi: gingiva, epulis, centralni sjekutići

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Review

Positive effects of dietary approach for the treatment of hypertension

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Summary

According to the World Health Organization (WHO) and the International Society for Hypertension, elevated blood pressure is defined as the blood pressure the readings of which consistently range ≥140 mmHg systolic and/or 90 mmHg diastolic. Having in mind the fact that hypertension is one of the leading risk factors for cardiovasluar disease, kidney failure and premature mortality, it is clear that preventive measures should be imposed before the diagnosis is established. The main nutritional measures used in preventing hypertension are: weight loss, Dietary Approaches to Stop Hypertension (DASH diet), reducing salt and alcohol intake and increasing potassium intake.

The aim of this paper was to show the preventive effect of the DASH diet on hypertension onset in normotensive patients as well as to highlight that the diet is an integral part of hypertension treatment, in addition to the use of drug therapy for hypertensive patients.

Key words: diet, DASH diet, hypertension

Introduction

Hypertension or high blood pressure is a serious health condition that significantly increases the risk of heart, brain, kidney and other diseases. It is estimated that 1.28 billion adults aged 30–79 worldwide have hypertension, with the majority (two-thirds) living in low-income and middle-income countries. It is estimated that 46% of adults with hypertension are

unaware that they have that condition. Less than half of adults (42%) with hypertension are diagnosed and treated. Approximately 1 in 5 adults (21%) with hypertension has it under control. Hypertension is a major cause of premature death worldwide. One of the global aims for noncommunicable diseases is to reduce the prevalence of hypertension by 33% between 2010 and 2030 [1].

Hypertension is particularly challenging because it is an asymptomatic silent killer and often remains hidden until detected during follow-up or proven to be a hypertension-related disease such as heart failure or stroke.

Blood pressure category	Systolic Blood Pressure		Diastolic Blood Pressure
Normal	<120 mmHg	and	<80 mmHg
Elevated	120–129 mmHg	and	< 80 mmHg
Hypertension			
Stage 1	130–139 mmHg	or	80–89 mmHg
Stage 2	≥140 mmHg	or	≥90 mmHg

High blood pressure is a worldwide problem, but the largest increase in the absolute burden of hypertension is currently seen in East Asia and the Pacific, Latin America and the Caribbean, South Asia, and Sub-Saharan Africa.

In 2017, the American College of Cardiology (ACC) and the American Heart Association (AHA) published new guidelines for controling hypertension and defined high hypertension as blood pressure equal to or above 130/80 mmHg. Stage 2 hypertension is defined as blood pressure equal to or above 140/90 mmHg [3].

Uncontrolled hypertension imposes a huge economic burden on society, in terms of direct health care costs and significant productivity losses resulting from disability and premature mortality. It is estimated that 10% of global spending on health care is directly related to hypertension and its complications [2].

Thus e.g. high blood pressure costs the United States about $ 131 billion each year, averaging 12 years from 2003 to 2014 [4].

According to the Centers for Disease Control and Prevention (CDC), the two main health conditions for developing high blood pressure are prehypertension and diabetes [5].

Many factors increase the risk of high blood pressure. Some risk factors, such as unhealthy lifestyle habits, can be changed. Other risk factors such as age, family history and genetics, race, ethnicity and gender cannot be changed. A healthy lifestyle can reduce the risk of developing high blood pressure.

Lifestyle habits can increase the risk of high blood pressure. These habits include: Frequent consumption of unhealthy food, especially the food with too much sodium and not enough potassium. Some people, including African Americans, older adults, and people with chronic kidney disease, diabetes, or metabolic syndrome, are more sensitive to dietary salt; Consuming too much alcohol or caffeine; Lack of physical activity; Smoking; Insufficient sleep quality [6].

Treatment decisions depend on whether there is cardiovascular disease, diabetes or chronic kidney disease. For patients with

stage I hypertension and without these conditions, the 2017 ACC/AHA guideline recommends calculating an estimated 10-year risk of cardiovascular disease (CVD).

If this risk is less than 10%, it is reasonable to apply life modifications only for a period of 3 to 6 months. For those with stage 2 hypertension or pre-existing cardiovascular disease, diabetes mellitus, chronic kidney disease, or a 10-year risk of KBC disease of 10% or more, lifestyle and treatment changes are recommended [7].

The aim of this study was to show the preventive effect of DASH diet, but also other diets on the development of hypertension in normotensive patients and that diet is an integral part of therapy in the treatment of hypertension in addition to drugs in hypertensive patients.

Epidemiology

According to the WHO, there are 1.13 billion people worldwide with hypertension [8].

The prevalence of hypertension varies depending on the region and groups in the country. The WHO African region has the highest prevalence of hypertension (27%), while the WHO region of the United States has the lowest prevalence of hypertension (18%).

