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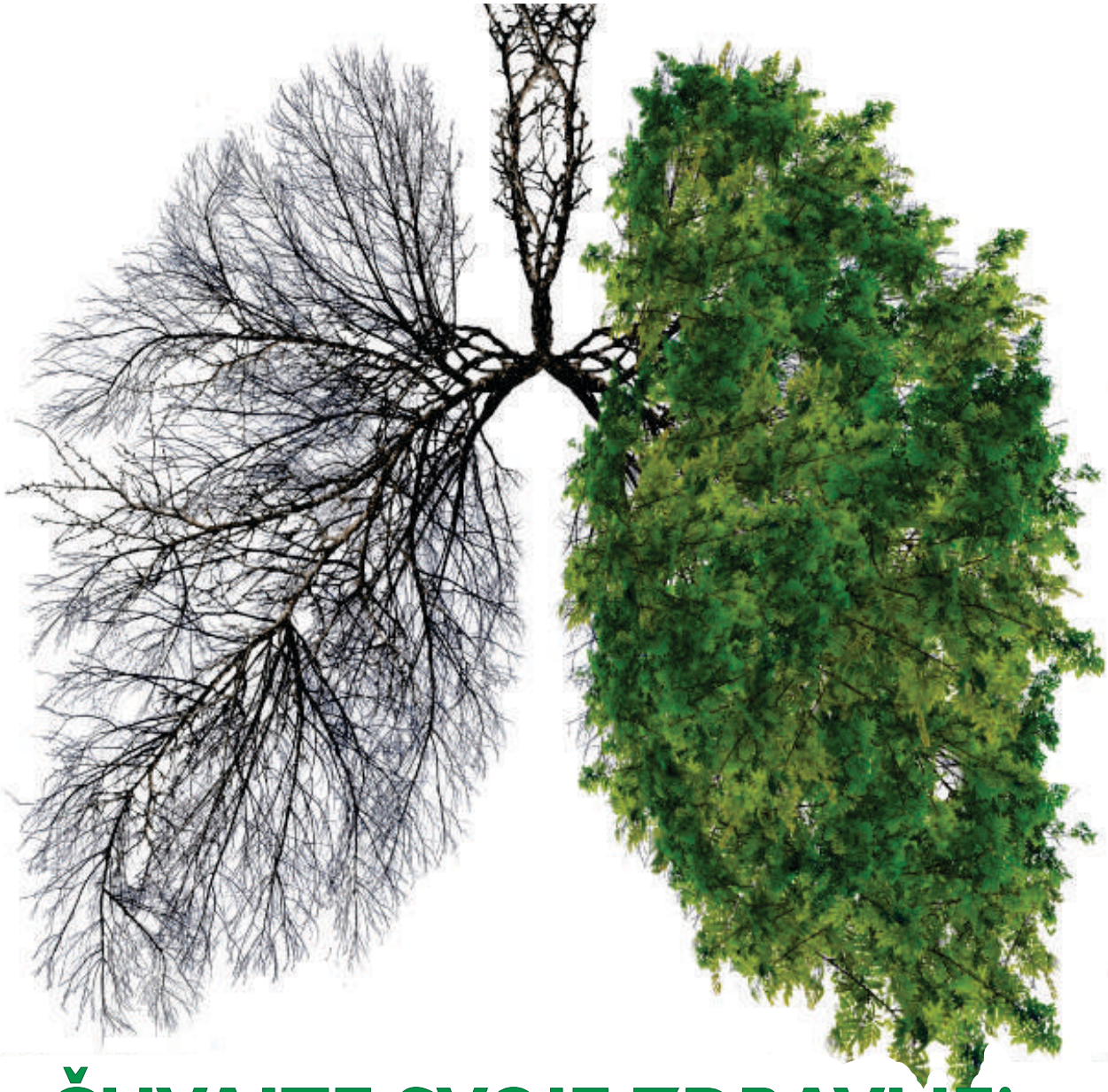

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CHA_2DS_2-VASc skor za procjenu rizika od tromboembolizma kod A Fib!

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

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

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

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Major risk factors	Clinically relevant non-major risk factors
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TIA or systemic embolism	Hypertension
Age ⊠75 years	Diabetes mellitus
	Age 65-74 years
	Female sex
	Vascular disease

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

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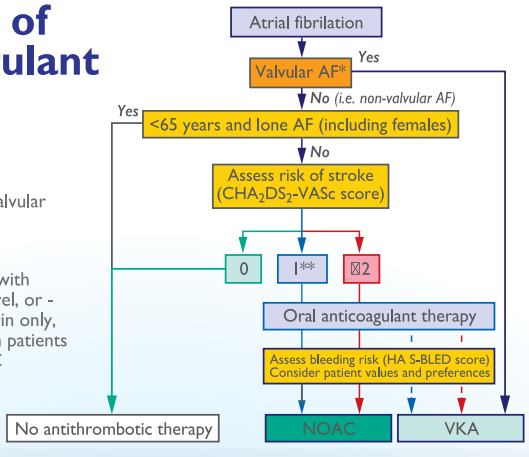

* Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

** Antiplatelet therapy with aspirin plus clopidogrel, or - less effectively - aspirin only, may be considered in patients who refuse any OAC

NOAC - Novel Oral Anticoagulants, VKA - Vitamin K Antagonists

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Evaluation of the diagnostic and surgical procedures in the treatment of compressive neuropathies of the upper extremity to gender, age distribution, and comorbidities

Evaluacija dijagnostičkih i hirurških procedura u tretmanu kompresivnih neuropatija gornjeg ekstremiteta u odnosu na pol, dobnu distribuciju i komorbiditete

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ABSTRACT

Introduction: compressive neuropathies of the upper extremity are most often associated with functional difficulties and reduced working capacity, which can be significant and very complex to treat if these lesions are not recognized and treated on time. The importance of these clinical entities is reflected in the fact that there is a possibility of simultaneous persistence of comorbidities, which may affect the final prognosis and recovery. The application of correct diagnostic and therapeutic procedures is an indispensable factor in the guidelines of treatment and achieving the expected recovery, taking into account all preexisting factors. Aim: to assess the types of diagnostic and surgical procedures to the specific type of compressive neuropathy, to gender and age distribution, and overexciting comorbidities Material and methods: we evaluated 77 cases of three types of compressive neuropathies of the upper extremity, treated at Clinic of Reconstructive and Plastic Surgery of the Clinical Center University of Sarajevo in the period from 2017 to 2021, with the evaluation of gender and age distribution, preexisting comorbidities, diagnostic and surgical procedures. Results: statistically significant difference was found in gender distribution, in terms of higher female representation, 52 (67.5%), $\chi 2 = 14{,}558$; $p = 0.001$. The mean age of the examined group of patients was 50.2 ± 14.6 years. No statistically significant difference was confirmed in the correlation of age and specific type of compressive neuropathy ($p < 0.05$). The evaluation of existing comorbidities confirmed in most cases the association of hypertension (27 cases; 39.7%) and diabetes (10 cases, 14.7%) with Carpal tunnel syndrome, but without statistical significance. In the overall assessment of the existence of preexisting comorbidities with other types of compressive neuropathies, no statistical significance was confirmed ($p < 0.05$). There was no statistically significant correlation between the type of preoperative diagnostic procedure ($\chi^2 = 1.466$; $p = 0.963$; $p = 0.556$) with the specific type of compressive neuropathy. The statistically significant correlation ($p > 0.05$) was confirmed between the type of surgical procedure to the specific type of compressive neuropathy ($\chi^2 = 0.591$; $p = 0.0001$; $p = 0.0001$). Conclusion: compressive neuropathies of the upper extremity, with the adequate clinical diagnosis of the specific functional failure, resulted in satisfactory postoperative recovery due to defined surgical protocol of treatment, with saitsfactory postoperative results, improving the functionality and overall quality of life

Keywords: compression neuropathy, comorbidities, decompression, neurolysis, anterior transposition

SAŽETAK

Uvod: kompresivne neuropatije gornjeg ekstremiteta su najčešće povezane sa funkcionalnim poteškoćama i smanjenjem radne sposobnosti, koja može biti značajna u slučajavima nepravovremenog prepoznavanja i tretmana. Značaj ovih kliničkih entiteta se ogleda i u činjenici da postoji mogućnost istovremene perzistencije komorbiditeta, što može utjecati na konačnu prognozu i oporavak. Primjena odgovarajućih dijagnostičkih i terapeutskih procedura je neizostavan činilac u smjernicama tretmana i postizanja očekujućeg postoperativne funkcionalnosti, uzevši u obzir sve preegzitirajuće faktore. Cilj: procjeniti vrste dijagnostičkih i hirurških procedura prema specifičnom tipu kompresivne neuropatije, u odnosu na dobnu i polnu distribuciju, i preegzitirajuće komorbiditete. Materijali i metode: procijenili smo 77 slučaja tri tipa kompresivnih neuropatija gornjeg ekstremiteta, tretiranih na Klinici za rekonstruktivnu i plastičnu hirurgiju Kliničkog centra Univerziteta u Sarajevu, u periodu od 2017 do 2021, sa evaluacijom polne i dobne distribucije, preegzitirajućih komorbiditeta, i primjenjenih dijagnostičkih i hirurških procedura. Rezultati: utvrđena statistički značajna razlika u polnoj distribuciji, u smislu veće zastupljenosti ženskog pola, 52 (67.5%), sa statistički značajnom razlikom, $\chi 2 = 14{,}558$; $p = 0{,}001$. Prosječna životna dob ispitivane grupe pacijenata je iznosila 50.2 ± 14.6 years. Nije potvrđena statistički značajna razlika u smislu korelacije životne dobi i specifičnog tipa kompresivne neuropatije ($p < 0.05$). Evaluacijom postojećih komorbiditeta utvrđena je u najvećem broju slučajeva asociranost hipertenzije (27 slučajeva; 39,7%) i diabetesa (10

slučajeva, 14,7%) sa Sindromom karpalnog tunela, ali bez postojanja statističke signifikantnosti (χ^2=1,705 p=0,988; p=0,254). U sveukupnoj procjeni preegzitirajućih komorbiditeta sa drugim tipovima kompresivnih neuropatija nije potvrđena statistička signifikantnost (p<0.05). Nije evidentirano postojanje statistički značajne korelacije između vrste preoperativne dijagnostičke procedure (χ^2=1,446; p=0,963; p=0,556) sa specifičnim tipom kompresivne neuropatije. Statistički signifikatna korelacija (p>0,05) je potvrđena između tipa hirurške procedure u odnosu na specifični tip kompresivne neuropatije (χ^2=0,591; p=0,0001; p=0,0001). Zaključak: kompresivne neuropatije gornjeg ekstremiteta, uz odgovarajuću kliničku dijagnostiku sa evaluacijom specifičnog tipa funkcionalnog ispada, rezultiraju zadovoljavajućim postoperativnim oporavkom zbog primjene definiranog hirurškog protokola tretmana sa očekujućim rezultatima u smislu poboljšanja funkcionalnosti i sveukupnog kvaliteta života

Ključne riječi: kompresivna neuropatija, komorbiditeti, dekompresija, neuroliza, anteriorna transpozicija

INTRODUCTION

Compressive upper extremity neuropathies are a relatively common clinical entity in everyday practice, associated with functional difficulties that significantly incapacitate the patient and affect the overall quality of life (1). Timely recognition of clinical signs typical of a particular type of compression neuropathy is essential for the overall assessment and determination of treatment (2). The potential association of compression neuropathies with certain occupations is important for the overall assessment, although there is no clear correlation with the occurrence of compression neuropathy with specific occupation, still long-term recurrences of repetitive movements over time represents the possible etiologic factor of the chronic peripheral nerve irritation (3), therefore, compressive neuropathies, which can be acute and chronic, are the most common traumatic etiology (4). When evaluating the problem of compression neuropathies, the existence of comorbidities with worsening of the clinical picture must be taken into account, as in the case of diabetes, which in severe forms results in diabetic neuropathy with the complication of the clinical picture (5), especially due to frequent association of depressive neuropathies with diabetes (6). The potential association of upper compression neuropathies with comorbidities and certain occupations is very important due to the potentially compromised results of surgical treatment (7), especially in the cases of combined cervical lesions (8). Clinical examination with the adequate diagnosis are factors in deciding on the time and method of treatment, as well as the exclusion of surgical therapy probable recurrence (9). The goal of surgical treatment of these lesions is based on nerve decompression, neurolysis, and change of peripheral nerve localization to eliminate chronic pressure and the resulting muscular hypotrophy (10).

AIM

The aim of the study was to assess the type of preoperative diagnostic procedures and surgical treatment of upper extremity compressive neuropathies according to sex and age distribution and the potential presence of comorbidities

MATERIALS AND METHODS

We assessed 77 patients with different levels of compressive neuropathies of the upper extremity treated at the Clinic of Reconstructive and Plastic Surgery, Clinical Center of the University of Sarajevo, in the period from 2017 to 2021, with the evaluation of the type of compressive neuropathies, indicated diagnostic and surgical procedures to gender and age distribution, and preexisting comorbidities.

Statistical data processing was done through IBM SPSS Version 20.0 for Windows. Analysis of categorical variables was performed using Pearson's χ^2-test or Fisher's exact probability test. Spearman rank correlation coefficients were used to examine the linear correlation. Statistical significance was set at the conventional level (α = 0.05). The results were shown in the graph and contingency tables (numbers with three decimal places). The level of significance is p<0.0.

Study inclusion criteria: patients of all ages and genders with compressive neuropathies of the upper extremities, patients treated by decompression, neurolysis combined with decompression, and anterior nerve transposition depending on the specific type of compressive neuropathy and preferred surgical procedure

Study exclusion criteria: conservatively treated compressive neuropathy of the upper extremity, patients primarily treated in other hospital facilities, cases without the possibility of adequate pre and postoperative evaluation.

RESULTS

The research included 77 patients who met the criteria for inclusion in the study. Out of the total number of estimated cases in this research, 52 (67.5%) were female and 25 (32.5%) were male. We confirmed statistically significant difference in the frequency of gender representation, female subjects dominated, $\chi 2$ = 14,558; p = 0.001. The average age of the estimated group was 50.2 ± 14.6 years. (Table 1). Analysis of gender representation to the type of compressive neuropathy showed a statistically significant difference (p <0.05) in terms of higher female representation in patients with carpal tunnel syndrome and Guyon's canal syndrome, and relation to male predominance in cases of Cubital canal syndrome

Table 1 **Gender distribution of the estimated group with compression neuropathies.**

			Type of Compression Neuropathy			Total
			Carpal Tunnel Syndrome	Guyon`s Canal Syndrome	Cubital Tunnel Syndrome	
Gender	Female	N	49	3	0	52
		%	72.1	100.0	0.0	67.5
	Male	N	19	0	6	25
		%	27.9	0.0	100.0	32.5
Total		N	68	3	6	77
		%	88.3	3.9	7.8	100.0

χ^2=14.558; df=2; p=0.001
r=0.354; p=0.002

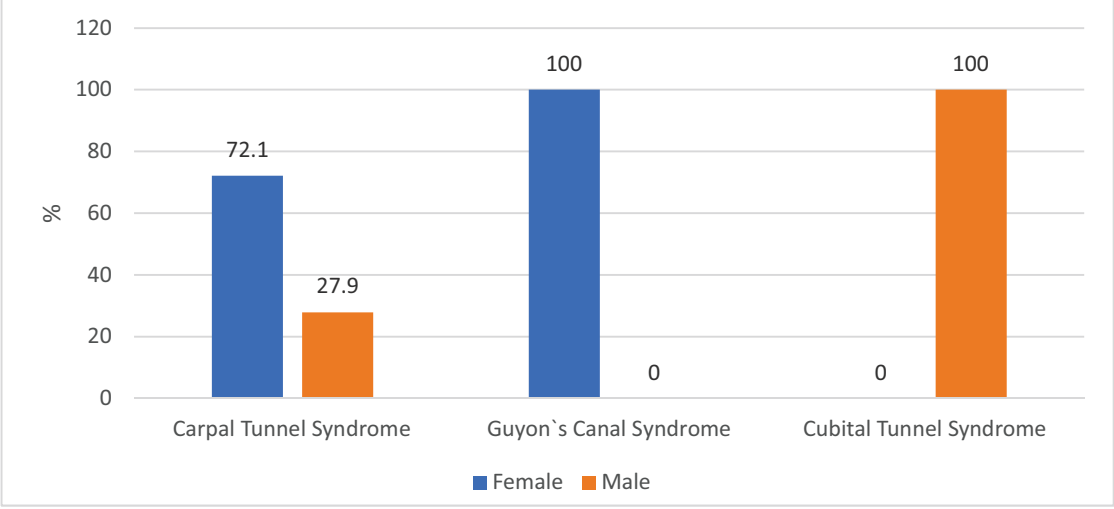


Figure 1 **Percentage presentation of gender distribution.**

Correlation between the age and the type of compressive neuropathy (Table 2, Figure 2) in the total sample (regardless of gender), showed no statistically significant difference (p> 0.05). Certain differences existed in the higher prevalence of Carpal tunnel syndrome over 65 years (38.2%), and only this type of compressive neuropathy was present in the age group from 16-30 years. Patients aged 31-45 years, 46-60 years, and over 65 years were equally represented in the assessed group with Guyon's Canal Syndrome (33.3%), while the age groups 31-45 years and 46-60 years were present in Cubital tunnel syndrome (50.0%), other age groups were not present in this type of compressive neuropathy.