The number of adults with hypertension rose from 594 million in 1975 to 1.13 billion in 2015, with an increase mainly in low-income and middle-income countries. This increase is mainly due to increase in risk factors for hypertension in these populations [1].

In 2019, more than half a million of deaths in the United States had hypertension as the primary or contributing cause [9].

According to the data of the Public Health Institute of the Republic of Srpska from 2019, the first cause of death in the RS is also CVD with a total of 7473 or 49.5% of deaths [10].

The five leading groups of diseases that were the cause of mortality in the Federation of BiH in the period from 2017 to 2019 are the leading diseases of the cardiovascular system with 47%, which decreased compared to 2018 when the parte of CVD in mortality of BiH population was 51.5% [11].

In Croatia, CVD is the leading cause of death. In 2020, they were the cause of death in 40.0% of cases, a total of 22,817 people died, of which 13,106 were women and 9,711 were men [12].

Effects of dietary approach to stop hypertension

Numerous studies have shown that eating habits are able to modify cardiovascular risk factors [13, 14, 15].

They affect endothelial function, favoring inflammatory processes underlying atherosclerosis [16]. Under physiological conditions, the vascular endothelium maintains its tone by releasing signaling molecules with vasodilators (such as nitric oxide (NO)) and vasoconstrictors such as (angiotensin II) [17]. Endothelial dysfunction occurs when there is abnormal production of reactive oxygen species (ROS) of proinflammatory cytokines, such as interleukin I (IL) -1 and tumor necrosis factor (TNF) -α, and decreased release of nitric oxide (NO) [18]. This condition triggers the process of atherosclerosis [17].

For this reason, it is important, if not necessary, to undertake nutritional treatment in patients with high blood pressure [19].

If lifestyle changes cannot normalize blood pressure, it is mandatory to start pharmacological treatment in order to return blood pressure values to normal [20].

Among the dietary patterns studied, the Dietary Approaches to Stop Hypertension (DASH) has been consistently endorsed by the National Heart, Lung and Blood Institute, the American Heart Association, the Dietary Guidelines for Americans, and the United States Guidelines for blood pressure

treatment as an effective diet to control blood pressure [21].

The DASH diet originated in the 1990s. In 1992, the National Institute for Health (NIH) launched several research projects to see if specific dietary interventions were helpful in treating hypertension. Respondents included in the study were advised to follow only dietary interventions and not include any other life modifications, to avoid any confusing factors. They found that dietary intervention itself could reduce systolic blood pressure by about 6 to 11 mmHg. This effect occurs in hypertensive as well as in normotensive people. Based on these results, DASH was advocated as first-line pharmacological therapy along with life modification [22].

Every type of food included in the DASH diet has its purpose:

Whole grain cereals that provide a lot of fiber, potassium, magnesium, and contain antioxidants, all of which help in maintaining CVS health and lower blood pressure.

Fruits and vegetables, which offer an abundance of nutrients suitable for blood pressure including a wide range of vitamins, and antioxidants plus potassium and fiber.

Low-fat dairy products are strongly associated with a lower risk of hypertension, as they are rich in vitamin D, calcium, magnesium and potassium, high in protein, and low in saturated fat and calories.

Lean meats, fish and poultry provide plenty of protein to build a healthy and strong body, while exposure to saturated fats and calories is limited.

Nuts, seeds and legumes contain plant-based proteins suitable for the heart, along with healthy fats, fiber and magnesium [23].

Processed and dried meat products are not recommended, because it has been shown to cause hypertension and also contains carcinogens.

DASH diet, therefore, refers to the inclusion of foods rich in potassium, calcium, magnesium, because they prevent endothelial dysfunction and urge the release of endothelium and smooth muscles [24, 25].

The key fact is that this diet should be promoted to patients. Prior to discharge, nurses are at the forefront of educating all patients and their families about the DASH diet and its benefits. The most important feature of the DASH diet is that it requires a change in lifestyle and the adoption of a healthy diet. Furthermore, patients should be encouraged to stop smoking, abstain from alcohol, and engage in physical activity [26, 27, 28]. The implementation of the DASH diet should be led by an interprofessional team that includes clinicians, mid-level practitioners, nurses, pharmacists and dieticians. This will lead to optimal outcomes for patients during the use of this diet.

One study compared the effects of low versus high sodium intake, the DASH diet versus control diet, and both (the low sodium diet — the DASH diet versus the high sodium diet — the control diet) on systolic blood pressure. Out of the 412 study participants, 57% were women with prehypertension or stage 1 hypertension. In the context of high sodium, the DASH diet compared to the control diet was associated with mean systolic blood pressure differences of -4.5, -4.3, -4.7, and 10.6 mmHg, respectively. The combined effects of the low-sodium - DASH diet versus the high-sodium - control diet on systolic blood pressure were -5.3, -7.5, -9.7, and -20.8 mmHg, respectively [29].

A systematic review of the literature, which included 30 randomized clinical trials with 5,545 participants, monitored the effects of the DASH diet in normotensive and hypertensive adults. Compared to the control diet, the DASH diet reduced both systolic and diastolic blood pressure (difference in mean values: -3.2 mmHg; 95% CI: -4.2, -2.3 mmHg; P< 0.001 and -2.5; 95% CI: -3.5 -1.5 mmHg P< 0.001, respectively). The DASH diet compared to the control diet reduced systolic blood pressure to a greater extent in sodium-intake

> 2400 mg/ day trials than in < 2400 mg/day trials while both systolic and diastolic blood pressure decreased more in middle-aged < 50 than in trials with older participants [30].

Numerous studies, including randomized clinical trials, have investigated the effect of individual nutrients on blood pressure. For example, a recent meta-analysis showed that a reduction in salt intake (sodium chloride) of mean values 4.4 g/day (1716 mg sodium/ day) resulted in a 5/3 mmHg reduction in blood pressure in hypertensive subjects and 2/1 mmHg in normotensive subjects [31]. Similarly, a large meta-analysis involving 29 randomized clinical trials showed that increased potassium intake of 20 mmol per day (780mg/ day) resulted in a decrease of 4.9 mmHg and 2.7 in systolic and diastolic blood pressure, respectively, without the use of antihypertensive drugs [32].

Also, another meta-analysis of seventeen randomized clinical trials evaluated current evidence on the impact of dietary patterns on blood pressure in adults. Significant reductions in systolic blood pressure of 4.26 mmHg and diastolic blood pressure of 2.38 mmHg were observed [33].

Application of other innovative nutritional-dietary approaches in the treatment of hypertension

The Caloric Restriction Diet (CRD) consists of a chronic reduction in daily calorie intake of about 25–30% compared to normal calorie intake, without any effect [3]. As this regime is not standardized, numerous studies show its effectiveness. Currently, according to the Calorie Restriction Society, entities that follow a self-imposed CRD regimen are characterized by extended life expectancy. This regimen consists of a calorie restriction with a daily intake of less than 1800 kcal for an average period of 15 years and with an energy intake 30% less than the group of individuals (homogeneous in age, gender and socioeconomic status) who consumed the Western diet model [34, 35].

The first animal study to assess the beneficial effects of the CRD was carried out in rats in 1900 [36].

Animal studies on CRD have shown that initial food restriction followed by alternating fasting had a positive effect on glycemic control, body weight reduction, insulin sensitivity and blood pressure control [37].

Recent studies have shown that CRD can determine the damaged DNA repair and decrease fat mass, systolic and diastolic blood pressure values, and the production of free radicals [38].

To explain the mechanism underlying the reduction in CRD-induced blood pressure, it has been suggested that it may act through activation of the autonomic nervous system. This hypothesis was investigated by Nakano et al., who observed a reduction in systolic and diastolic blood pressure in obese hypertensive patients in the treatment of CRD (800 kcal/ day) with normal sodium level for two weeks [39].

While CRD focuses on the number of calories consumed, reducing them by 25–30%, the DASH diet mainly focuses on the quality of micro- and macro-nutrients assumed. Numerous studies have shown that the DASH diet induces a greater reduction in blood pressure values than other dietary interventions or physical activity programs [40].

Most of the studies on salt reduction and weight loss were carried out on middle-aged subjects. In particular, the Trial of Nonpharmacological Interventions in The Elderly (TONE) study showed that, in subjects with arterial hypertension, a moderate salt restriction and weight loss reduce the dosage of antihypertensive drugs [40].

A recent meta-analysis conducted by D'Elia et al. examined the impact of dietary sodium restriction on central blood pressure. The authors found a statistically significant

association between the reduction of blood pressure and central pulse pressure, speculating that sodium restriction also impacts on central blood pressure values. For this reason, a diet with a low sodium intake is a useful tool to counteract the onset and/or the progression of CVS disease, especially in normotensive subjects and in prehypertensive patients [19].

Vegetarian and Mediterranean diets are also associated with lowering blood pressure [41, 42]. A meta-analysis of seven randomized control trials with a total number of 311 participants reported that vegetarian diets (defined as diets that never or rarely included meat) were associated with a mean reduction in systolic blood pressure of 4.48 mmHg (95% CI 3.1–6.6) and diastolic 2.2 mmHg (95% CI 1.1–3.5) [41].

The Mediterranean diet is characterized by moderate fat intake (primarily from olive oil and nuts), low consumption of red meat and high consumption of vegetables [42].

A meta-analysis of 6 trials with a total number of 2650 participants reported a modest but significant reduction in systolic blood pressure of 1.7 mmHg (95% CI 0.05–3.4) and diastolic blood pressure of 1.5 mmHg (95% CI 0.8–2.1) in the Mediterranean diet compared to a low fat diet [42].

Probably due to the heterogeneity of Mediterranean diet patterns in different regions and countries, evidence of clinically important effects of the Mediterranean diet and reduced salt intake is limited [43].