Table 2 **Representation of age structure in the total sample of patients with compression neuropathies.**

				Type of Compression Neuropathy			Total
				Carpal Tunnel Syndrome	Guyon`s Canal Syndrome	Cubital Tunnel Syndrome	
	Age	from 16-30 years	N	3	0	0	3
			%	4.4	0.0	0.0	3.9
		from 31-45 years	N	17	1	3	21
			%	25.0	33.3	50.0	27.3
		from 46-60 years	N	22	1	3	26
			%	32.4	33.3	50.0	33.8
		>61 years	N	26	1	0	27
			%	38.2	33.3	0.0	35.1
	Total		N	68	3	6	77
			%	88.3	3.9	7.8	100.0

χ^2=4.513; df=6; p=0.608
r=-0.158; p=0.162

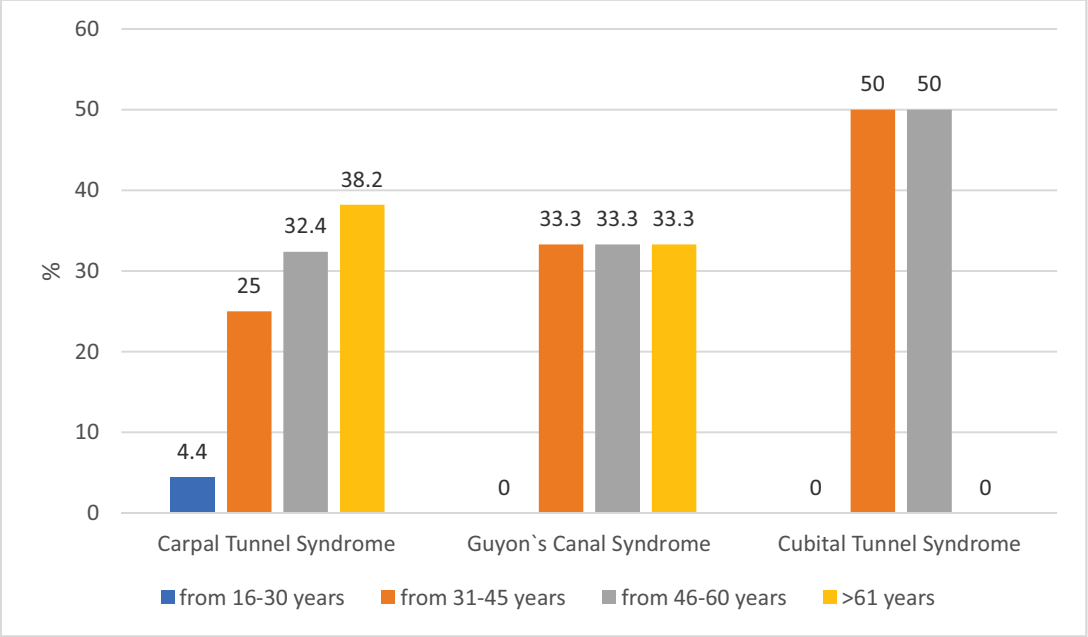
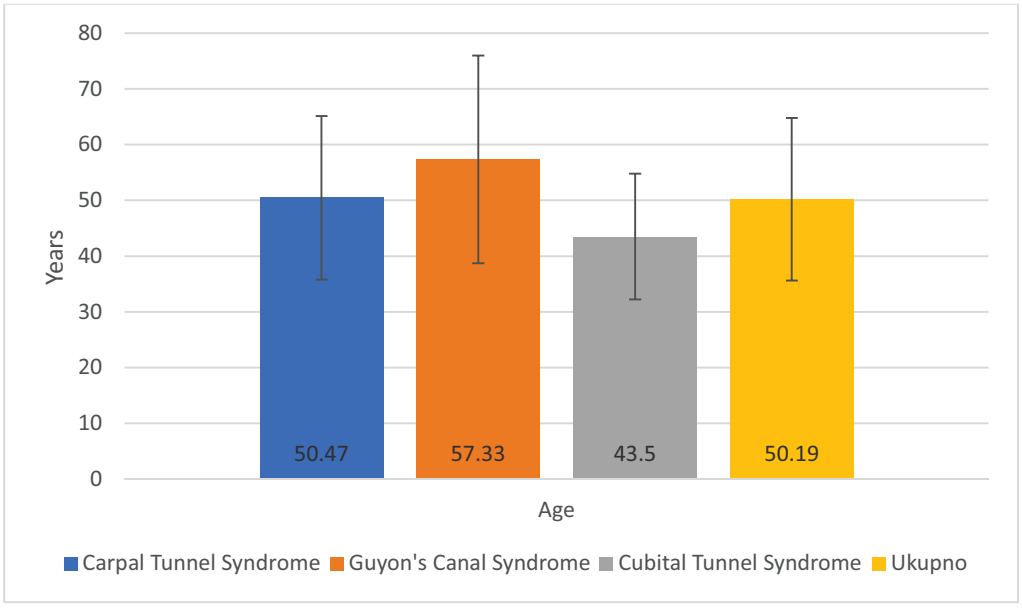


Figure 2 **Percentage presentation of age distribution.**

The average age of our estimated group to the specific type of assessed compression neuropathy (Figure 3) showed variability, but without significant deviations (p>0.05). The oldest age group was in the cases with Guyon`s canal syndrome, with an average age of 57.3± 18.6 years (range 40-77 years). The youngest one was in the cases with Carpal tunnel syndrome, with an average age of 43.5 ± 11.3 years (range 28-55 years) but without statistically significant differences or correlations (p>0.05).



F=1.006; p=0.371
r=-0.095; p=0.414

Figure 3 **The average age of examined group with different types of compression neuropathies.**

The association of compression neuropathies with comorbidities (Table 3, Figure 4) evaluated the most common association of Carpal tunnel syndrome with hypertension (27 cases, 39.7%) and diabetes (10 cases, 14.7%). This type of compression neuropathy wasassociated with other types of comorbidities in 11 cases (16.2%). Hypertension and diabetes in other types of compressive neuropathies were present in lower percentages, 3 cases (100%) in Guyon`s canal syndrome and 1 case with 1 case of diabetes mellitus (33%). Low prevalence of these types of comorbidities was also present in Cubital tunnel syndrome, 2 cases (33.3%) and 1 case (16.7%), respectively. No statistically significant difference or correlation was evaluated ($p<0.05$), although it was evident that all patients with Guyon`s canal syndromes have hypertension as comorbidity

Table 3 **Correlation of compression neuropathies with the most common comorbidities.**

		Type of Compression Neuropathy			Total
		Carpal Tunnel Syndrome	Guyon`s Canal Syndrome	Cubital Tunnel Syndrome	
Arterial hypertension	N	27	3	2	32
	%	39.7	100.0	33.3	41.6
Diabetes	N	10	1	1	12
	%	14.7	33.3	16.7	15.6
Rheumatoid arthritis	N	1	0	0	1
	%	1.5	0.0	0.0	1.3
Hypo/Hyperthyroidism	N	3	0	0	3
	%	4.4	0.0	0.0	3.9
Other associated diseases	N	11	1	2	14
	%	16.2	33.3	33.3	18.2

χ^2=1,705; df=8; p=0,988
r=0,164; p=0,254

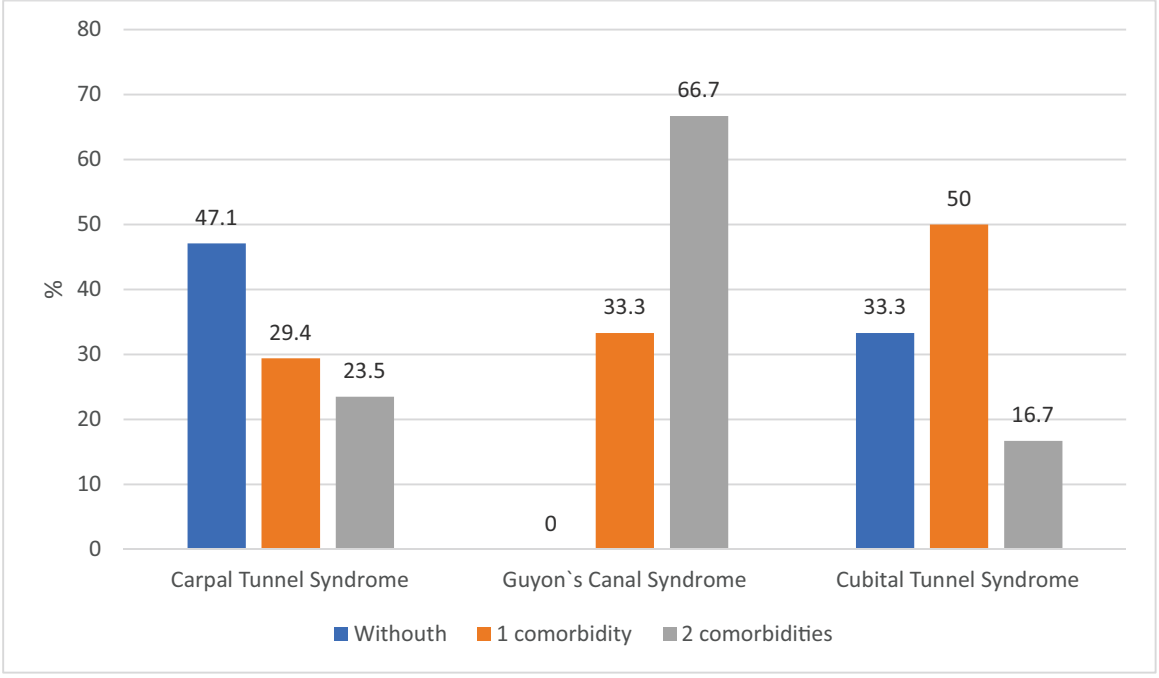


Figure 4 **Percentage distribution of comorbidities.**

The most commonly used diagnostic modalities (Table 4, Figure 5) in the preoperative evaluation of compression neuropathies was an ultrasound, 50 cases (73.5%) in carpal tunnel syndrome, 5 cases (83.3%) in Cubital tunnel syndrome, and 3 cases (100%) in preoperative evaluations of cases with Guyon Canal Syndrome. The second most commonly used diagnostic modality in preoperative evaluation is EMG in Carpal tunnel syndrome, 15 cases (22.1%). Other available diagnostic modalities used in a far lower percentage, MRI evaluation in Carpal tunnel syndrome in 2 cases (2.9%), and X-ray in 1 case (1.5%) in the same type of compressive neuropathy. Statistical analysis had confirmed that there was no significant differences between diagnostic modalities as part of preoperative preparation to the type of compression neuropathy ($p>0.05$).

Table 4 **Diagnostic procedures in a specific type of compression neuropathy.**

			Type of Compression Neuropathy			Total
			Carpal Tunnel Syndrome	Guyon`s Canal Syndrome	Cubital Tunnel Syndrome	
Diagnostic modalities	EMG	N	15	0	1	16
		%	22.1	0.0	16.7	20.8
	MRI	N	2	0	0	2
		%	2.9	0.0	0.0	2.6
	Ultrasound	N	50	3	5	58
		%	73.5	100.0	83.3	75.3
	X-ray	N	1	0	0	1
		%	1.5	0.0	0.0	1,3
Total		N	68	3	6	77
		%	88,3	3.9	7.8	100.0

χ^2=1.446; df=6; p=0.963
r=0.068; p=0.556

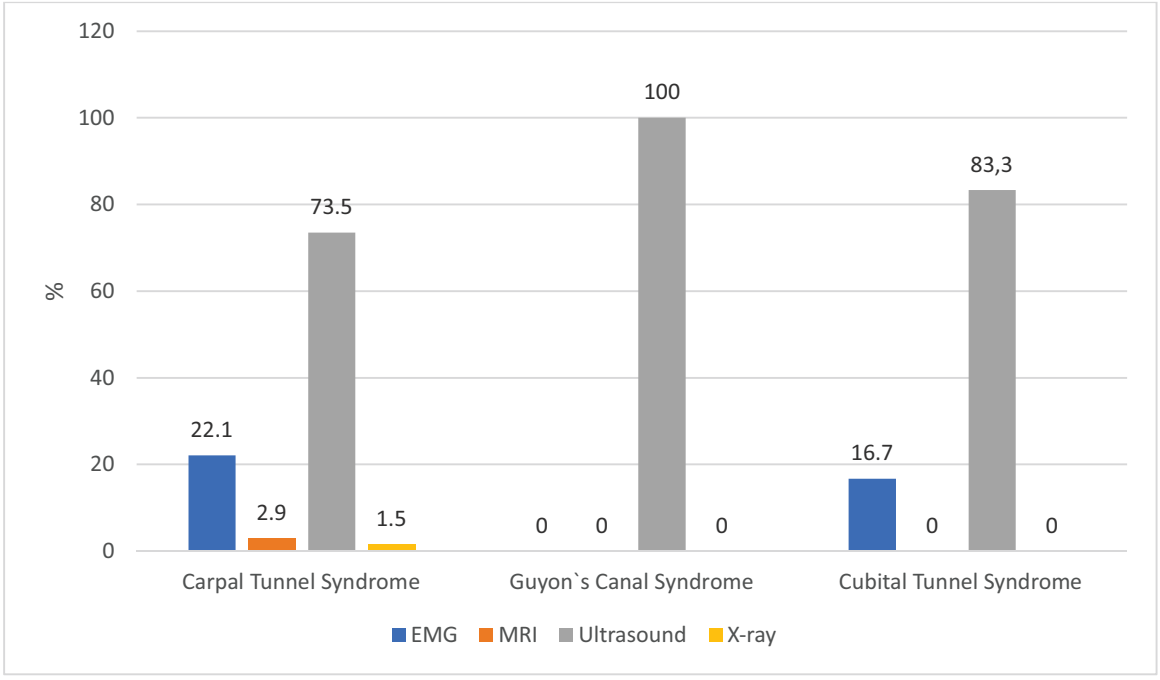


Figure 5 **Percentage presentation of diagnostic procedures in preoperative evaluation of compression neuropathies.**

Different surgical treatment modalities were correlated with the level of assessed compressive neuropathy (Table 5, Figure 6). Decompression was the most commonly used in Carpal tunnel syndrome treatment (69.1%), neurolysis with decompression was the preferred method of Guyon's canal syndrome (66.7%), while ulnar nerve anteroposition was the method of choice for the treatment of Cubital tunnel syndrome (83.3%), which was not indicated in the other two types of compression neuropathies. Evaluation of surgical treatment procedures confirmed a statistically significant correlation (p>0.05).

Table 5 **Correlation of the specific surgical procedure to the type of compressive neuropathy.**

			Type of Compression Neuropathy			Total
			Carpal Tunnel Syndrome	Guyon`s Canal Syndrome	Cubital Tunnel Syndrome	
Treatment modalities	Decompression	N	47	1	1	49
		%	69.1	33.3	16.7	63.6
	Neurolysis and decompression	N	21	2	0	23
		%	30.9	66.7	0.0	29.9
	Anterior transposition	N	0	0	5	5
		%	0.0	0.0	83.3	6.5
Total		N	68	3	6	77
		%	88.3	3.9	7.8	100.0

χ^2=65.176; df=4; p=0.0001
r=0.591; p=0.0001

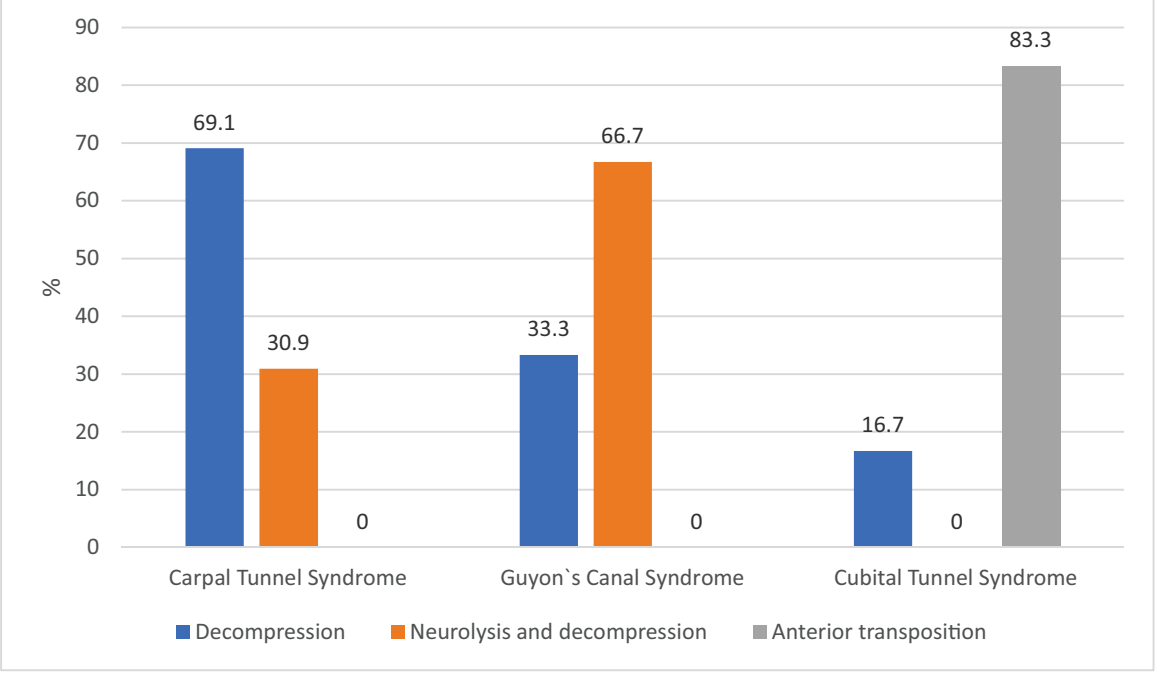


Figure 6 **Correlation of the specific surgical procedure to the type of compressive neuropathy presented in percentages.**

DISCUSSION

Compressive neuropathies, as a specific clinical entities, have to be assessed in terms of potential sequelae in cases of inadequate recognition of clinical signs as a key factor for he proper surgical treatment (6), which has to be correlated with the algorithms of diagnostics, and the most optimal surgical treatment (12). Electromyography (EMG) was proven in clinical practice as a useful diagnostic tool for all compressive neuropathies, condition of the peripheral nerves can be evaluated successfully by an experienced radiologist (13). MRI was the method of choice in the evaluation of compression neuropathies, which is superior to other available diagnostic procedures, and very useful when the condition of peripheral nerves cannot be assessed preoperatively using EMG or ultrasound. (14). X-ray evaluation is not part of the standard diagnostic algorithm for the compressive neuropathies, but in the case of combined bone lesions it could be very important for the assessment of the associated nerve and bone injuries, or bone and joint diseases, which potentially affect the expected recovery (15, 16). Considering the significant association of upper extremity compression neuropathies with comorbidities, which was present in our evaluated group, the approach to the patient should be serious in terms of preventing additional postoperative complications, which may or may not be directly related to surgery (17). In the more serious clinical cases, surgical treatment was preferred (18) as the first modality and the golden rule for most cases, which relieves the patient of functional difficulties during the early postoperative period, with resulting improvement life quality, instead of conservative treatment with very variable results and uncertain long-term benefits (19). Nerve decompression was indicated in most cases, as an effective solution due to the very nature of the

pathophysiological process on peripheral nerves (20). Decompression was often combined with external and internal neurolysis as an indispensable combining procedure, due to the proliferation of connective tissue as a pathological substrate of long-term peripheral nerve compression, with resulting worsening of the clinical picture (21). Anterior ulnar nerve transposition was the typical surgical procedure for Cubital tunnel syndrome, often combined with neurolysis, although anterior transposition itself resulted in relief of clinical symptoms (22).