Blood pressure is lower in vegetarians than in people who mostly eat meat, and maintaining a vegetarian diet can lower blood pressure. The effect of lowering blood pressure is not the result of a reduction in the intake of animal proteins, but an increase in the intake of vegetables and fruit in combination with a reduction in the intake of saturated fatty acids. In a study in the elderly, blood pressure decreased by 3/1 mmHg when the intake of fruits and vegetables increased alone, but by 6/3 mmHg when combined with a decrease in fat intake [44–46]. As it contains several food groups, the DASH diet is likely to have additional beneficial effects [44, 46, 47]. In Korea, diets consisting of tofu cheese, soy, fruits, vegetables, and fish have been associated with a low prevalence of hypertension with high dietary intake [48].

Negative effects of DASH diet

Bloating is one of the most common gastrointestinal problems. One such randomized clinical study examined the effects of a high-fiber DASH diet and sodium intake on bloating. The study included 412 participants (mean age 48 years) who reported bloating at the beginning. Regardless of diet, high sodium intake increased the risk of bloating (risk ratio = 1.27; 95% confidence interval: 1.06–1.52; R = 0.01). The DASH diet rich in fiber also increased the risk of bloating (risk ratio 1.41; 95% confidence interval: 1.22–1.64; R < 0.001) [49].

The study was of clinical significance because millions of adults in the United States visit a doctor for gastrointestinal disease, with bloating as one of the most common symptoms, reported by approximately 15% to 30% of the general population [50, 51, 52, 53].

The results of the study showed that although a high-fiber diet, such as the DASH diet, may increase the risk of bloating, reducing the sodium intake in such a diet may reduce some of these side effects.

In conclusion, a diet rich in fiber increased the symptoms of bloating, while reduction in sodium decreased these effects. Sodium reduction is an important dietary intervention to reduce bloating symptoms and can be used to improve compliance with healthy high-fiber diets, such as the DASH diet [49].

Conclusion

In order to treat hypertension, one should focus on changes in lifestyle habits and the use of medications. When it comes to lifestyle habits, it is necessary to change the diet, include regular physical activity, limit salt intake, limit alcohol intake and ban the use of cigarettes.

A large number of studies have just confirmed that a diet that has a preventive effect, and also positive effects on the control of this disease as a type of diet that is supportive of drug therapy and has a role in regulating body weight is just described DASH diet.

In the prevention of hypertension and treatment if it occurs, a multidisciplinary approach is needed by physicians and nutritionists to provide patients with a simple way to control blood pressure.

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Pozitivni efekti dijetetskog pristupa za liječenje hipertenzije

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Prema Svjetskoj zdravstvenoj organizaciji (SZO) i Internacionalnom udruženju za hipertenziju, kao povišen krvni pritisak se definiše krvni pritisak kada je nivo sistolnog krvnog pritiska od 140 mmHg ili više i/ili nivo dijastolnog krvnog pritiska od 90 mmHg ili više, u ponovljenim mjerenjima. Kada se ima u vidu činjenica da je hipertenzija jedan od najvažnijih faktora rizika za kardiovaskularne bolesti, bubrežnu insuficijenciju i preranu smrtnost, jasno je da bi se preventivne mjere trebalo preduzeti prije nego se postavi dijagnoza. Glavne nutritivne mjere koje se koriste u sprečavanju nastanka hipertenzije su: smanjenje tjelesne težine, DASH dijeta (Dietary Approaches to Stop Hypertension), smanjen unos soli, povećan unos kalijuma i smanjen unos alkohola.

Cilj ovoga rada je bio da se pokaže preventivni efekat DASH dijete na sam nastanak hipertenzije kod normotenzivnih pacijenata, kao i da dijeta predstavlja sastavni dio terapije u liječenju hipertenzije pored upotrebe lijekova kod hipertenzivnih pacijenata.

Ključne riječi: dijeta, DASH dijeta, hipertenzija

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Review

Post-chemotherapy cognitive dysfunction in women with breast cancer

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Summary

Cancer-related cognitive dysfunction is an important clinical problem that can interfere with the daily functioning, work productivity, childcare, and other responsibilities of women with a history of breast cancer. Risks of cancer-related cognitive impairment include cancer and cancer treatment, as well as patient-related vulnerabilities. There is no established standard of neuroprotective care or treatment for breast cancer-related cognitive impairment.

Key words: cancer-related cognitive impairment, breast cancer, women

Introduction

Breast cancer is the most common malignancy in women, and its incidence is increasing in most countries of the world [1, 2]. Cognitive dysfunction in breast cancer patients has been reported since 1990. These reports are consistent with the increased use of adjuvant chemotherapy, especially in women who received very high doses of chemotherapy. Subsequent studies have documented cancer-related cognitive impairment (CRCI) in patients with a history of breast cancer, before cancer-targeted treatment, and in combination with other topical and/or systematic breast cancer treatments. These side effects of chemotherapy treatment of malignant tumors have been known as post-chemotherapy cognitive impairment (PCCI) or chemotherapy-induced cognitive impairment (CICI). In the era of more selective use of chemotherapy, cognitive dysfunction

symptoms continue to appear after cancer-targeted treatment, endocrine therapy, and in other situations, including radiation therapy and surgery [3–6].

Cognition is an important part of the quality of life for both healthy people and those suffering from malignant illnesses. Breast cancer is the most studied type of cancer in CRCI, but there is increasing literature data on the condition of patients with other types of cancer such as lymphoma, head and neck cancer, brain cancer, and those who have undergone stem cell transplantation. Cognitive impairment is also an independent prognostic factor for some malignant tumors [3–6].

There is no established standard of neuroprotective care against CRCI or the treatment of CRCI for breast cancer. Cognitive rehabilitation and behavioral therapy are the most promising interventions for CRCI. Physical activity is a promising intervention, but it has not been fully evaluated. Some drugs (psychostimulants, dementia drugs, etc.) have been studied without definitive efficacy and require further research [3–7].

There are several reports of short-term and long-term cognitive impairment and difficulties that these patients have experienced. This can last for years not only during treatment, but also after the end of treatment, and for many years after the end of treatment compared to the most commonly reported first breast cancer treatment.

Patients who develop cognitive impairment in the acute phase of breast cancer treatment may take months to a year to recover, and in some individuals, cognition, supported by reports of neuroimaging abnormalities, will never return completely to baseline. In the case of dementia, symptoms often impair function, work, and quality of life [4–7].

Many studies have confirmed that cognitive impairment is associated with negative emotions, the frequency, and intensity of which may be sufficient to meet the criteria for anxiety and mood disorders. This comorbidity reflects a feedback loop between physical symptoms and psychological/psychiatric difficulties [4–8].

The CRCI reported by breast cancer patients is common, but the frequency and type may vary depending on the population studied. The magnitude of cognitive impairment depends on the treatment that this patient's profile is receiving, and it is also important for the patient to be aware of the extent to which cognitive impairment is impaired. There is also a discrepancy between the scores obtained from the self-assessment scale and the scores obtained by the patient in the objective test of cognitive function/skills [3–6].

The main model of CRCI suggests that mechanisms and vulnerabilities overlap with cognitive aging and may represent accelerated aging. Based on clinical and preclinical studies, several possible mechanisms of CRCI have been hypothesized. Increased systemic inflammation occurs in response to cancer, chemotherapy, radiation therapy, and surgery. Chronic inflammation can cause neuroinflammation, which can lead to increased neurotoxicity and oxidative damage. Evidence also suggests neuronal mitochondrial dysfunction, as well as neurogenesis and neuroplasticity disorders. The potential cognitive effects of immunotherapy, a new breast cancer treatment, have been reported [7, 9–11].

Estrogen plays an important role in women's brain health, and down-regulating natural estrogen production and blocking its activity with endocrine therapies are associated with cognitive effects [3, 4, 7, 8].

Evaluation by cancer-related cognitive dysfunction

Neuroradiological (especially functional magnetic resonance imaging fMRI), neuropsychological, and neurophysiological methods were used to assess CRCI [11]. These methods certainly contribute to greater objectivity and

reliability of the results obtained, and provide deeper insight into the analysis and interpretation of the process of solving the task of testing cognitive function. Previous studies were inconclusive, and the author himself attributed it to the lack of sufficiently sensitive and practical measuring instruments that were not sufficient to detect minimal changes in cognitive ability [8].

The National Cancer Network Guidelines for Assessment and Management of CRCI suggest that strengthening patient education on CRCI is important. Many breast cancer patients are unaware of the potential for cognitive decline after treatment. Dementia screening tools are inadequate for CRCI assessment but screening for mood disorders and survival problems can identify cognitive symptoms. Careful assessment of cognitive impairment using the CRCI validated questionnaire can be used to track disability in the event of clinical suspicion. When patients voluntarily report these symptoms to their doctor, they should not be ignored. It is important to recognize the patient›s symptoms and perform a thorough examination. The first step is to assess and address potentially controllable comorbidities that are common and often co-occurring in this patient population, such as depression, sleep disorders, and fatigue. If CRCI symptoms do not improve, you should follow the referral of a neuropsychological assessment. It helps to characterize specific cognitive symptoms, provide targeted recommendations, and provide relief and information to patients who are concerned about developing dementia [8, 11].

Results of neuropsychological surveys

Berndt et al. show that person with breast cancer rate their memory as average, and point out that this negative self-reporting of mental function was almost consistently associated with higher levels of anxiety and depression. However, patients' scores on an objective measure of the degree of cognitive impairment did not correlate with their level of anxiety. In general, subjects in this study performed poorly on mental rotation tasks as an indicator of spatial cognition and memory-examining tasks. Author compared four groups formed by the type of treatment the patient received for general memory and verbal memory, and found that the treatment had a statistically significant effect. This means that memory loss in breast cancer patients is related to the type of treatment they receive, but in some cases memory may be normal or visibly impaired [12].