CONCLUSION

Compressive neuropathies require serious clinical evaluation. Detection of the specific type of compression neuropathy with appropriate diagnostics enables the selection of the most optimal treatment with the expected functional improvement. Compressive neuropathies cannot be considered as an isolated clinical entity due to possible associated with comorbidities and worsening of the definitive prognosis. In the case of correct diagnosis and treatment, compressive neuropathies result in functional improvement and permanent pain and paresthesias relief. The selection of surgical techniques in our study was guided by the principle of efficacy in diagnostics and surgical treatment that was specific and preferred for each type of compression neuropathy.

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Is early postoperative PTH value a reliable predictor of hypocalcaemia in patients with total thyreoidectomy

Da li je rana postoperativna vrijednost PTH pouzdan prediktor hipokalcemije kod pacijenata sa totalnom tireoidektomijom

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ABSTRACT

The primary role of Parathyroid hormone (PTH) is to maintain calcium homeostasis via its interaction with calcitonin. PTH measurement is an important aid in the diagnosis of disorders of calcium metabolism. One of the most common complications of thyroid gland surgery is postoperative hypocalcaemia due to the injury of parathyroid glands. Aim: to evaluate prognostic value of measuring value of PTH in the peri-operative period upon performed thyreoidectomy. Materials and methods: total of thirty patients treated with thyreoidectomy were evaluated in the period from October 2019 to November 2020 in the Clinical Center University of Sarajevo. PTH values were measured one hour upon performed operative treatment. Results: PTH value was in correlation with postoperative hypocalcaemia. Conclusion: PTH value can be considered as a reliable predictor of postoperative hypocalcemia in patients treated with thyreoidectomy.

Keywords: thyroid gland, PTH, hypocalcemia, thyroidectomy, parathyroid gland

SAŽETAK

Primarna uloga parat hormona (PTH) je očuvati homeostazu kalcijuma kroz interakciju sa kalcitoninom. Mjerenje vrijednosti PTH je važan alat pri dijagnosticiranju poremećaja u metabolizmu kalcijuma. Jedna od najčešćih komplikacija hirurgije štitne žlijezde je postoperativna hipokalcemija prouzrokovana povredom paratireoidnih žlijezda. Cilj: evaluirati prognostičku vrijednost mjerenja razine serumskog PTH u perioperativnom periodu po učinjenoj tireoidektomiji. Pacijenti i metode: ukupno trideset pacijenata tretiranih tireoidektomijom su evaluirani u periodu od oktobra 2019. do novembra 2020. godine na Kliničkom Centru Univerziteta u Sarajevu. Vrijednosti PTH su mjerene u prvom satu po provedenom operativnom zahvatu. Rezultati: vrijednost PTH je u korelaciji sa postoperativnom hipokalcemijom. Zaključak: vrijednost PTH se može smatrati pouzdanim prediktorom postoperativne hipokalcemije kod tireoidektomiranih pacijenata.

Ključne riječi: štitna žlijezda, PTH, hipokalcemija, tireoidektomija, paratireoidna žlijezda

INTRODUCTION

The primary role of Parathyroid hormone (PTH) is to maintain calcium homeostasis via its interaction with calcitonin. PTH measurement is an important aid in the diagnosis of disorders of calcium metabolism. One of the most common complications of thyroid gland surgery is postoperative hypocalcemia due to the injury of parathyroid glands. Depending on the type of damage and the number of glands involved, hypocalcemia may be transient or permanent (1). Transient hypocalcemia frequently complicates post-operative care of patients who have undergone thyroid surgery (2). It is the most common complication following total thyroidectomy, and occurs in 10% to 50% of cases (3). Establishing a simple, yet reliable method to predict hypocalcemia could be a very useful tool in preventing hypocalcemia as well as reducing the length of postoperative stay thus bringing down overall treatment costs. Another issue that needs to be addressed is whether or not Calcium and Vitamin D supplementation should be commenced immediately upon surgical procedure or should we base our decision on early postoperative PTH value?

AIM

The aim of the study was to evaluate prognostic value of PTH in the peri-operative period upon performed thyroidectomy in order to successfully determine its ability to predict postoperative hypocalcemia.

MATERIALS AND METHODS

The study was conducted prospectively at the Clinical Center University of Sarajevo in the period from October 2019 to November 2020). The study included 30 patients subjected to total thyreoidectomy. The normal values for serum calcium were 2.1-2.55 mmol/L, while for PTH physiological values ranged from 14 to 86 pg/mL. VITROS 5600 system was the immunometric immunoassay technique used to determine the value of PTH and it was used in all the patients who were included in this study. Serum calcium levels were determined by colorimetric assay.

Serum calcium and PTH levels were measured as follows: serum calcium and PTH were measured before surgical procedure, PTH value was measured one hour upon surgical treatment (PTH1 value), serum calcium levels were measured 24 hours after surgery (Ca1value) and 48 hours after surgery (Ca2 value). All surgical procedures were performed by the same surgical team consisted of five surgeons experienced in the field of endocrine surgery. All procedures involving human participants were in accordance with the 1964 Helsinki declaration and its subsequent amendments. Statistical analysis was made in the IBM SPSS Statistics v. 21.0 for Windows with the most important results being represented in the form of tables.

RESULTS

The study included 30 patients aged from 24 to 74. The average age was 52.83±13.51 Patient population was predominantly female with female accounting for 28 patients, and there were 2 male patients.

Table 1 **Characteristics of patients.**

Category	Patients (N)	Patients (%)
Male	2	6.7
Female	28	93.3
Age (Mean± SD)	52.83±13.51)	

Depending on the type of pathological diagnosis all patients were divided into three groups, multinodular goiter, malignant disease and Graves' disease. Out of the total number of treated patients 17 suffered from Multinodular goiter (MNG), 11 patients were diagnosed with thyroid cancer and 2 were treated for toxic goiter. The toxic goiter group consisted of only two cases which could not be used as statistically significant, thus our related to the two remaining groups.

Table 2 **Pathological characteristics.**

Category	Patients (N)	Patients (%)
Multinodular goiter (MNG)	17	56.7
Thyroid cancer (TC)	11	36.7
Toxic goiter (TG)	2	6.7

The study examined average age in the aforementioned groups. In the MNG group we had 17 patients ranging from 24 to 70 years of age. The average age was 51.94±13.78. In the TC group, which consisted of 11 patients, age ranged from 26 to 75, and the average age was 58.45±13.72.

Table 3 **Average age by pathological subtypes.**

Category	Age (Mean±SD)
Multinodular goiter (MNG)	51.94±13.78
Thyroid cancer (TC)	58.45±13.72

In the thyroid cancer (TC) group we analyzed subtypes of thyroid cancer which were determined on pathological review. The results were as follows: papillary cancer was present in 6 cases (54.5%), whereas follicular cancer was noted in 3 cases (27.3%), with Insular (poorly differentiated) and oncocyte types represented in one case, respectively (9.1%).

Table 4 **Thyroid cancer subtypes.**

Category	Patients (N)	Patients (%)
Papillary cancer	6	54.5
Follicular cancer	3	27.3
Insular cancer	1	9.1
Oncocyte cancer	1	9.1

Analyses of the serum calcium and PTH levels revealed that serum calcium and PTH preoperative values were within the normal range with no statistical difference.

With regard to laboratory findings performed upon thyroidectomy, a total of eight (26.7%) patients with PTH value below the normal range were determined one hour after the surgery. As for serum calcium levels Ca1 value (24 hours after surgery) total of nine (30%) patients were below the normal range. All (100%) of those patients were female.

Table 5 **Patients with reduced PTH1 and Ca1 values.**

Category	Patients (N)	Patients (%)
Reduced PTH1	8	26.7
Reduced Ca1	9	30

In the PTH1 group, we observed a total of eight patients with low values of PTH, and within this group, five patients (62.5%) had low levels of Ca1, two patients (25%) had low level of serum Calcium in Ca2 and one (12,5%) patient remained with normal levels of serum calcium even after 48 hours upon surgery. Our data revealed that PPV value of Ca1 was 62.5%, whereas Ca2 PPV was 89%.

Table 6 **Patients with reduced PTH value.**

Category	Ca1 value	Ca2 value
Patients (N)	5	2
Patients (%)	62.5	25

The average age was 48.87±15.97. Regarding pathological diagnosis, seven patients (87.5%) suffered from Multinodular goiter, whereas one patient (12.5%) was diagnosed with papillary carcinoma.

DISCUSSION

Thyroid gland surgery represents one of the most commonly performed surgical procedures worldwide. The two most common early complications of thyroid surgery are hypocalcemia (20–30%) and recurrent laryngeal nerve injury (5-11%) (4). Our study referred

to the postoperative hypocalcemia, and we determined a total of nine patients out of thirty who suffered from hypocalcemia, and required supplementation therapy, which was in accordance with the aforementioned literature.

The study was designed in a manner that serum Calcium levels were measured twenty four and forty eight hours upon surgery, while PTH value was measured one hour upon surgery. We determined that out of eight patients diagnosed with low PTH levels, five developed low serum calcium levels on the first (Ca1) measuring, with another two patients developing hypocalcemia on the second (Ca2) measuring. One patient remained with normal Ca levels although her PTH level was low. We believe that the study's design and the fact that we measured Ca serum levels in early postoperative period were the reason why not all the patients with low PTH levels did not develop hypocalcemia. However, there was no consensus on the most appropriate timing or threshold value for PTH measurement that would optimally guide the management of postoperative hypocalcemia, as there was also not universal consensus as to the routine or selective use of calcium and/or calcitriol supplementation (5,6).

The importance of experienced surgeons in the field of thyroid gland surgery is emphasized in numerous studies, highlighting the fact that the incidence of postoperative complications is decreasing when is performed by an experienced surgeon (7).

In cases with low PTH, therefore, introducing supplementation with Ca and vitamin D seems as a reasonable option, since nearly all patients with low levels of postoperative PTH did end up developing hypocalcemia. Administrating calcium and vitamin D supplementation upon thyroidectomy were proven as a successful tool to prevent postoperative hypocalcemia (8). In our experience, administration of calcium and vitamin D supplementation in case of low early postoperative PTH value was a trustworthy procedure, thus preventing onset of hypocalcemia, which is in accordance with current literature.

Regarding age and gender distribution of our patients, female population was overwhelmingly predominant with 93.3% of patients, average age was 52.83 years, most common thyroid gland diseases operatively treated were multinodular goiter (56.7%) and thyroid cancer (36.7%). Distribution of thyroid cancer was in favor of papillary cancer with over fifty percent of all cases (54.5%), followed by follicular cancer (27.3%). We find this accordingly to available sources (9,10).

CONCLUSION

Early postoperative PTH value can be considered as a reliable predictor of postoperative hypocalcemia in patients treated with thyroidectomy and in patients with low PTH value supplementation therapy can reduce complication rate as well as hospital stay.

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Non-interventional pilot study to monitor the efficacy and safety of lysozyme-based therapy in the treatment of acute sore throat in COVID-19 patients

Neinterventna pilot studija praćenja efikasnosti i sigurnosti terapije preparatima na bazi lizozima u liječenju akutne upale grla kod bolesnika s COVID-19 infekcijom

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ABSTRACT

Introduction: Ear, Nose and Throat (ENT) manifestations are frequent symptoms of COVID-19. Usual empirical doctor's practice in the treatment of sore throat in COVID-19 mild patients in Bosnia and Herzegovina refers to the use of oral antiseptics where lysozyme-based lozenges and sprays are often prescribed. Unlike other antiseptics, lysozyme has anti-inflammatory and immunomodulatory activities. As an integral component of the immune system, it is one of the most crucial elements of the local non-specific mucosal resistance to microbes. Aim: to evaluate the efficacy and safety of lysozyme-based products in the treatment of sore throat in mild forms of COVID-19 infection. Materials and methods: a post-marketing non-interventional pilot study was conducted at the University Clinical Center of Republic of Srpska, Banja Luka, Bosnia and Herzegovina. The eligible patients were SARS-CoV-2 PCR positive, both genders, aged over 18, with symptoms of acute tonsillopharyngitis. For the first 5 days, patients received lysozyme-based spray and for the next 5 days, lysozyme-based lozenges. Participants were examined by infectologists on days 0 (baseline), 1, 3, 5, 7, and 10. The assessment included evaluation of the clinical condition with a focus on the sore throat of the patient, temperature measurement, and safety evaluation. Results: 50 patients were enrolled in the study. Symptoms of the sore throat improved in all patients one day after the start of the treatment. The axillary temperature value significantly decreased after the third day of enrolment ($p<0.001$) and continued to decrease. The mean temperature value for all patients was below 37°C on the fifth day after the enrolment and was significantly lower compared to the third day of enrolment ($p<0.001$). The majority of patients had the improvement of the clinical condition related to sore throat within three days after the enrolment compared to the baseline visit ($p=0.001$). No adverse events were reported during the study. Conclusion: Lysozyme-based products showed positive effects in the treatment of sore throat in COVID-19 patients. At the same time, they showed excellent tolerability with no adverse events reported during the study. Further studies evaluating the effects of lysozyme-based products in COVID-19 patients are urgently warranted.

Keywords: lysozyme, COVID-19, sore throat

SAŽETAK

Uvod: simptomatologija od strane uha, nosa i grla česta je kod COVID-19. Uobičajena empirijska praksa ljekara u liječenju grlobolje kod pacijenata sa blagom bolešću COVID-19 u Bosni i Hercegovini odnosi se na primjenu oralnih antiseptika pri čemu se često propisuju pastile i sprejevi na bazi lizozima. Za razliku od drugih antiseptika, lizozim ima protuupalno i imunomodulatorno djelovanje. Kao sastavni dio imunološkog sistema, jedan je od najvažnijih elemenata lokalne nespecifične rezistencije sluznice na mikrobe. Cilj: procijeniti efikasnost i sigurnost proizvoda na bazi lizozima u liječenju grlobolje u blagim oblicima infekcije COVID-19. Materijali i metode: postmarketinško neinterventno pilot istraživanje provedeno je u Univerzitetskom kliničkom centru Republike Srpske, Banja Luka, Bosna i Hercegovina. Kriteriji za uključivanje su bili SARS-CoV-2 PCR pozitivan nalaz, oba spola, stariji od 18 godina, sa simptomima akutnog tonzilofaringitisa. Prvih 5 dana ispitanici su primali sprej na bazi lizozima, a sljedećih 5 dana pastile na bazi lizozima. Ispitanike su pregledali infektolozi 0. dana (početno), 1., 3., 5., 7. i 10. dana bolesti. Pregled je uključivao procjenu kliničkog stanja s naglaskom na grlobolju ispitanika, mjerenje temperature i procjenu sigurnosti korištenih lijekova. Rezultati: u ispitivanje je uključeno 50 ispitanika.

Simptomi grlobolje su se poboljšali kod svih ispitanika jedan dan nakon početka liječenja. Vrijednost aksilarne temperature značajno se smanjila nakon trećeg dana terapije ($p<0,001$) i nastavila opadati. Srednja vrijednost temperature za sve bolesnike bila je ispod 37°C peti dan nakon početka terapije i bila je značajno niža u odnosu na treći dan terapije ($p<0,001$). Većina ispitanika je imala poboljšanje kliničkog stanja povezanog s grloboljom unutar tri dana nakon početka terapije u odnosu na početnu posjetu ($p=0,001$). Tokom ispitivanja nisu zabilježene neželjene reakcije. Zaključak: proizvodi na bazi lizozima pokazali su pozitivne efekte u liječenju grlobolje kod pacijenata oboljelih od COVID-19. Istovremeno, pokazali su izvrsnu podnošljivost bez prijavljenih neželjenih reakcija tokom studije. Potrebno je sprovesti dodatne studije koje procjenjuju efekte proizvoda na bazi lizozima u liječenju COVID-19 pacijenata.

Ključne riječi: lizozim, COVID-19, grlobolja

INTRODUCTION

Since its first appearance in Wuhan City in China in December 2019 up to beginning of March 2022, there has been more than 435 million registered cases of SARS-CoV-2 infection worldwide (1). Multiple manifestations of COVID-19 have been described in the literature to date (2). Ear, Nose and Throat (ENT) manifestations are frequent symptoms of COVID-19, especially in mild or moderate form of the disease. The most common ENT dysfunctions observed in patients infected with SARS-CoV-2 are cough, sore throat and dyspnea (3). El-Anwar, et al. reviewed eleven published studies reporting the ENT manifestations in COVID-19 laboratory-confirmed positive patients and found that the sore throat was the most common ENT manifestation of COVID-19 (11.3%) followed by headache (10.7%) (4). In a systematic review of 215 studies published between December 1st, 2019 and January 1st, 2021 comprising 132,647 COVID-19 participants, sore throat was found in 14.1% of patients (5). Sore throat is a common symptom of infection for all SARS-CoV-2 variants known so far (6). In a study evaluating symptoms of the SARS-CoV-2 B.1.1.529 variant (omicron) infected cases, 48% of patients had symptom of sore throat (7).