Chen et al. compared patients before and after chemotherapy and healthy subjects on various measures of cognitive performance. They found that these subjects were statistically tested for delayed recall and content recognition as an indicator of memory impairment, back-calculation as an indicator of concentration, and Stroop test. They have been found to have a significantly smaller effect on executive function. Subjects in this group also showed statistically significantly longer reaction times and diminished attention to the presented stimuli. However, when it came to assessing general cognitive performance, the treated subjects mentioned did not differ from the sample in the healthy population [13].

Henneghan et al. founded that objective and self-assessment of cognitive ability by breast cancer patients are moderately negatively correlated with perceived stress, anxiety, depression, loneliness, malaise, and sleep problems, and are statistically significantly correlated. On the other hand, the number of treatments and the time elapsed since the end of chemotherapy were not statistically significantly correlated with the objective and self-assessed cognitive function measurements in this group of cancer patients [14].

Hermelink et al. found that people with breast cancer generally show reduced cognitive

ability. However, only patients who received chemotherapy extended reaction time. Author found a small but statistically significant correlation between respondents› scores for an objective measure of cognitive performance and self-reporting of these types of abilities. In addition, post-traumatic stress disorder (PTSD) has been shown to have the potential to alleviate the association between breast cancer and cognitive impairment in these individuals [15].

Jung et al. found that breast cancer patients who received chemotherapy had statistically significantly lower scores on the language working memory test compared to healthy subjects. Chemotherapists showed statistically significantly higher deficiencies in the area of executive function not only in healthy individuals but also in breast cancer patients who did not receive chemotherapy. Interestingly, patients treated with chemotherapy and those not treated that way did not report statistically significantly greater cognitive impairment compared to healthy subjects. The level of anxiety and perceived stress was statistically significantly correlated with self-assessed memory loss. On the other hand, the association between anxiety and stress and patient scores on objective memory tests was not statistically significant. In addition to a neuropsychological examination, functional magnetic resonance imaging (fMRI) was also used in this study [8].

Kama et al. investigated connection with the electrophysiological aspects of cognitive impairment, and concluded that breast cancer survivors had statistically significantly more problems focusing attention on specific tasks or objects compared to healthy women. In addition, their response to visual stimuli appears to be less intense [11].

Kessler et al. compared the potential of functional magnetic resonance imaging with standard medical (patient-centric) testing to predict cognitive impairment in breast cancer patients one year after the end of chemotherapy. fMRI turned out to be a more accurate modality of this assessment, and the incidence of cognitive impairment in this patient profile was found to be 55% one year after the end of chemotherapy [7].

Lange et al. conducted a study of older women with breast cancer, and found that 49% of respondents have a cognitive impairment, which is primarily related to working memory, and 64% of respondents have problems in this area of cognitive function/skills. In addition, subjects who received chemotherapy were more likely to complain of cognitive impairment than those who received radiation therapy. Therefore, the subjective assessment of cognitive decline was higher [4].

Manning et al. found that patients in their sample who received chemotherapy and endocrine therapy reported statistically significantly weaker physical and social functions than healthy subjects [10]. However, subjects in these two groups did not show a statistically significant difference in self-assessment of cognitive function. However, an objective test of their cognitive abilities revealed that the group of subjects who received chemotherapy and hormone therapy for breast cancer had statistically significantly greater cognitive impairment than healthy subjects. Another result of this study is related to a statistically non-significant difference in IQ levels between breast cancer subjects and a group of healthy subjects. However, this difference was not large enough to declare it to be statistically significant [10]. In another study the authors used fMRI to observe the neurophysiological correlation of cognitive impairment in patients treated with chemotherapy and endocrine therapy. They found that performing tasks designed to test executive function resulted in high parietal lobe activation in patients, reflecting the cognitive load generated by solving such tasks. The correlation of this phenomenon was patient complaints about fatigue, physical dysfunction, and cognitive dysfunction. The authors explained this phenomenon by disrupting the integration of

processes in the brain, due to the potential neurotoxicity of the treatment the patient received [16].

Paquet et al. found that differences in the subjective assessment of cognitive function between breast cancer subjects and healthy subjects could be explained by increased fatigue and depression in the first group of subjects. Both groups reported that forward-looking memory was worse than backward-looking memory. However, self-assessment of forward and backward memory did not statistically significantly correlate with objective measurements of these two types of memory. In addition, one group of patients achieved statistically significantly lower scores in objective measurements of both forward and backward memory, compared to healthy subjects. The subjective assessments of forward and backward memory were also strongly correlated with each other. Patients' results on objective measurements of forward and backward memory were also statistically significant, but still poorly correlated [17].

Lamar found that the development of cognitive impairment in breast cancer patients was statistically significantly associated with chemotherapy compared to other therapies: radiation therapy, endocrine therapy, immunotherapy, etc. in subjects who were not anxious at the time of diagnosis. In addition, the authors found that 38% of the women in the sample reported clinically significant levels of anxiety, and that incidence of cognitive impairment one year after the diagnosis of breast cancer is 8.1%, which is significantly lower than in other studies [18].

Two studies observed the greatest cognitive impairment in the combination of chemotherapy and hormone therapy for breast cancer. The three findings are positive, which can be concluded from the statistically significant difference in size between groups of patients treated differently, namely the degree of cognitive impairment. On the other hand, none of the results of the studies included in the meta-analysis were negative [10, 16]. In addition, six studies found that breast cancer patients (most commonly when receiving some available treatments) had statistically significantly worse cognitive function compared to healthy subjects. However, in three studies, these differences were not statistically significant. In a study conducted by Manning et al., patients complained of cognitive problems more than healthy individuals, but objective tests showed that these differences were not statistically significant. There were no results that general intelligence could decline but in contrast, the study by Manning et al. gave negative results [16]. Attention and concentration appear to be a mental function that is impaired in breast cancer patients, and we observed two positive and no negative findings [11, 13].

Four studies gave statistically significant results suggesting different memory deficits in breast cancer patients, but this effect was not seen in two studies. Interestingly, in one study, this cognitive deficiency was identified by an objective measurement (test), but in the same study, when self-assessment was measured, the patient was unaware of such a deficiency, and this can be due to the nature of the measurements used. Patients may know that they must control their problems and difficulties without admitting that their abilities and skills are weakened. Memory impairment includes three major flaws: working memory problems, problems related to retrospective memory, and future memory problems, and these are more pronounced than the problem of retrospective memory [12].

In two studies, Chen et al. and Henneghan et al. found that cognitive problems in women with breast cancer are often associated with discomfort and anxiety, sadness and depression, higher levels of stress, and a type reaction similar than post-traumatic stress disorder (PTSD). These findings were conducted in seven analyzed studies (i.e. more than half of the studies included in the meta-analysis),

and negative findings were conducted in two studies [13, 15].

In two studies conducted by Berndt et al., and Jung et al., there should be noted that the assessment of depression and anxiety is mostly self-reported, and herefore, this finding is not surprising [8, 12].

Results of neuroimaging surveys

There is compelling evidence from imaging studies showing cognitive changes associated with cancer treatment in some people. Several neuroimaging studies have, for example, described brain changes comparable to aging, such as compensatory overactivity during cognitive tasks and gray matter reduction [19].

Miao et al. in their study found that the functional connectivity of the anterior cingulate cortex (ACC) was significantly lower in patients with breast cancer treated with chemotherapy than in healthy subjects. We have known that functional connectivity of ACC was significantly correlated with executive function. These results provide evidence that these changes in functional connectivity may be the pathophysiological basis for long-term chemotherapy-related cognitive dysfunction, as well as executive dysfunction, in breast cancer patients [20]. Zheng et al. localized brain region with increased amplitude of low-frequency fluctuation in patients treated with breast chemotherapy 1 month after therapy: lower left inferior temporal gyrus, right medial temporal gyrus, left medial and superior temporal gyrus, and the anterior precuneus on both sides. After conventional chemotherapy for breast cancer patients, memory, attention, executive function, and processing speed also decrease in the short term. Chemotherapy alters neural activity in the resting, local brain regions, and primarily, there is an increase in the bilateral activity of the middle temporal gyrus and the anterior cuneiform gyrus, where the brain region constitutes the standard network [21].

Li et al. in their study found that gray matter density was reduced in the inferior frontal gyrus, right middle frontal gyrus, right fusiform region, and bilateral in cerebellar region in breast cancer patients compared to healthy controls. Also, a decrease in gray matter density in the right medial frontal gyrus may mediate the effect of chemotherapy on speech fluency performance. These results indicate that the dose-response relationship between chemotherapy and cognitive impairment may be dependent on a decrease in gray matter density in the frontal cortex structure [22].

In some post-treatment cross-sectional studies, using magnetic resonance imaging, gray matter reduction has been proven mainly in the frontal cortical structure and hippocampus, and also white matter in cancer survivors treated with chemotherapy. However, negative results have also been documented [23–28]. Similar results have been reported in longitudinal studies. Gray matter density decreased in bilateral frontotemporal, temporal (including hippocampus), cerebellar region, and right thalamus one month after chemotherapy, with only partial recovery one year after therapy compared with no significant changes in gray over time in cancer group patients without chemotherapy or healthy controls. Also, there was reduced frontal, parietal, and occipital white matter integrity in patients exposed to chemotherapy, and there was no change in the non-chemotherapy group or the healthy controls after treatment [29, 30].