Following the claim that "in respiratory viral infection those who are already infected will expel less active virus if they are throat medicated" (8), usual empirical doctor's practice in treatment of sore throat in COVID-19 mild patients in Bosnia and Herzegovina refers to use of oral antiseptics in pharmaceutical form of lozenges or sprays. Lysozyme-based lozenges and sprays are often prescribed. Although the sore throat is a symptom of an upper viral respiratory tract infection associated with viral infection, little is known whether lysozyme-based products exert beneficial effect in treatment of sore throat in COVID-19 patients. Natural enzybiotic lysozyme is a molecule of great importance that can help in the fight against the virus. Unlike other antiseptics, lysozyme possess anti-inflammatory and immunomodulatory activities. As an integral component of the immune system, it is one of the most critical elements of the local mucosal resistance to microbes (9). Lysozyme can be found in secretions, body fluids, mucous membranes, liver, and blood cells of the immune system (10). Human milk is very rich in lysozyme, which is a part of the body's defence system from the first days of life (11). Lysozyme, as an integral part of nonspecific innate immunity, is an important component of the anatomical barriers at the first contact line with virus. Intact anatomical barriers are the main defence against the entry of the virus into the body and its further penetration and entry into deeper segments of the respiratory system, i.e. the lungs (12). Lysozyme prevents the spread of inflammation. Sakurai et al have shown that lysozyme inhibits the production of pro-inflammatory cytokines (interleukin-6, interleukin-1β, G-CSF) in epithelial cells infected with respiratory syncytial virus (RSV) (13). Lysozyme helps in maintaining respiratory function. In the respiratory system, lysozyme originates from a variety of sources including submucosal tracheal glands, superficial epithelial cells, and pulmonary alveolar macrophages (14). Protection within the respiratory system from the onset of infection involves a complex interaction between components of innate (where lysozyme belongs) and acquired immunity (15). Pang and co-workers have shown that the influenza A virus significantly reduces the capacity of neutrophils in saliva to secrete lysozyme. A sudden decrease in the capacity of the control neutrophil mechanism with a decrease of lysozyme that controls bacterial colonization after influenza virus infection is considered a potential critical factor in the pathogenesis of clinically pronounced bacterial respiratory infection and consequent development of pneumonia (15). The antibacterial activity of lysozyme has been well investigated and the mechanisms of action have been largely elucidated. There are studies that show the antiviral activity of lysozyme. According to Altamar-Ríos the lack of lysozyme in the body causes increased susceptibility to viral infections (16). There is an activity of lysozyme against the HIV-1 virus. Lee-Huang, et al showed that lysozyme isolated from human milk, neutrophils, and urine, and lysozyme isolated from hen egg whites inhibited the action of the HIV-1 virus in infected cells. These authors assume that the hydrolytic action of lysozyme is responsible for this activity (17). Oderinde, et al. demonstrated the inhibitory effect of lysozyme from hen egg white on the Polio virus and indicated a very significant antiviral effect of this enzyme (18). Lysozyme in higher concentrations, compared to those naturally present in the body, acts against the herpes virus (19). Only in human tears and breast milk, lysozyme is present in a sufficient concentration to exhibit this antiviral action (20). The use of lysozyme-based preparations could enable the achievement of adequate concentrations that have a direct antiviral effect.

AIM

The aim of this study was to monitor the efficacy and safety of lysozyme-based therapy in the treatment of acute sore throat in mild forms of COVID-19 infection.

MATERIALS AND METHODS

A post-marketing non-interventional pilot study to evaluate the efficacy and safety of lysozyme-based therapy in the treatment of acute sore throat in patients with confirmed COVID-19 was conducted at the University Clinical Center of Republic of Srpska, Banja Luka, Bosnia and Herzegovina. The selection and enrolment of the participants were done consecutively. The eligible patients were SARS-CoV-2 PCR positive, both genders aged over 18, with symptoms of acute tonsillopharyngitis, able and willing to sign the inform consent form. The study was conducted according to the criteria set by the declaration of Helsinki of 1975, as revised in 2000,

and each patient signed an informed consent before enrolment in the study.

Participants were examined by infectologists and followed for a period of 10 days. Clinical data were recorded in hard-copy case report forms (CFRs). Patients were examined on day 0 (baseline), days 1, 3, 5, 7, and 10. The assessment included the evaluation of the clinical condition with focus on the sore throat of the patient, the temperature measurement, and safety evaluation. For the first 5 days, patients received lysozyme-based spray (Lysobact Spray® (lysozyme hydrochloride 20 mg/ml + 1.5 mg/ml cetylpyridine chloride), Bosnalijek d.d., Bosnia and Herzegovina) and for the next 5 days, lysozyme-based lozenge (Lysobact® lozenges (lysozyme hydrochloride 20 mg + pyridoxine chloride 10 mg), Bosnalijek d.d., Bosnia and Herzegovina).

Shapiro-Wilk Test was used for normality check. Friedman test followed by Post hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied, resulting in a significance level set at $p<0.003$ was used for comparison of axillary temperature and clinical condition with focus on the sore throat improvement measures between different days from the therapy start.

RESULTS

The study was conducted in the period from April to August 2020 and it included 50 patients. All enrolled subjects completed the study, 24 (48%) women and 26 men (52%). The mean age of the subjects was 41.8 (±11.7) years. The mean number of days from the onset of symptoms to the COVID-19 confirmation was 1.9 (±1.5) (Figure 1).

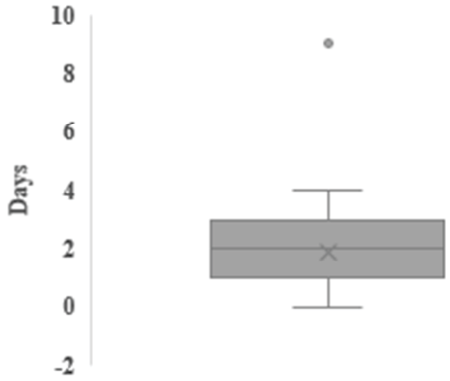

Figure 1 **The period from the onset of symptoms to COVID-19 confirmation.**

During the study, 43 participants (86%) received a concomitant therapy. Of these, 39 subjects received antibiotic therapy (24 subjects received azithromycin, and four subjects received more than one antibiotic).

According to the subjective assessment of investigators, an improvement in sore throat of all enrolled patients was observed already after the first day of therapy.

There was a statistically significant difference in the improvement of clinical condition related to sore throat depending on the duration of the therapy, $\chi 2(2)=74.484$, $p<0.001$. The significant clinical condition improvement was recorded on the third day after the baseline visit ($Z=-3.317$, $p=0.001$) and continued to improve until seventh day when all participants experienced clinical condition improvement (Figure 2).

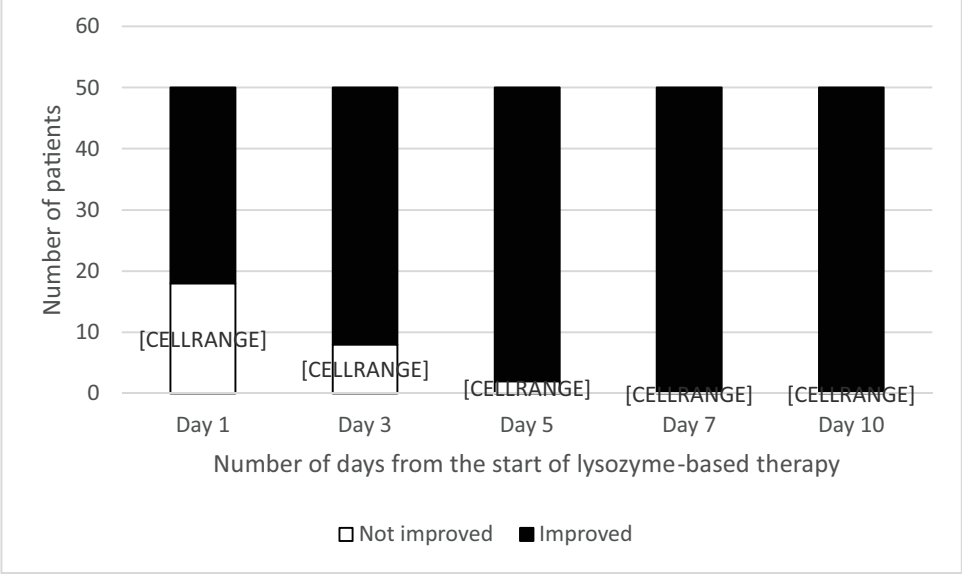

Figure 2 **Improvement of the clinical condition with focus on the sore throat.**

There was a statistically significant difference in the axillary temperature value depending on the duration of the therapy, $\chi 2(2)=176.481$, $p<0.001$. The axillary temperature value significantly decreased on the third day after the therapy was started ($Z=-4.796$, $p<0.001$). The mean value of axillary temperature decreased below 37°C on the fifth day and was significantly lower compared to the third day after the therapy was started ($Z=-4.763$, $p<0.001$) (Figure 3).

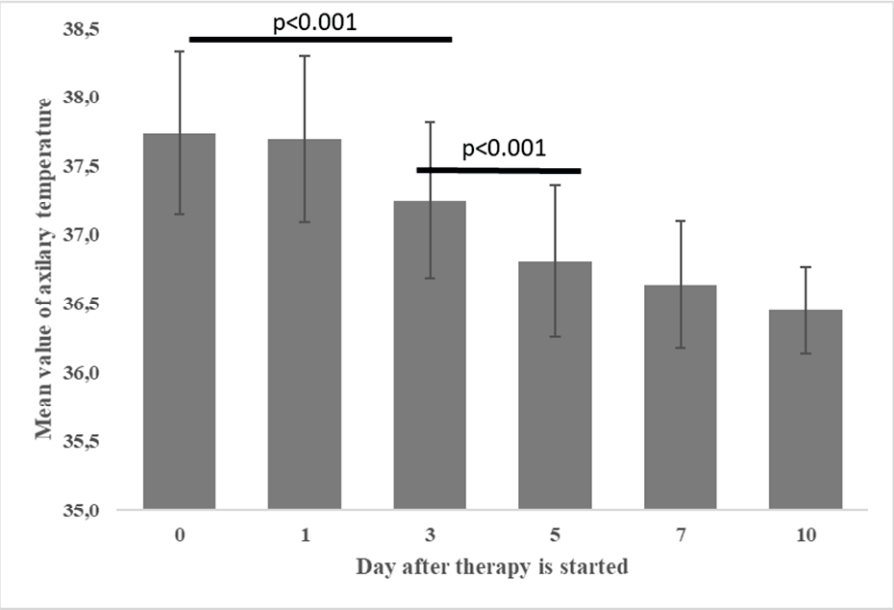

Figure 3 **Mean (± standard deviation) of axillary temperature comparing to the first day of the treatment.**

At the baseline visit, 12% of patients had axillary temperature below 37°C, while on day 5, axillary temperature below 37°C was present in 40% of patients (Figure 4).

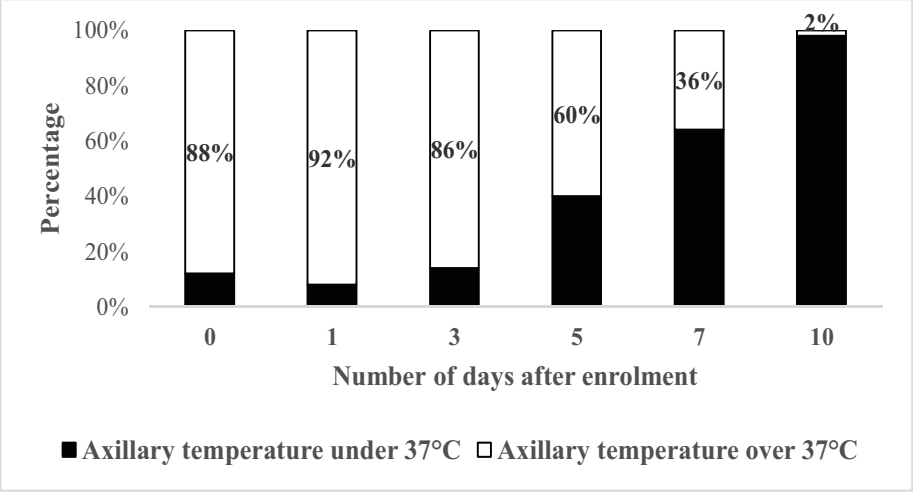

Figure 4 **Axillary temperature overview.**

No adverse events were reported during the study.

DISCUSSION

Lysozyme-based products showed positive effects in the treatment of sore throat in COVID-19 patients. At the same time, they showed excellent tolerability with no adverse events reported during the study.

Sore throat is a symptom accompanying infections with different SARS-CoV-2 variants (6). COVID-19 symptoms are overlapping with other respiratory diseases but it is recommended to further test patients for SARS-CoV-2 infection if sore throat, fever, and olfactory disturbances are present, but not accompanied by nasal and pharynx clinical findings (21). Sore throat usually starts within three days from the positive SARS-CoV-2 test, but can also start in the later periods (between four and six days, or even after seven days) (22). Generally, sore throat can be one of the symptoms at the beginning of COVID-19 and is often present during the course of the disease (23). Persistent sore throat is one of the symptoms of "long COVID" (24). Prathipati, et al. found that the duration of sore throat in the majority of COVID-19 patients was four to seven days (25), Savtal, et al. stated that duration of sore throat was six days (26) while in our study already one day after the lysozyme-based treatment initiation, symptoms of the sore throat improved in all patients. Also, the majority of patients treated with lysozyme-based products had an improvement of the clinical condition related to sore throat within three days after the therapy was started (p=0.001). Improvement of

the clinical condition related to the sore throat was seen in 84% of patients after three days and 96% of patients after five days of therapy indicating a fast recovery in almost all tested participants.

Fever is also one of the most common COVID-19 symptoms. Similar to sore throat, it can be present from the beginning and during the course of the disease (23). The axillary temperature value in our study significantly decreased on the third day after the therapy was started ($p<0.001$). On the fifth day of disease mean axillary temperature decreased below 37°C and was significantly lower compared to the third day from the therapy start ($p<0.001$). The results are in accordance with previously published results that fever is present in the majority of COVID-19 patients within the first three days of the disease (25).

Lysozyme is a natural compound with antiviral and immunomodulatory activities. It has great potential in the treatment of COVID-19 patients (27,28) and further studies evaluating the effects of lysozyme-based products in COVID-19 patients are urgently warranted.

CONCLUSION

Lysozyme-based drugs showed positive effects in the treatment of sore throat in COVID-19 patients. According to the subjective assessment of the investigator, one day after the start of the treatment, symptoms of the sore throat improved in all patients. A decrease in mean axillary temperature and improvement of the clinical condition related to sore throat were recorded on the third day after the enrolment. On the fifth day after the enrolment, 96% of patients were stable. Lysozyme-based drugs showed excellent tolerability with no reported adverse events during the study. Further studies evaluating the effects of lysozyme-based products in COVID-19 patients are urgently warranted.

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Seasonal pattern of food poisoning

Sezonski obrazac trovanja hranom

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ABSTRACT

Introduction: food-borne diseases are considered to be any food-related disease or a disease in which a sample is introduced into the body through food. The occurrence of such a disease is considered to be the case when two or more persons experience a similar disease, usually gastrointestinal, after eating ordinary food, if the analyzes indicate that the source of this disease is food. Approximately 66% of all foodborne illness is caused by bacterial pathogens, and approximately 60% of the causes have not been identified. People with health conditions related to kidney disease, liver disease, diabetes, autoimmune diseases are more susceptible. Aim: to determine the characteristics of food poisoning by the season and age of patients from 1-6, 7-14, 14-18, 19-30, 30-40, 50-60 and patients over 60 years of age, and the male-female ratio of hospitalized patients. Materials and methods: the research was a retrospective average study. The study was conducted at Clinic of Infectious Diseases of the Clinical Center University of Sarajevo in the period from 2016 to 2017. The results are presented in tables and graphs by number of cases and percentage. The analysis was performed using the statistical package for sociological research IBM Statistics SPSS v 21.0 with the preparation and presentation of results in Microsoft Word and Excel. Results: the results include subjects hospitalized at the Infectious Diseases Clinic in the period from 2016 to 2017, in which the cases of food poisoning were proven. These results were compared with other studies conducted in the Republic of Croatia, the Republic of Serbia and in the rest of the world. Conclusion: it was concluded that the symptoms of food poisoning may occur at any time regardless of the season. The highest number of patients hospitalized at Clinic of Infectious Diseases of the CCUS was aged 1 to 14 in both years (2016 and 2017). Based on the gender structure, it was proven that male gender was more represented in our study.