Cross-sectional studies of cancer survivors using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have showed areas of reduced activation during the performance of cognitive task in the area similar to the structural differences described, in survivors exposed to chemotherapy compared to controls. McDonald's et al. in longitudinal studies using fMRI, found frontal lobe hyperactivity to support pretreatment work memory tasks, reduced activation

one month after chemotherapy, and pretreatment hyperactivity one year after treatment [31–36].

Cimprich et al. studied selective attention and working memory in women using functional magnetic resonance imaging before chemotherapy for localized breast cancer. Compared to healthy controls, these patients have bilateral brain activation in demanding tasks, adoption of additional components of attention / working memory circuits, and less accurate and slower task execution. These results show cognitive dysfunction before chemotherapy [37].

Scherling et al. also reported over-activation in memory tasks in cancer patients during pretreatment compared to healthy controls, consistent with reports of neuropsychology test. This over-activation in pretreatment period is an attempt to compensate for the pre-existing deficit. However, over the years, patients lose the ability of that compensation as a result of exposure to cancer treatment and/or age-related changes in the brain [38].

Conclusion

CRCI is an important clinical issue and can interfere with the daily functioning, work productivity, childcare, and other responsibilities of patients with a history of breast cancer. Risks for CRCI include type of cancer and cancer treatment, as well as patient-related vulnerabilities. Treatment recommendations include treating the symptoms reported by the patient with a thorough symptom-based assessment. Cognitive and behavioral therapies are primarily recommended interventions.

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Kognitivna disfunkcija nakon hemoterapije kod žena oboljelih od karcinoma dojke

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Kognitivna disfunkcija povezana sa karcinomom je važan klinički problem koji može ometati svakodnevno funkcionisanje, radnu produktivnost, brigu o djeci i druge odgovornosti žena sa istorijom karcinoma dojke. Rizici od kognitivnih oštećenja povezanih sa karcinomom uključuju karcinom i liječenje karcinoma, kao i ranjivosti pacijenata. Ne postoji utvrđen standard neuroprotektivne njege ili liječenja kognitivnih oštećenja povezanih sa karcinomom dojke.

Ključne riječi: kognitivno oštećenje uzrokovano karcinomom, karcinom dojke, žene

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Uređivačkom odboru časopisa „Biomedicinska istraživanja"

INSTRUCTIONS FOR AUTHORS

''Biomedicinska istraživanja" is a journal of the Faculty of Medicine Foca, University of East Sarajevo, with an open access and blind peer review, which is published twice a year, in June and December.

The journal ''Biomedicinska istraživanja" publishes original scientific papers, previous or short announcements, review and professional papers, papers for practice, educational articles, comments on published articles, case reports, literature reviews, papers on the history of medicine, book reviews, reports from scientific and professional gatherings, news and letters from all fields of medicine, dentistry, special education and rehabilitation and nursing.

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The text of the article should be written clearly and concisely, avoiding unnecessary extensiveness in Serbian Latin or English with a short content, obligatory in both Serbian and English. Due to better availability and greater citation, authors are recommended to submit papers of all forms in English. Original papers, previous or short announcements, patient or case reports, review papers and current topics are published exclusively in English, and other types of papers can be published in Serbian only by the decision of the Editorial Board. Abbreviations should be used exceptionally, and only for very long names of chemical substances or for names that are known as abbreviations (i.e. AIDS, DNA, etc.). The names of symptoms and signs, as well as the names of diseases, anatomical or histological features, cannot be shortened. Use metric units in accordance with the International System of Units, and generic names for medicines, while devices should be marked by their trade names, with the name and location of the manufacturer in brackets.

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Number the pages in order within the bottom margin starting from the title page. Data on the used literature in the text are indicated by Arabic numerals in square brackets - e.g. [3, 4] in the order in which they appear in the text.

Use standard graphic programmes for Windows, Microsoft Office (Excel) to design graphic attachments. Avoid colouring and shading of the background in computer design of graphs.

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List all those who contributed to the creation of the paper and did not meet the authorship criteria, such as the individuals providing technical assistance. Financial and material assistance in the form of sponsorships, scholarships, gifts, equipment, medicines and other should also be mentioned. Paid services are not provided, e.g. professional translations into English.

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Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: Mc-Graw-Hill; 2002. p. 93-113.

Book:

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

Article from a congress or meeting:

Vuković B, Šeguljev Z, Virusni hepatitisi – aktuelan epidemiološki problem 32. Dani preventivne medicine. Niš, 1998. Zbornik rezimea. Institut za zaštitu zdravlja, Niš, 1998; 51-64.

Dissertation:

Radosavljević V. Faktori rizika za nastanak malignih tumora mokraćne bešike. Doktorska disertacija. Univerzitet u Beogradu, 1999.

Journal article in an electronic format:

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Web page on the Internet:

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