Keywords: food poisoning, subjects, seasons, gender and age structure

SAŽETAK

Uvod: pod bolestima koje se prenose putem hrane se smatra svaka bolest koja je povezana sa hranom ili kod koje je uzorčnik unijet u organizam preko hrane. Pod pojavom takve bolesti smatra se slučaj kada dvije ili više osoba dožive sličnu bolest, obično gastrointestinalnu, nakon konzumiranja obične hrane, ako analize ukažu da je izvor ove bolesti hrana. Približno 66% svih pojava bolesti koje se prenose putem hrane su izazvane bakterijskim patogenima, a za približno 60% uzroka nije identificirano. Podložnije su osobe sa zdravstvenim stanjima vezanim za bolesti bubrega, bolesti jetre, dijabetesa, autoimunim oboljenjima. Cilj: odrediti karakteristike trovanja hranom prema sezoni i dobi bolesnika od 1-6, 7-14, 14-18, 19-30, 30-40, 50-60 i bolesnika starijih od 60 godina, te omjer između muških i ženskih hospitaliziranih pacijenata. Materijali i metode: ovo je retrospektivna prosječna studija provedena na Infektivnoj klinici Kliničkog centra Univerziteta u Sarajevu (KCUS) u periodu 2016. i 2017. godina. Rezultati su prikazani tabelarno i grafički putem broja slučajeva i procenta. Analiza je provedena korištenjem statističkog paketa za sociološka istraživanja IBM Statistics SPSS v 21.0 uz pripremu i prezentaciju rezultata u programima Microsoft Word i Excel. Rezultati: uključeni su ispitanici koji su ležali na Infektivnoj klinici u period 2016. i 2017.godine , kod kojih je dokazano trovanje hranom. Ovi rezultati su komparirani sa drugim studijama koji su sprovedeni u Republici Hrvatskoj, Srbiji i ostatku svijeta. Zaključak: simptomi trovanja hranom se mogu javiti bilo kada bez obzira na godišnje doba. Najviše je hospitaliziranih slučajeva bilo na Infektivnoj klinici na KCUS 1-14 godina starosti u obje istaživane godine (2016. i 2017). Prema spolnoj strukturi je dokazano da je muški spol bio zastupljeniji u našoj studiji.

Ključne riječi: trovanje hranom, ispitanici, godišnje doba, spolna i dobna struktura

INTRODUCTION

Food-borne diseases are considered to be any food-related disease or in which a sample is introduced into the body through food. The occurrence of such a disease is considered to be the case when two or more persons experience a similar disease, gastrointestinal, after eating ordinary food, if the analyzes indicate that the source of this disease is food. Approximately 66% of all foodborne illness is caused by bacterial pathogens, and approximately 60% of the causes have not been identified. The most common causes of food poisoning are; Salmonella and Campylobacter spacies, Staphylococcus aureus, Clostridium perfringens, Clostridium botulinum, Listeria monocytogenes, Escherichia coli, Shigella, Vibrio and Yersinia enterocolitica. A large number of dishes prepared at home or prepared for sale were the causes of foodborne illness. Foods of animal origin, such as poultry products, eggs, red meat and dairy products, are a more common cause of poisoning than foods of plant origin (1).

Food poisoning lasts for about two days and usually ends without sequelae, but occasionally dehydration, goiter, kidney, pancreas and liver problems. Therefore, even the slightest hint of poisoning should be taken and the unpleasant symptoms resolved. The characteristics

of food poisoning are: constant nausea, copious watery stools, diarrhea sometimes with admixtures of blood. Increased body temperature, fever, dark urine, lowered blood pressure, loss of consciousness, dizziness, weakness and malaise. Occasionally there is pain, swelling, headaches, tachycardia, muscle cramps (2). Foods that very often cause food poisoning are raw or undercooked meat, unpasteurized dairy products, raw sea shells, unwashed fruits and vegetables. People with health conditions of kidney disease, liver disease, diabetes, autoimmune diseases are also more susceptible (3).

Salmonellosis

The bacterial genus Salmonella belongs to the family of enterobacteriaceae, so they are Gram-negative rod-shaped bacteria that can live in the digestive system of animals and humans. (4). The most common route of salmonella infection is the consumption of contaminated (i.e., contaminated or contaminated) food, which often has no unusual appearance or odor. This is why non-compliance with hygienic postulates during cooking (especially in large kitchens and restaurants) or inadequate heat treatment of food can lead to significant epidemics of salmonellosis. The place where bacteria enter humans is the gastrointestinal tract, so we are talking about the feco-oral route of infection transmission. On the other hand, the infection can be transmitted (and contaminated with food) by an infected person or a carrier, for which direct contact is sometimes sufficient, especially in maternity hospitals or nursing homes (5).

Salmonella in humans is mainly retained in the digestive tract. However, in 5-10% of people with bacteremia (i.e. the transfer of bacteria into the blood) there is an abscess in the abdominal cavity and liver, pyelonephritis, inflammation of the joints and purulent meningitis (6).

Campylobacter

The most common form of Campylobacter infection is gastroenteritis, which can be acquired by drinking contaminated water, eating undercooked chicken or meat, and touching infected animals. The organism that causes stomach ulcers was once called Campylobacter pylori, but its name was changed to Helicobacter pylori (7).

Clostridium perfringens

Food poisoning caused by Clostridium perfringens is an acute gasoenteritis that occurs after consuming contaminated food. C. perfringens is widespread in feces, soil, air, and water. (8)

Listeriosis

Infectious disease of many species of animals and humans. It appears sporadically, sometimes enzootic. Manifested by encephalitis, miscarriage, septicemia, mastitis, spinal myelitis or keratoconjunctivitis Listeriosis encephalitis is a unilateral acute inflammation of the brainstem.

Escherichia coli

Many species of E. coli are harmless, but those that produce verocytotoxin (VTEC) can cause serious diseases. Risky foods are undercooked, ground beef and unpasteurized or improperly pasteurized milk. It can also be contracted through direct contact with an infected person or animal and through soil contaminated with animal feces (9).

AIM

To determine the characteristics of food poisoning by season and age of patients from 1-6, 7-14, 14-18, 19-30, 30-40, 50-60 and patients over 60 years of age, and the male-female ratio of hospitalized patients.

MATERIALS AND METHODS

The research used patients' data from Clinic of Infectious Disease of the CCUS with confirmed poisoning based on microbiological findings. The research used medical documentation, personal data of patients who reported to Clinic of Infectious Diseases of the CCUS. In addition to using patients' experiences, relevant literature related to food poisoning was used.

The research method was a retrospective average study conducted in the 2016-2017 period.

The inclusion criterion related to those who had food poisoning and the causative agent was proven in that period.

The exclusion criterion related to people who had food poisoning but the causative agent was not proven during that period.

The results are presented in tables and graphs by number of cases and percentage.

The analysis was performed using the statistical package for sociological research IBM Statistics SPSS v 21.0 with the preparation and presentation of results in Microsoft Word and Excel.

RESULTS

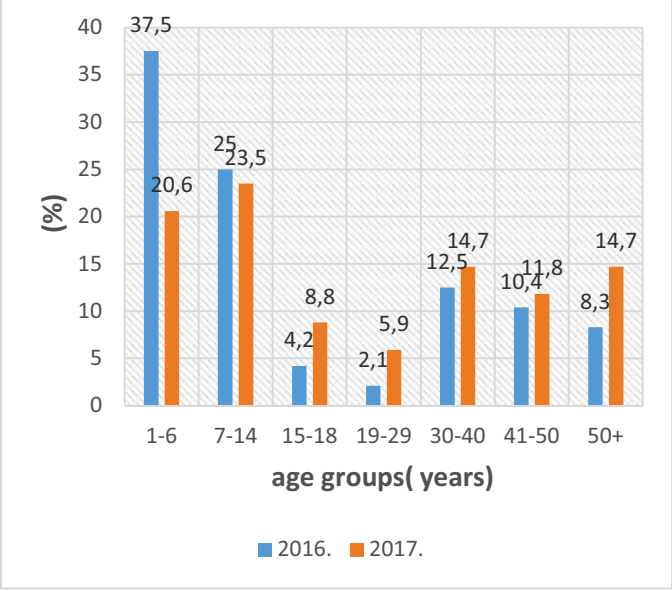

Figure 1 **Age among patients included in the 2016 and 2017 sample.**

Based on the age ratio between the two groups taken at two different years, reported and hospitalized for food poisoning symptoms, it was conclude that they had similar values. Most hospitalized cases were at Clinic of Infectious Diseases of the CCUS aged 1 to 14 years in both years (2016 and 2017), values for the group 1-6 years of age were 37.5% of the total number of hospitalized patients for 2016, while in 2017 it amounted to 20.6%, and for the age group 7-14 in 2016 it amounted to 25%, while in 2017 this percentage was 23.5% out of the total number of hospitalized patients.

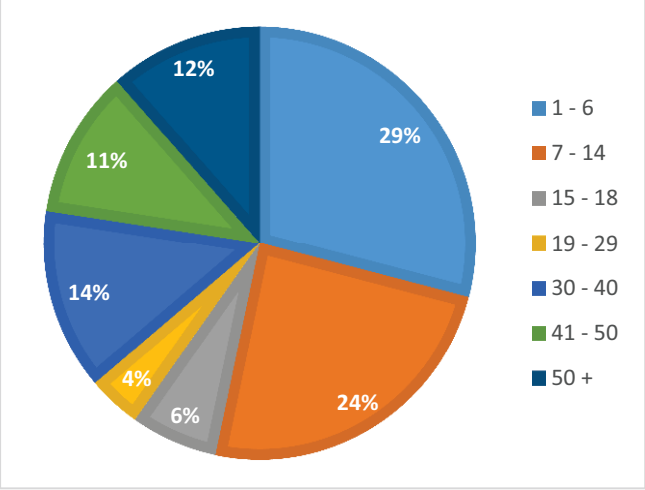

Figure 2 **The percentage summation of both research years (2016/17) by age.**

Table 1 **Percentage of patients hospitalized due to suspected food poisoning in 2016 and 2017 by season.**

Season	2016.	2017.	In total
Spring	21.4%	0%	12%
Summer	8.3%	38.2%	24%
Autumn	0%	61.8%	34%
Winter	54.3%	0%	29%

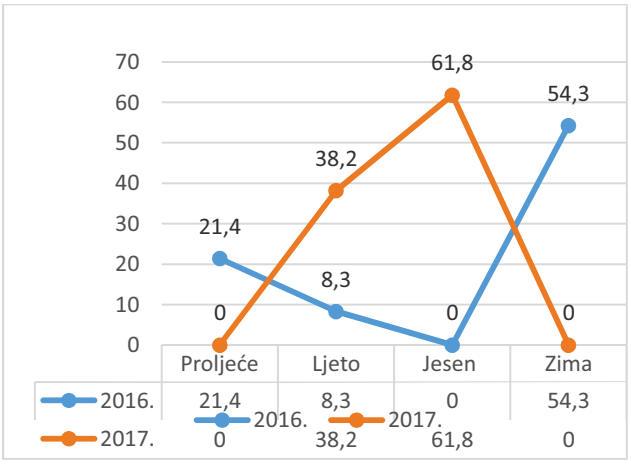

Figure 3 **Percentage of patients hospitalized due to suspected food poisoning in 2016 and 2017 by season**

Figure 3 shows the reverse sequence of hospitalized patients who reported to Infectious Diseases Clinic of the CCUS due to suspected food poisoning. It can be concluded that the symptoms of food poisoning can occur at any time regardless of the season.

Table 3 **Distribution of patients' gender structure in 2016.**

Sex	*Number of patients*	*%*
Male	30	62
Female	18	38

The gender ratio in the total sample taken in 2016 (N = 48) was 30 male (62%) and 18 female patients (38%).

Table 4 **Distribution of patients' gender structure in 2017.**

Sex	*Number of patients*	*%*
Male	21	62
Female	13	38

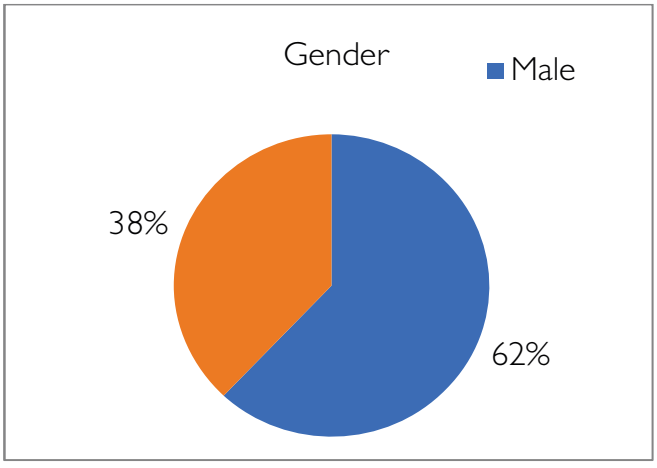

Figure 4 **Percentage presentation of the patients' gender structure distribution in 2016 and 2017**

Based on the gender distribution, out of the total number of patients (82), the majority of the sample, i.e. persons who reported signs of food poisoning, related to male patients with 62% (51), whereas 38% (31) related to female patients.

DISCUSSION

It is estimated that a total of 29% of the 22 food-borne diseases were around 582 million in 2010, and 38% of the cases were children under 5 years of age. The causative agents in most cases were norovirus, Campylobacter spp., non-typhoid Salmonella spp., and Shigella spp. A high proportion of infections in the African region belong to the causative agent of cholera, salmonella (S. Typhi and S. Paratyphi). These data match our data where most patients were under the age of 6.

About 351.000 people died from contaminated food in 2010 and 33% were children under the age of 5. Most deaths were recorded in Africa and South-East Asia. In the Republic of Croatia, salmonella infection is in the first place as the most common cause of food poisoning. In the period from 1990 to 2009, 58.268 infectious diseases were reported to the Hygienic and Epidemiological Department of Novi Zagreb. 4.492 salmonellosis were reported, which was 8% (10-11).

Between 20.000 and 25.000 cases of food-borne diseases are registered annually in the Republic of Serbia through epidemiological surveillance prescribed by law. Despite all precautions, the most common cause of food poisoning in Europe is Salmonella. According to the World Health Organization (WHO) data from 2004, around 2.2 million people die of diarrhea worldwide each year, and the cause is not defined (12).

In the Republic of Croatia, the highest frequency of bacterial intestinal infections is from May to October. In addition to campylobacteriosis, salmonellosis is the most common bacterial intestinal infection in humans in the developed world. These data do not match ours where food poisoning was found throughout the year (13).

Women get sick slightly more often than men. The ratio of affected women and men was 2:1, in the Republic of Croatia for 2010, which does not coincide with our results. Our research showed that men were more likely to get sick than women, with the ratio 62% :38% (10).

CONCLUSION

The study showed the inverse seasonal frequency of hospitalized patients who reported to Clinic of Infectious Diseases of the CCUS due to suspected food poisoning. Thus, it can be conclude that symptoms of food poisoning may occur at any time regardless of the season. The study has proven that the highest number of patients report during the summer and autumn, which coincide with world research.

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Reliability of C-reactive protein as an early predictor in the diagnosis of colorectal anastomosis dehiscence

C-reaktivni protein kao rani prediktor u dijagnozi dehiscence kolorektalne anastomoze

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ABSTRACT

Introduction: colorectal anastomosis dehydration is one of the most severe complications in colorectal surgery, which significantly prolongs treatment, occasionally requires re-surgery and can end in death. Early diagnosis of dehiscence anastomosis is very important because it can prevent and mitigate these complications. Aim: to investigate the efficacy of C reactive protein (CRP) as an early predictor of septic complications, i.e. anastomosis dehiscence. Materials and methods: in all patients operated on for colorectal cancer, a 2 mL blood sample was taken for analysis, without special preparation of the patient before sending to the laboratory. CRP values were collected on the second and fourth postoperative day, and in all patients with elevated CRP values the occurrence of dehiscence was confirmed both clinically and radiologically. Results: the study was conducted on 94 patients who underwent surgery for colorectal cancer and in whom a colorectal anastomosis was created. Anastomotic dehiscence occurred in 8 patients. Elevated CRP values were found in all patients with dehiscence. Elevated CRP values gave 85% sensitivity and 90% specificity. Conclusion: CRP can be considered a reliable biomarker for detecting dehiscence after colorectal anastomosis creation.

Keywords : C-Reactive Protein, colorectal neoplasms, treatment

SAŽETAK

Uvod: dehiscencija kolorektalne anastomoze predstavlja jednu od najtežih komplikacija u kolorektalnoj hirurgiji koja značajno produžava liječenje, povremeno zahtjeva ponovnu operaciju a može završiti i smrtnim ishodom. Rana dijagnoza dehiscence anastomoze je veoma važna jer se tako mogu spriječiti i ublažiti navedene komplikacije. Cilj studije je bio da se istraži efikasnost C reaktivnog proteina (CRP) kao ranog prediktora septičkih komplikacija, odnosno dehiscencije anastomoze. Materijali i metode: kod svih pacijenata operisanih zbog kolorektalnog kacinoma za analizu se uzimala mala količina krvi a pri tome nije bila potrebna posebna priprema prije slanja u laboratoriju. Vrijednosti CRP prikupljane su 2 i 4 postoperativnog dana, i kod svih pacijenata sa povišenim vrijednostima kojih je kreirana kolorektalna anastomoza. Dehiscencija anastomoze nastupila je kod 8 pacijenata. Kod svih pacijenata sa dehiscencijom utvrđeno je prisustvo povišenih vrijednosti CRP. Povišene vrijednosti CRP dale su 85% osjetljivosti i 90% specifičnosti. Zaključak: CRP i bijela krvna loza su pouzdani makeri za otkrivanje dehiscencije nakon kreiranja kolorektalne anastomoze.

Ključne riječi: C-reaktivni protein, kolorektalna neoplazme, tratman

INTRODUCTION

Rectal cancer is one of the three leading malignancies in the world. Rectal cancer is the third most common cancer, after lung cancer and breast cancer. Rectal cancer is the fourth leading cause of death from cancer, after lung, stomach and liver cancer (1). The frequency of postoperative complications on the colon and rectum is higher than on other organs in the abdomen, and one of the most severe complications is anastomosis failure, i.e. anastomotic dehiscence (2). Some studies have indicated that early and late colorectal anastomosis dehiscence can be observed separately, both in symptomatology and postoperative care (3,4). The occurrence of colorectal anastomosis dehiscence is influenced by a number of factors that can be divided into systemic, local and technical (5). Despite the increasing knowledge of risk factors for the development of colorectal anastomosis dehiscence as well as the improvement of the surgical technique, the anastomosis dehiscence remains a serious complication that endangers the patient's life, often requiring urgent intervention with prolonged and expensive treatment. (6) The frequency of this complication is 3-25% and only clinically manifested dehiscence are significant. Early dehiscence of the colorectal anastomosis is clinically manifested between the 5th and 7th postoperative day (7,8). Precisely because of all the above, it is necessary to provide an early diagnosis of dehiscence and thus reduce morbidity and mortality. (9) C-Reactive Protein (CRP) is an important immune protein produced by the liver that serves as an important inflammatory marker of postoperative complications (10,11,12). In healthy people, CRP is present in very low concentrations, while in cases of inflammatory changes, its values rise

to high concentrations. Also, the concentration of CRP normalizes very quickly with the recovery of patients (12,13).

AIM

The main goal of this study was to measure CRP values on the second and fourth postoperative day and to determine the correlation of high CRP values with the development of dehiscence of colorectal anastomosis.

MATERIALS AND METHODS

This observational study included 94 patients who underwent surgery for endoscopically and pathohistologically verified rectal cancer, and for whom a stapler colorectal anastomosis was created by open surgical approach. All patients were operated according to an elective operative protocol. The patients included in the study ranged in age from 55 to 75. There were 57 male patients, and type 2 diabetes mellitus was verified in 23 operated patients. All data for the study were used from medical histories, operative protocols and clinical examinations of patients who underwent surgery at the Clinic for General Surgery of the University Clinical Center of the Republic of Srpska (UCC RS) in the period from 2017 to 2020. All operated patients underwent identical surgical treatment, which included dissection, high ligation and resection of the lower mesenteric blood vessels. Then, with the help of a cautery and LigaSure device, rectal dissection and total mesorectal excision are performed, and bowel resection is performed using a linear TA stapler (mechanical instrument for automatic suturing). Colorectal anastomosis in all patients was performed using a circular stapler. All surgical procedures were performed by open access, which includes supraumbilical and infraumbilical laparotomy. In all patients, CRP and leukocyte values and their correlation with the occurrence of dehiscence were measured preoperatively and then on the second and fourth postoperative days. The correlation between the age of the patient and the occurrence of dehiscence anastomosis, the height of the anastomosis created during surgery and the development of dehiscence, the correlation of radiotherapy and the development of dehiscence, and the correlation of gender and BMI and the development of dehiscence anastomosis were also determined in patients. Glycemic values were also measured preoperatively and postoperatively in all patients with diabetes. The occurrence of dehiscence was confirmed by clinical examination, by the contents of the abdominal drain and echosonography. The goal of the study was to determine the correlation of CRP values with the occurrence of dehiscence colorectal anastomosis.

RESULTS

Out of the total number of operated patients, there were 57 male patients (60.63%). The methods of statistical analysis of the Fishers Exact test determined that there was no statistically significant influence of gender on the development of dehiscence anastomosis (Table 1). The total number of the colorectal anastomosis dehiscences was 8 (8.51%). Reoperation had to be performed in 3 (37.5%) patients with anastomotic dehiscence, while conservative treatment was sufficient in 5 (63.5%) patients. Of all those operated on, one patient with anastomotic dehiscence had a fatal outcome. Radiochemotherapy was performed preoperatively in 24 patients, and based on the analysis, it was determined that there was no statistically significant effect on the development of dehiscence of the colorectal anastomosis.

Also, the methods of statistical analysis determined that the value of Body Mass Index (BMI) in patients operated on for rectal cancer did not have statistical significance for the development of anastomotic dehiscence.

Table 1 **Frequency of dehiscence of colorectal anastomosis related to gender, age, chemoradioterapy and type ofanastomosis. Incidence of death in patients with and without dehiscence of colorectal anastomosis.**

			Dehiscence		
			Yes	No	Total
CRP>100	No	N	1	51	52
		%	12	59.3	55.3
	Yes	N	7	35	42
		%	87.5	40.7	44.7
Total		N		86	94
		%	100.0	100.0	100.0

Dehiscence of anastomosis with anastomotic leakage significantly prolonged hospitalization of patients, so that in patients without dehiscence the average hospitalization lasted 8 days, while in patients with dehiscence hospitalization was on average 17.5 days.

Table 2 **CRP values of the second postoperative day in operated patients with and without dechiscence of colorectal anastomosis.**

			Dehiscence		
			Yes	No	Total
Age	Age from 55 to 65	N	2	39	41
		%	4.9	95.1	100.0
	Age 65 and over	N	6	47	53
		%	11.3	88.7	100.0
	Total	N	8	86	94
		%	8.5	91.5	100.0
Sex	Male	N	6	51	57
		%	10.5	89.5	100.0
	Female	N	2	35	37
		%	5.4	94.6	100,0
	Total	N	8	86	94
		%	8.5	91.5	100.0
Radiochemotherapy	Yes	N	3	24	27
		%	11.1	88,9	100,0
	No	N	5	62	67
		%	7.5	92.5	100.0
	Total	N	8	86	94
		%	8.5	91.5	100.0
Anastomosis height	Less than 10 cm	N	3	31	34
		%	8.8	91.2	100.0
	More than 10 cm	N	5	55	60
		%	8.3	91.7	100.0
	Total	N	8	86	94
		%	8.5	91.5	100.0
Body Mass Index	Lower than 19	N	0	4	4
		%	00	100.0	100.0
	From 19 to 25	N	2	38	40
		%	5.0	95,0	100.0
	Higher than 25	N	6	44	50
		%	12.0	88.0	100.0
	Total	N	8	86	94
		%	8.5	91.5	100.0
Dead patients	Yes	N	1	0	1
		%	12.5	0.0	1.1
	No	N	7	86	93
		%	87.5	100,0	98,9
	Total	N	8	86	94
		%	100.0	100.0	100.0

With assumption of 10% prevalence for dechiscence of colorectal anastomosis (WHO statistic for elderly group), and for patients who obtain CRP>100 result of the second postoperative day, this observation shows that sensitivity is 87.5% and specificity is 59.3% (Figure1).

However, if patient has CRP>100 result second postoperative day, there is a 19.28% chance that the patient get the dehiscence. Also if patient has not CRP>100 result second postoperative day, there is a 97.71% chance that the patient has not get the dehiscence.

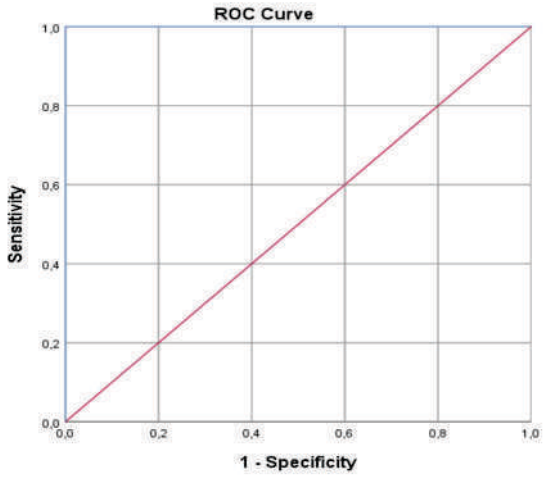

Figure 1 **Presentation of specificity and sensitivity for CRP of the second postoperative day.**

Using the ROC curve analysis we can see that the area under the curve for this particular logistic regression model is 1.000, with p <0.0001, which is extremely high and this indicates that, in statistical meaning, the model predicting completely whether or not a patient with CRP>100 result of the second postoperative day, will get dehiscence or not.

Also, we could conclude that cut of point of CRP in second postoperative day is 135.50 mg/L.

For example, using CRP=130.50 mg/L as a cutoff point, sensitivity would be 100% that did not get dehiscence for each patient who has CRP less than 130.50 mg/L second postoperative day, and our 1 – specificity would be 2.9%.

Table 3 **CRP values of the fourth postoperative day in operated patients with and without dechiscence of colorectal anastomosis.**

			Dehiscence		
			Yes	No	Total
CRP>150	No	N	0	71	71
		%	0.0	82.6	75.5
	Yes	N	8	15	23
		%	100.0	17.4	24.5
Total		N	8	86	94
		%	100.0	100.0	100.0

Fishers Exact test found that there was a statistically significant correlation between elevated CRP values above 100mg/L on the second, and 150mg/L on the fourth postoperative day, and dehiscence of the anastomosis, and that there was a higher probability of the occurrence of dehiscence in patients in whom these CRP values were in the observed postoperative days (second and fourth day), (Table 2,3).

In patients with a CRP value greater than 150 on the fourth postoperative day, sensitivity was 100.00% and specificity was 82.56%. However, if patient has CRP>150 result fourth postoperative day, there is a 38.92% chance that the patient get the dehiscence (Figure 2).

Also if patient has not CRP>150 result fourth postoperative day, there is a 100.00% chance that the patient has not get the dehiscence.

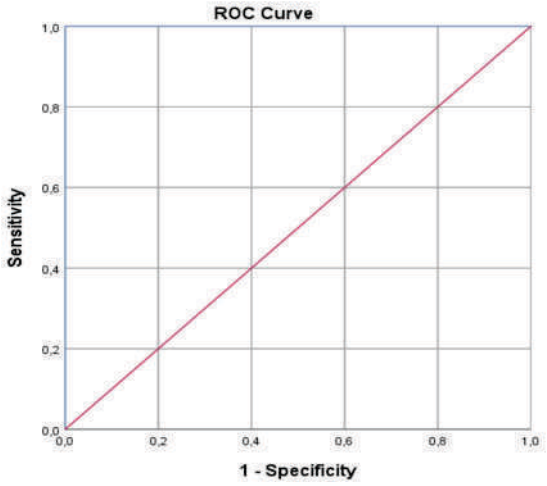

Figure 2 **Presentation of specificity and sensitivity for CRP of the fourth postoperative day.**

Using the ROC curve analysis we can see that the area under the curve for this particular logistic regression model is 1.000, with p <0.0001, which is extremely high indicating that, in statistical meaning, the model predicting completely whether a patient with CRP>150 result of the fourth postoperative day will get dehiscence or not.

Also, we could conclude that cut of point of CRP in fourth postoperative day is 166.50 mg/L.

For example, using CRP=163.00 mg/L as a cutoff point, sensitivity would be 100% that did not get dehiscence for each patient who has CRP less than 163.00 mg/L fourth postoperative day, and our 1 – specificity would be 13.3%.

DISCUSSION

Dehiscence of colorectal anastomosis is the most serious complication of colorectal surgery, which is still present in a large percentage and significantly increases the cost of treatment and often ends in death (14). Because of all this, early diagnosis of anastomotic dehiscence is very important in order to reduce treatment costs as well as mortality (15). In patients diagnosed with dehiscence after 5 postoperative days, mortality ranged up to 18%, while in those previously diagnosed, mortality was not proven (16). CRP is produced by liver hepatocytes and due to its short half-life of 19 hours it is very important as an early predictor of inflammatory changes and especially dehiscence of the anastomosis (17,18). Postoperative measurements of CRP values are important because it has the ability to identify patients at risk of anastomotic leakage and exclude patients with low risk of anastomotic leakage and other infections (18).

It is very important to assess in cases of dehiscence of colorectal anastomosis when it is necessary to perform surgical intervention and when it can be solved by peritoneal drainage. It was found that in the case of a double consecutive increase in CRP values of 50 units, CRP has a high sensitivity and specificity for the development of dehiscence and anastomotic leakage (19). In our study, it was also found that in the group with dehiscence and anastomosis leakage there was a significant increase in CRP values on the second and fourth day, which were significantly higher compared to the group without anastomotic leakage.

The study found that on the second postoperative day CRP values in patients with dehiscence were on average higher than 100 mg/L, and on the fourth day over 150 mg/L. Similar results could be found in other studies when a double increase in CRP was found in patients with anastomotic dehiscence (20,21). In their study, Nason, et al. found that CRP values above 148 mg/L had 86% sensitivity and 77% specificity (22). Almeida, et al. also found that there was a statistically significant difference in CRP values on the second postoperative day in patients with and without anastomotic leakage (23).

In their meta-study, Warschkow, et al. found that elevated CRP values on the fourth postoperative day had the highest accuracy as an indicator of anastomotic dehiscence with an average CRP value of 135mg/L (17). In our study, we found that patients who experienced a high increase in CRP value in the first postoperative days required urgent surgical treatment. In several patients, the clinical picture was not dramatic, there was no intestinal content on the drains, but CRP values ranged over 200 mg/L.

Several studies have confirmed that elevated CRP values precede radiological and clinical diagnosis of anastomotic dehiscence, and that early detection of high CRP values may reduce the time to decide on surgery and thus lead to lower mortality rates and reduced treatment costs (21).

Based on everything presented in this and other studies, it can be said that postoperative level of serum CRP in patients who underwent colorectal surgery with a created colorectal anastomosis, could be a useful marker for determining anastomotic dehiscence and exclusion of other inflammatory processes.

CONCLUSION

This study showed a significant correlation between CRP as a diagnostic marker of anastomosis dehiscence and anastomotic leakage. An increase in CRP values on the second postoperative day and an increase in CRP values on the fourth postoperative day is a significant indicator of anastomotic leakage. Additional diagnostic procedures should be performed in all patients with elevated CRP on the second postoperative day to confirm or rule out the existence of anastomosis dehiscence.

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Anticoagulant therapy in post-COVID-19 syndrome

Antikoagulantna terapija u post-COVID-19 sindromu

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ABSTRACT

Introduction: post-COVID-19 syndrome, also known as "long-term COVID" - is a term used to describe a condition experienced by people who have had COVID-19 and who suffered from related symptoms 12 or more weeks later. The disease is associated with several abnormalities coagulations that may be responsible for thrombotic incidents both during illness and in the post-COVID-19 period, dominated by venous thromboembolism (VTE) and pulmonary embolism (PE). (3) Aim: to consider the most favorable scheme for the use of anticoagulant therapy in post-COVID syndrome, relying on current recommendations and scientific facts. Materials and methods: review of the medical literature on current views on the administration of anticoagulant therapy in COVID-19, with a critical review of the administration of anticoagulant therapy in post-COVID-19 syndrome. Results: posthospital thromboprophylaxis for up to 42 (45) days is recommended if the D-dimer is greater than 2x the reference value, and if the patient has one of the risk factors (immobilization, previous VTE, hormone therapy, body weight> 120 kg or BMI> 35 kg / m2, oncological process). Conclusion: any decision to use thromboembolic incident prophylaxis in post-COVID-19 syndrome should be based on an individual patient approach.

Keywords: COVID-19, anticoagulants, thromboembolism, prophylaxis

SAŽETAK

Uvod: post-COVID-19 sindrom, također poznat kao „dugi COVID" - izraz je koji se koristi za opisivanje stanja koje imaju ljudi koji su prebolovali COVID-19 i koji pate od povezanih simptoma 12 ili više sedmica kasnije. Bolest je povezana s nekoliko abnormalnosti koagulacije koje mogu biti odgovorne za trombotičke incidente kako za vrijeme bolesti, tako i u post-COVID-19 periodu, među kojima dominiraju venska tromboembolija (VTE) i plućna embolija PE (3). Cilj: razmotriti najpovoljniju shemu za primjenu antikoagulantne terapije u post-COVID sindromu, oslanjajući se na aktualne preporuke i znanstvene činjenice. Materijali i metode: pregled medicinske literature po pitanju trenutnih stanovišta o ordiniranju antikoagulantne terapije kod COVID-19 uz kritički osvrt na ordiniranje antikoagulantne terapije u post-COVID-19 sindromu. Rezultati: posthospitalna tromboprofilaksa do maksimalno 42 (45) dana se preporučuje ako je D-dimer veći od 2x od referentne vrijednosti, te ako pacijent ima jedan od riziko faktora (imobilizacija, prethodni VTE, hormonalna terapija, tjelesna težina >120 kg ili BMI >35 kg/m2 , onkološki proces). Zaključak: svaka odluka o korištenju profilakse tromboembolijskih incidenata u post-COVID-19 sindromu trebala biti zasnovana na individualnom pristupu pacijentu.

Ključne riječi: COVID-19, antikoagulanti, tromboembolizam, profilaksa

INTRODUCTION

Post-COVID-19 syndrome, also known as "long-term COVID," is a term used to describe conditions in people who have had COVID-19 and who suffered from related symptoms 12 or more weeks later and could not be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time (1). The goal of medical treatment of the condition after COVID for most patients is to optimize function and quality of life. Some patients experience multiorgan effects or autoimmune conditions with symptoms lasting for weeks or months after COVID-19 disease. Multiorganic effects can affect many, if not all, body systems and functions, including coagulation disorders and thrombosis (2). Although respiratory manifestations are a major feature of COVID-19 disease, caused by SARS-CoV-2 virus, data in the modern literature from the outset of the pandemic suggest that the disease is associated with several coagulation abnormalities that may be responsible for thrombotic incidents related to this disease. disease time, as well as in the post-COVID-19 period, among which venous thromboembolism (VTE) and pulmonary embolism PE predominate (3). The exact mechanism of coagulation disorders is unknown. There are several theories about the pathophysiology of prothrombotic conditions in this disease. One possible explanation is that the SARS-CoV-2 virus affects the individual processes involved in the Virhof triad, namely hypercoagulability, endothelial injury, and slowing of blood flow (3,4)

The incidence of VTE has been reported in about 20%-30% of patients in several studies, while some other studies have reported that it is as high as 70% (5). A study from China predicted that up to 40% of patients had a higher risk of developing deep vein thrombosis (DVT) according to the Padua Prediction Score (6). A French prospective study reported the development of PE despite prophylactic anticoagulation in 16.7% of patients (7). A Dutch study

reported an incidence of VTE of 27% despite prophylaxis (8). An Italian study found that the rate of VTE in sick patients was 22.2% (9).

More research and more rigorous observational cohort studies are needed to better understand the pathophysiology and clinical course of post- COVID-19 sequelae and to identify management strategies for patients (10).

AIM

The aim of this study is to present current guidelines and recommendations as well as ongoing studies on the use of anticoagulants in COVID-19, and to draw a conclusion about the potentially most favorable scheme of their administration in post-COVID-syndrome.

MATERIALS AND METHODS

Using Boolean logic using the „AND", „OR" or „NOT" operators and the PICO search strategy, a review of the medical literature was performed through PubMed and Medline databases using the terms: anticoagulant therapy, COVID-19, venous thromboembolism, guidelines. In addition to emphasizing the importance of the presence of coagulation disorders in patients with COVID-19, a critical review of the efficacy, safety, duration, and conditions of anticoagulant therapy during post-COVID syndrome according to the Modified International Registry of Veous Thromboembolism (MIV) was given.

RESULTS

Anticoagulant therapy in post-COVID-19 syndrome

The CHEST guidelines for antithrombotic therapy issued by the American College of Thoracic Physicians reject the use of anticoagulant drugs in post-COVID-19 syndrome due to a lack of relevant studies. However, the guidelines of the National Institutes of the Health (NIH), updated on 11 February 2021, as well as the International Society for Thrombosis and Haemostasis, ISTH), The British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN) mention thromboprophylaxis after hospitalization of patients with COVID-19, based on based on expert opinions (level of evidence IIIa) (10-13).

Decisions on prophylactic anticoagulant therapy in post-COVID-19 syndrome should be individualized. Based on current recommendations, as well as past and ongoing anticoagulant studies, it could be concluded that patients with moderate to severe disease who meet any of the following criteria would be ideal candidates for post-COVID thromboprophylaxis, resulting from the Modified of the Modified International Medical Prevention Registry on Venous Thromboembolism (MIV), (Table 1) (10).

1. MIV score ≥4
2. MIV score ≥2 with a D-dimer value> 2 times the upper limit of the normal range
3. Age ≥75 years
4. Age> 60 years with a D-dimer value> 2 times the upper limit of the normal range
5. Age 40-60 years with a D-dimer value> 2 times the upper limit of normal range and a history of VTE or patients diagnosed with malignancy

Table I **Modified International Register of Medical Prevention for Venous Thromboembolism (MIV).**

VTE risk factor	*VTE score*
Formerly VTE	3
Thrombophilia	2
Existing paresis or paralysis of the lower extremity	2
Personal history of malignancy	2
Complete immobilization ≥7 days	1
Age ≥ 60 years	1
*Hospitalization in ICU / CCU**	1
D-dimer ≥ 2x of the reference value	2

* ICU - Intensive care unit /CCU - Critical care unit

Selected patients should be assessed for the risk of venous thromboembolism using MIV scores in accordance with the clinical picture, the findings of computed tomography of the thorax, ie the verification of possible VTE (14,17). In the case of verified VTE, the therapeutic modality is the same. The decision to administer anticoagulants should be balanced with HASBLED (Hypertension, Abnormal Liver / Renal Function, Stroke History, Bleeding History or Predisposition, Labile INR, Elderly, Drug / Alcohol Usage, HASBLED) or VTE BLEED point scale. If no risk of bleeding is identified, the patient may be prescribed thromboprophylaxis.

The role of routine D-dimer measurement during patient follow-up in post-COVID-19 syndrome has not been demonstrated. Direct Oral Anticoagulants (DOACs) do not require INR monitoring and are preferable to Vitamin K Antagonists (VKAs) in terms of patient comfort with post-COVID-19 syndrome. Preferred DOAC drugs include rivaroxaban (10 mg once daily), betrixaban (160 mg on the first day followed by 80 mg once daily) and apixaban (2.5 mg twice daily) according to relevant studies (14,15).

Regarding the duration of post-COVID prophylaxis, the FDA recommends the use of rivaroxaban (10 mg daily) for 31 to 39 days and betrixaban on soil where it is approved (160 mg on the first day, followed by 80 mg once daily) for 35 to 42 days (10). The ACC has proposed prolonged thromboprophylaxis with (Low Molecular Weight Heparin, LMWH) or DOAC for a maximum period of 45 days in the case of high risk for VTE, such as D-dimer twice the upper limit of normal or the presence of active cancer. (Scinetifix and Standardization Committee-International Society for Thrombosis and Haemostasis, SCC-ISTH) suggests a duration of thromboprophylaxis of 14-30 days in these cases (16).

In renal insufficiency, warfarin is preferred over DOAC with INR monitoring. However, at an estimated glomerular filtration rate (eGFR) of 30-15 mL / min, apixaban 2.5 mg twice daily may be used. In eGFR <15 mL / min and in patients with end-stage renal disease on hemodialysis, DOAC should be avoided. The US Food and Drug Administration (FDA) has approved apixaban 2.5 mg twice daily at eGFR <15 mL / min and 5 mg twice daily in patients with end-stage renal disease on dialysis since it can be partially dialyzed. However, as European guidelines deny the use of DOAC at eGFR <15 mL / min, avoiding the use of these drugs in such a clinical scenario may be useful (11, 13-16).

VTE prophylaxis after hospital discharge is not recommended for pregnant patients. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient should be individualized, considering concomitant VTE risk factors (17).

The Guide to Thromboprophylaxis in Patients Diagnosed with COVID-19 in Bosnia and Herzegovina publishes the following recommendations (Table 2) (18):

Table 2 **Posthospital therapy and justification of the use of anticoagulant therapy.**

Risk	*Posthospital therapy (post-COVID-19 syndrome)*
Low risk (D-dimer normal, or less than 2x than reference values, no other risk factors)	Neither antiplatelet nor anticoagulant therapy is indicated
Moderate risk (D-dimer greater than 2x than reference values, no other risk factors)	Use of acetylisalicylic acid in prophylactic dose
High risk (D-dimer greater than 2x than reference values and one of the risk factors: immobilization, previous venous thromboembolism, hormone therapy, body weight> 120 kg or body mass index (BMI)> 35 kg / m2), oncological process (take into account the risk of bleeding)	Up to 42 days (maximum 45 days) - enoxaparin 40 mg daily, apixaban 2x2.5 mg daily, rivaroxaban 10 mg daily - control by a competent doctor after the mentioned period; "Off-label" use of this therapy in accordance with clinical experience

The results of a recent study published in the Lancet in early December 2021 on the use of aspirin in hospitalized patients with COVID-19 suggest that aspirin use reduces thromboembolic events, but also increases the incidence of massive bleeding from the digestive tract. Also, Aspirin does not lead to a reduction in 28-day mortality and risk of disease progression toward mechanical ventilation, but does lead to a slight increase in the chances of a patient coming out of the hospital alive within 28 days of hospitalization (19).

Randomised study in the field of extended post-discharge thromboprophylaxis for patients with COVID-19, MICHELLE (Medically Ill hospitalized patients for Covid-19 Thrombosis Extended prophylaxis with Rivaroxaban Therapy, MICHELLE), showed a significant reduction in thrombotic events after discharge from home treatment in preliminary study results and death after 35 days of rivaroxaban 10 mg daily treatment compared with placebo in a population of patients selected for an increased risk of VTE based on the IMPRO scale. Symptomatic and fatal venous thromboembolism occurred in one (0.63%) of 159 patients in the rivaroxaban group compared with eight (5.03%) of 159 patients in the control group (RR 0.13, 95% CI 0.02– 0.99; p = 0.0487); symptomatic venous thromboembolism and all-cause mortality occurred in four (2.52%) of 159 patients in the rivaroxaban group and nine (5.66%) of 159 patients in the control group (RR 0.44, 95% CI 0.14–1.41; p = 0.1696); and a combination of symptomatic venous thromboembolism, myocardial infarction, stroke, or cardiovascular death occurred in one (0.63%) of 159 patients in the rivaroxaban group and nine (5.66%) of 159 patients in the control group (RR 0.11 , 95% CI 0.01–0.87; p = 0.0360). (20). The MICHELLE trial is the first randomized study in the field of extended post-discharge thromboprophylaxis for patients with COVID-19 that has shown clinical benefit. The MARINER trial that did not show an overall statistically significant difference between rivaroxaban and placebo in reducing venous thromboembolism-related death after 45 days post discharge, this extended thromboprophylaxis strategy reduced the rate of symptomatic venous thromboembolism by 56% with no increase in major bleeding. Other ongoing clinical studies are actively assessing extended thromboprophylaxis in patients with COVID-19 (21).

CONCLUSION

A review of the medical literature suggests that any decision to use prophylaxis of thromboembolic incidents in post-COVID-19 syndrome should be based on an individual approach to the patient. Posthospital thromboprophylaxis for up to 42 (45) days is recommended if the D-dimer is greater than 2x the reference value, and if the patient has one of the risk factors (immobilization, previous VTE, hormone therapy, body weight> 120 kg or BMI> 35 kg / m2, oncological process). Daily reading of clinical studies and monitoring and application of the latest guidelines in practice is a condicio sine qua non in the fight against COVID-19. Further medical research is needed to help treat humanity during this pandemic.

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The concept of enhanced recovery after surgery (ERAS) for minimally invasive aorto-coronary bypass in re-do cardiac revascularization: a case report

Koncept unaprjeđenja postoperativnog oporavka nakon minimalno invazivnog zahvata aorto-koronarnog premoštenja kod re-do srčane revaskularizacije: prikaz slučaja

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ABSTRACT

Introduction: enhanced recovery after surgery (ERAS) is a multimodal, multidisciplinary concept of surgical patient care. There is an increasing interest worldwide in the implementation of ERAS programs, especially in cardiac surgery. The primary goal of these patient care concepts is to improve outcomes, shorten the length of hospital stay and reduce treatment costs. Aim: to present a successful implementation of ERAS in cardiac surgery in a high-risk patient who underwent minimally invasive re-do revascularization surgery. Case report: we present a 69-year-old male NYHA IV diabetic patient who underwent a high risk re-do coronary artery bypass surgery. The choice of surgical technique was the minimally invasive approach through the left anterior mini-thoracotomy to decrease the risk of surgical complications. The concept of perioperative care included main parts of enhanced recovery protocols such as early extubation, opioid-sparing analgesia, early mobilization, blood glucose level control and early oral intake. The patient was discharged home early in a stable condition. Conclusion: the multidisciplinary ERAS concept of perioperative patient care in combination with minimally invasive surgical approach enhances the overall recovery of high-risk patients and decreases the length of hospital stay as well as the treatment costs.

Keywords: enhanced recovery after surgery, minimal invasive surgery, re-do coronary artery grafting

SAŽETAK

Uvod: koncept unapređenja postoperativnog oporavka je višemodalni, multidisciplinarni pristup perioperativne njege pacijenta. Širom svijeta ovaj koncept izaziva veliki interes naročito u kardiohirurgiji sa ciljem unapređenja ishoda skraćenjem dužine tretmana i troškova bolničkog liječenja. Cilj ovog prikaza slučaja je uspješna implementacija koncepta unapređenja postoperativnog oporavka kod dijabetičara NYHA IV klase delegiranog za ponovni operativni zahvat revaskularizacije miokarda. Izbor operativne tehnike podrazumijevao je minimalno-invazivni pristup putem prednje lijeve mini-torakotomije kroz četvrti interkostalni prostor u svrhu očuvanja osteoporotične grudne kosti i prevencije postoperativnih komplikacija. Primijenjeni dijelovi protokola ranog oporavka uključivali su ranu ekstubaciju, ne-opioidnu analgeziju, ranu mobilizaciju i rani peroralni unos. Pacijent se otpušta kući optimalno oporavljen devetog postoperativnog dana. Zaključak: multidisciplinarni koncept unaprijeđenog oporavka u kombinaciji sa minimalno invazivnim pristupom aortokoronarno premoštenju putem lijeve prednje minitorakotomije doprinosi ubrzanom oporavku visokorizičnih pacijenata skraćujući boravak u bolnici i troškove bolničkog liječenja.

Ključne riječi: unapređenje postoperativnog oporavka, minimalno invazivna hirurgija, re-do aortokoronarno premoštenje

INTRODUCTION

Enhanced recovery after surgery (ERAS) is a multimodal, multidisciplinary concept of the surgical patient care. In the 1990s, Professor Henrik Kehlet was the first to introduce and popularize the idea of enhanced recovery after surgery, initially in colorectal surgery, presenting improvements in patient's recovery in terms of shortening the length of hospital stay and the costs, the highest burden of health care in low-income countries. Since the initial introduction of ERAS, almost 20 years ago, there has been an increasing interest in further development of programs of the ERAS Society, employing a standardized method to identify evidence-based perioperative care elements to improve outcomes after major surgery (1). These evidence-based modern care elements include essential changes in practice, from overnight fasting to carbohydrate drinks two hours before surgery, non-opioid analgesic regimes, management of fluids to achieve balance, early drains and tubes removal, early mobilization and fluid and food intake on the day of surgery (2). These concepts also included the term of fast-track surgery developed in the USA as a bundle of care elements to improve the recovery after cardiac surgery (3). Over the past decades, the evolution in cardiac surgery has resulted in development of minimal invasive surgical approaches for better comfort of the patient, reduced blood loss, less pain, lower morbidity and shorter recovery time especially in high-risk patients. Minimal invasive surgery in combination with ERAS protocols is designed to reduce the surgical stress and retain the homeostasis. Many studies have proven the reduction in hospital stay by 30% to 50%. These concepts offer a feasible treating option in patients with increased risk of surgery-related complications (2,4). The ERAS pathways were developed to maintain physiological processes in the perioperative period, thus optimizing patient's outcomes without increasing postoperative complications or hospital re-admissions (5). Enhanced recovery after surgery process implementation involves a team consisting of surgeons, anesthesiologist, an ERAS coordinator and staff from units that take care of surgical patients. Successful change of management and ERAS implementation remain as a process that evolves from leadership, climate creation for changes, staff empowerment, implementation of pathways and sustained changes with continued improvement (2,6).

AIM

The aim of this case report is to present a successful implementation of the ERAS concept in cardiac surgery in a high-risk elderly patient who underwent minimally invasive surgery for re-do myocardial revascularization.

CASE REPORT

A 69-year-old male patient was admitted to a Clinic for Cardiovascular Surgery complaining of shortness of breath, symptoms of unstable angina pectoris, with a history of coronary artery bypass surgery nine years before. The patient was classified as NYHA IV with history of arterial hypertension and diabetic disease. The angiography showed patent saphenous graft to right coronary artery and occluded left anterior descendent artery graft. Computed tomography showed an osteoporotic sternal bone with hypertrophic chest wall scarring tissue. Signs of irregular sternal osteosynthesis due to previous sternal wound infection were present on the CT. After the standard protocol of preoperative assessment for cardiac surgery, the patient was scheduled for myocardial re-revascularization via the left anterolateral mini-thoracotomy through the 4th intercostal space (Figure 1) (7).

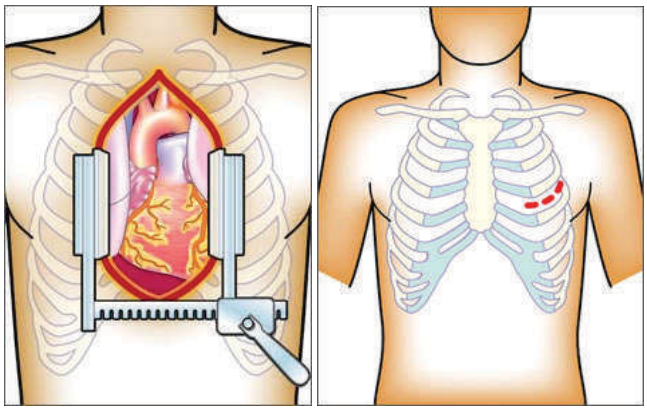

Figure 1 **Conventional approach vs. minimal invasive approach via left anterolateral mini-thoracotomy for coronary artery bypass surgery** (Mid-Atlantic Surgical Associates, Morristown Medical Center, New Jersey)(7).

After the induction of anesthesia by institutional protocols, the patient was intubated with a double lumen tube to achieve left lung isolation in supine position. Heparinization for minimally invasive off pump surgery was provided with unfractioned heparin. After accomplishment of distal anastomosis with great saphenous graft, the space between lung lobes was deliberated and the long saphenous graft was passed (Figure 2). The patient was turned into the lateral decubitus position and proximal anastomosis were performed through the posterior 6th intercostal space, without approach to cardiopulmonary bypass. Patients' hemodynamic stability was maintained with minimal inotropic support. After reversal of heparin, chest tube placement and chest closure, the patient was reintubated with a single lumen endotracheal tube and hemodynamically stable admitted to Intensive care unit. The postoperative drainage was minimal and the patient was extubated by fast-track protocol. The postoperative analgesia management was achieved in accordance with the non-opioid drug protocol. After successful early mobilization and peroral intake establishment, the patient was discharged to the ward. The control computed tomography on the 8th postoperative day showed patent descending aorta to left anterior descending artery bypass and the patient was discharged from hospital treatment on the next postoperative day (Figure 3).

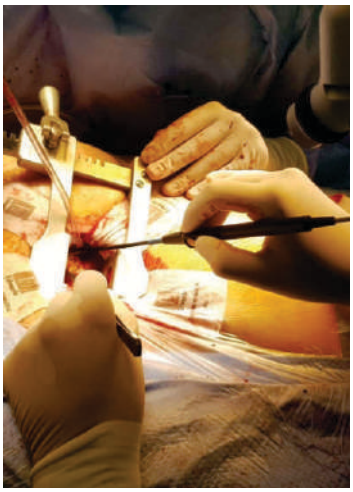

Figure 2 **Accomplishment of distal anastomosis through 5 cm mini-thoracotomy access on left anterior descending artery.**

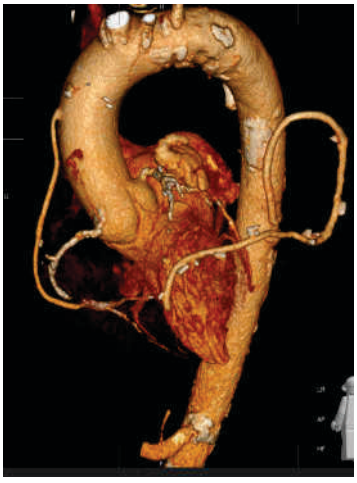

Figure 3 **Postoperative computed angiography of descendent aorta and patent left anterior descending artery graft.**

DISCUSSION

Since almost 20 years of development of ERAS, the concept is still growing in advancement of postoperative care by implementing a multimodal and multidisciplinary concept that decreases the length of hospital stay and the costs. The interest to introducing of ERAS in cardiac surgery has grown over the past years (8). In this case report we presented an elderly NYHA IV classified patient, a candidate for re-do revascularization surgery with an increased risk for postoperative complications regarding the history of diabetes and osteoporotic sternal bone with hypertrophic tissue diagnosed after sternal wound infection during his previous revascularization surgery performed by open heart surgery. Osteoporosis is a systematic disease often seen in elderly patients, which remains to be a major risk factor for sternal postoperative complications after median re-sternotomy. Regarding the fragile nature of osteoporotic sternal bone complicated with tissue hypertrophy median full sternotomy can be associated with a higher risk of sternal dehiscence and wound infection especially in diabetics (9). Recent studies have identified several risk factors for osteoporosis, some of which are complex due to the multiple mechanisms involved, one of them being type 2 diabetes (10). One of the essential parts of enhanced recovery protocols underlie the significance of minimal invasive surgical approach in high-risk patients as in our presented patient. Since the first introduction in 1990s, minimally invasive cardiac surgery has been wide accepted due to patient-related and cost lowering benefits (11, 12). As reported in the study of Reser et al., the advantages of left anterior small thoracotomy (LAST) are less trauma, decreased bleeding, less risk of wound infection, less pain, faster overall recovery and reduced hospital costs. The mid-term results of Reser's study conducted in minimally invasive direct coronary artery bypass (MIDCAB) patients showed an average intensive care unit stay of one day and hospital stay length of eight days, as presented in our case report. Many studies have shown that the outcomes of LAST are comparable with those of conventional sternotomy. As the complications are rare and manageable, the LAST surgical approach is a safe access for coronary artery bypass grafting in a selected group of patients (12). As presented in this case report, our surgical decision of minimally invasive approach instead of large incisions fits perfectly in the ERAS concept. Therefore, we consider that minimally invasive surgery is a feasible option to avoid full sternotomy with the goal to decrease sternum-related complications and possible graft injury by median sternotomy. The rationale to use the ERAS intensive care management in this elderly patient is justified with the expectancy of patient and re-do-surgery-related postoperative complications that could extend the hospital stay. Several studies examining the effects of ERAS have shown not only less postoperative complication, reduced hospital stay and costs also increased patient and staff satisfaction. Williams et al. presented in their trail the results of one-year experience of the first US-based enhanced recovery after cardiac surgery (ERAS Cardiac) program. The results showed significantly improved perioperative outcome in terms of early recovery, cost reduction, and increased patient/staff satisfaction (13).

We implemented standardized ERAS cardiac perioperative components as followed: preoperative patient education, carbohydrate intake two hours before general anesthesia, opioid reduced analgesia, goal-directed insulin infusion, early bowel activation and early mobilization protocol. As recommended by the guidelines of ERAS Society reported by Engelman et al, early extubation strategies within six hours of ICU arrival prevent ventilator-related complications. Early weaning of mechanical ventilation was successfully performed in our patient. This can be achieved with an opioid-sparing pain management. Until recently, intravenous opioids were the cornerstone of analgesia in cardiac surgery. Their use is associated with multiple side effects including sedation, respiratory depression, nausea, vomiting and ileus. The growing interests of implementation of evidence-based approaches of pain therapy include synergistic effects of different types of analgesics to permit lower opioid doses in cardiac surgery patients (14). The studies of Allegranzi et al. and Schiraldi et al. prioritized the importance of ERAS concepts, that include the surgical side infection prevention by perioperative management of hyperglycemia, enhanced nutritional support, and the appropriate antibacterial prevention within the optimal window (15,16). The early peroral intake and perioperative correction of nutritional deficiency leads to avoidance of increased catabolism and results in faster bowel function restoration as presented in the recommendations of ERAS Society by Engelman et al. (14). Recently studies showed that deficient perioperative nutritional status could be a strong predictor of mortality and poor overall survival (17). Therefore, we are underlying through our case report the importance nutritional status

optimization as an essential component of ERAS protocols as reported in the study of Patil and colleagues (18). In summary, these programs are attempted to modify physiological and psychological response to major surgery with the primary goal of a rapid postoperative functional status restoration achieving satisfaction of both patient and staff.

CONCLUSION

Although minimally invasive coronary artery grafting via the left anterior mini-thoracotomy approach is a surgical challenge, it is considered to be an excellent alternative for patients with high risk of perioperative graft injury by median sternotomy. The minimal invasive approach in combination with the ERAS protocols for cardiac surgery has been proven to reduce the length of hospital stay, surgery-related complications and hospital costs. This multidisciplinary concept of surgery and intensive care management enhances the overall recovery of the patient after cardiac surgery.

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Iatrogenic insertion of impression mould into middle ear: a case report

Jatrogeno utiskivanje materijala za uzimanje otiska uha u srednje uho: prikaz slučaja

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ABSTRACT

Introduction: the performance of an ear mould is considered to be a safe and routine procedure. Complications are rare but can occur, namely the entrance of impression material in the middle ear in case of iatrogenic preformation or in a preexistent perforation. Aim: to present a case report on surgical removal of materials that entered the middle ear cavity through the process of making a hearing mould. Case report: an 81-years - old male, with previous medical history of right chronic media, was advised to use a conventional hearing aid. During the process of impression taking, mould materials that not hardened entered his right tympanic membrane perforation. Conclusion: based on our experience from described case, and a literature review, the mould should be made by an experienced person trained in his field. Prevention should be the mainstay of treatment. In case of doubt or middle ear involvement we recommend that the impacted mould impression should be removed by an experienced Otorhinolaryngoilogist under general anesthesia.

Keywords: ear mould, foreign body, hearing aid, middle ear

SAŽETAK

Uvod: uzimanje otiska uha se smatra sigurnim i rutinskim postupkom. Komplikacije su rijetke, ali se mogu pojaviti u obliku prodorom materijala za uzimanje otiska u srednje uho u slučaju jatrogene perforacije ili preegzistirajuće perforacije. Cilj: prikazati slučaj operativnog uklanjanja materijala iz srednjeg uha zaostalog prilikom izrade otiska uha. Prikaz slučaja: 81 – godišnjem muškarcu koji u povijesti ima kroničnu upalu desnog srednjeg je predložena uporaba konvencionalnog slušnog aparata. Tijekom uzimanja otiska uha za slušni aparat, dio kalupa koji nije bio dovoljno čvrst, je ušao u desno srednje uho i uzrokovao napuknuće bubnjića. Zaključak: na osnovu našeg iskustva s opisanim slučajem i pregledom literature, otisak uha bi trebala raditi osoba s iskustvom u tom poslu. Prevencija bi trebala biti glavni oblik tretmana. U slučaju sumnje u prodor materijala u srednje uho preporučamo odstranjivanje materijala koje treba uraditi iskusan otorinolaringolog u općoj anesteziji.

Ključne riječi: otisak uha, strano tijelo, slušni aparat, srednje uho

INTRODUCTION

Unlike the outer ear, foreign bodies of the middle ear are rare. They are usually found as a result of trauma, damage to the eardrum with foreign body transfer to the middle ear, or penetration into the middle ear through an existing perforation (1,2).

In recent times, due to the increase in the number of users of hearing aids; the penetration of silicone materials use in the production of custom earplugs or ear moulds, is more frequent (2,3).The performance of an ear mould is considered to be a safe and routine procedure. The entrance of impression materials in the middle ear can occur in case of iatrogenic perforation or in a preexistent perforation (1). Patients at risk are those with tympanostomy tubes, perforations or retractions pockets of the tympanic membrane, as well as patients with a history of mastoidectomy (2,4,5). Notably, this is often exactly the population that requires either earplugs or hearing aids (4).Commonly, the standard procedure to create custom moulds or earplugs is performed by an audiology assistant. Routinely, a cotton ball is applied in external meatus, followed by colored silicone by means of a pistol (syringe). If the cotton ball is not applied orif it insufficiently occludes the external ear canal, the silicone, can reach the tympanic membrane and beyond.We present a case report on surgical removal of materials that entered the middle ear cavity through the process of making a hearing mould.

CASE REPORT

An81-years-old male, with previous medical history of right chronic media with large tympanic membrane perforation, was advised to use a conventional hiring aid. Two months before he visited our ENT department, during the process of impression taking, mould materials that not hardened entered his right tympanic membrane perforation. When the hardened mould materialwas removed some of it remained in his right middle ear cavity. ENT surgeon attempted to remove the mould in a private office but failed. Hence, the patient was referred to our department. On examination we found right chronic media with subtotal defect of eardrum and through a large perforation we saw that bluish materials filled the lower part of the right middle ear. CT scan was performed and the foreign body was located in the mesotympanon, hypotympanon and extended to internal Eustachian tube (Figure 1,2).

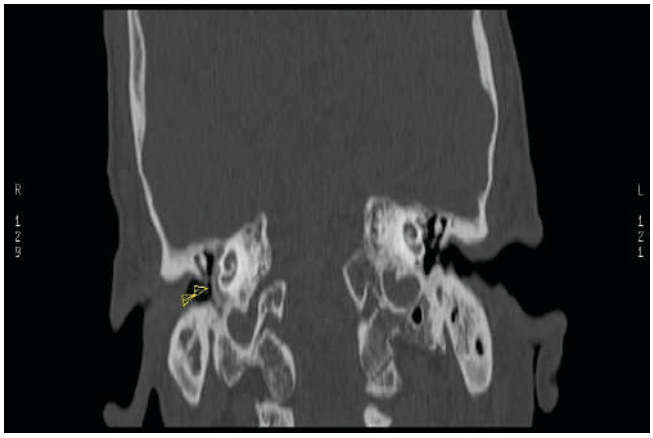

Figure 1 **The finding of temporal bone CT. The density of the foreign body in the middle ear was note din axial view.**

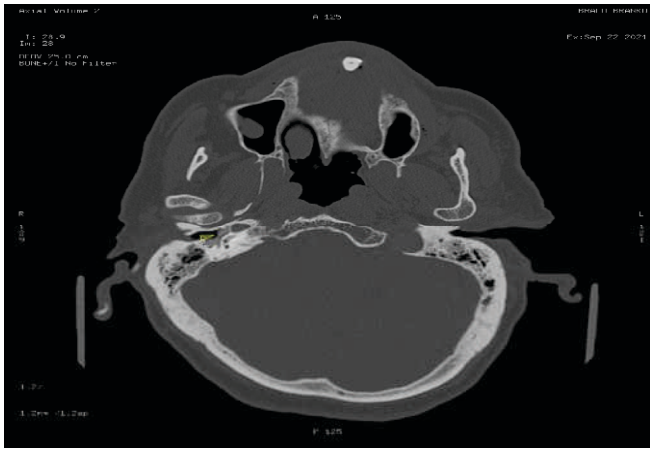

Figure 2 **The finding of temporal bone CT. The densiti of the foreign body in the middle ear was note din coronal view.**

We performed a surgical endoscopic procedure under general anesthesia and via the transcanal approach we carried middle ear foreign materials out carefully using a curved pick (Figure 3,4).

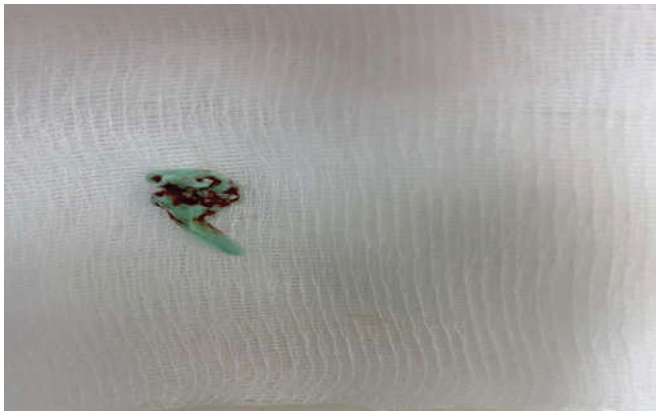

Figure 3**Photography of the removed foreign body.**

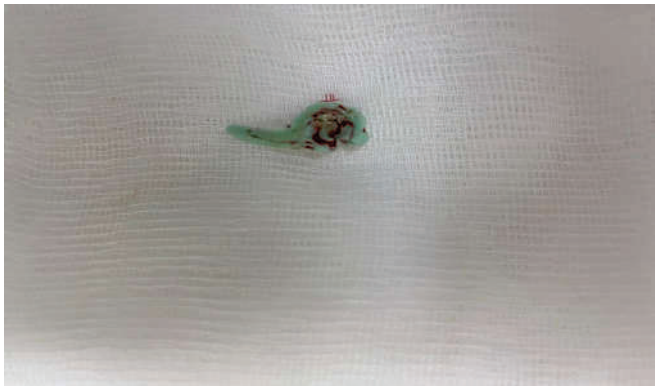

Figure 4 **Photography of the removed foreign body.**

Postoperatively, no vertigo was observed and the patient's hearing impairment was stable to his pre-operative situation.

DISSCUSION

The case presented leads us to some important consideration especially that the making of hearing aid mould is not without complications. This is the first case that we have encountered in our department but there are some case reports and short series descriptions such complications (1,2,6). These complications are rarely reported but are likely to be more frequent. As the number of hearing aid users' increase, reducing inconvenience and complications has become increasingly important.Our case is an example of preexistent perforation of tympanic membrane and resultant pouring of the mould materials into the middle ear cavity. This case highlights some important points for consideration.

Before the introduction of moulding materials into the external meatus it is absolutely necessary both to be informed about the previous history of patient and to perform proper otoscopic evaluation of the tympanic membrane (2,7). Patient at particular risk should beinformed and technician (audiology assistant) should know the patient's condition prior to the procedure (2,3).To prevent complicationswhen ear mould materials is inserted into the external auditory canal, the mould should be placed using otoblock (cotton ball), with care not to insert it too deeply or with too much pressure, and the ear mould should not to be too soft(3,8). If a foreign body

has entered the middle ear cavity, the symptoms related depend on the length of time that it is in the ear. In acute stage, patients present acute pain, tinnitus, hearing loss and dizziness during the process of mould-making (1,5). In the cases of asymptomatic patients the onset of symptoms may take several months. In cases of delayed presentation, symptoms such as perforation, persistent discharge, and conductive hearing loss may mimic chronic otitis media (1,6,9).

A CT scan of the temporal bone may be required to adequately asses the extension of middle ear by impressing material (1,2,5). This radiological examination is required to understand the patient's condition accurately and can be of additive value to determine the appropriate approach for removal.The treatment of retained impression material, in some instances, like the reported cases is surgical removal via the transcanal approach. In other cases well-established surgical techniques may be needed, including meatoplaty, middle ear exploration, atticotomy or tympanoplasty. In some cases it is possible to remove it in the office under microscope control, by an experienced doctor (1,9).

CONCLUSION

In summary, the mould should be made by an experienced person trained in this field. It is important to follow strictly proper protocol during the process of making ear mould impression. Prevention should be the mainstay of treatment. Furthermore there needs to be a close liaison between Otolaryngologist and audiology assistant during the making a mould as well as the event of complications.In case of doubt or middle ear involvement we recommend that the impacted mould impression material should be removed by an experienced Otolaryngologist under general anesthesia.

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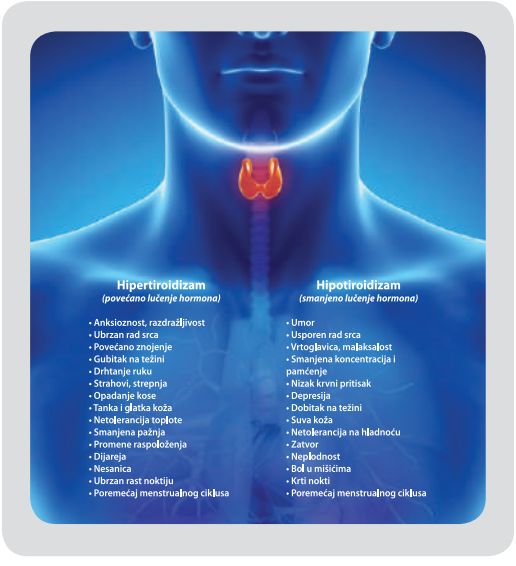

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OPSEG I OBLIK RUKOPISA

Radovi ne smiju biti duži od deset stranica na računaru, ubrajajući slike, grafikone, tabele i literaturu. CD zapis teksta je obavezan (Word of Windows), ili e-mail.
Prored: 1,5: lijeva margina: 2,5 cm; desna margina: 2,5 cm; gornja i donja margina: 2,5 cm.
Grafikone, tabele, slike i crteže unijeti/staviti u tekst rada, tamo gdje im je mjesto, bez obzira u kojem programu su rađene. Cijeli rad obavezno napisati na engleskom jeziku, a sažetak i naslov još i na našem jeziku.
Rad se dostavlja na CD-u, i/ili e-mailom, uz dva štampana primjerka (ako je moguće). CD se ne vraća.

RAD SADRŽI:

NASLOV RADA NA ENGLESKOM JEZIKU
NASLOV RADA NA NAŠEM JEZIKU

Ime i prezime autora i koautora

Naziv i puna adresa institucije u kojoj je autor-koautor/i zaposlen/i (jednako za sve autore), na engleskom jeziku, te na kraju rada navedena adresa kontakt-autora.

Sažetak na našem jeziku, kao i na engleskom - max. 200–250 riječi, s najznačajnijim činjenicama i podatcima iz kojih se može dobiti uvid u kompletan rad.
Ključne riječi - Key words, na našem jeziku i na engleskom, ukupno do pet riječi, navode se ispod Sažetka, odnosno Abstracta.

SADRŽAJ

Sadržaj rada mora biti sistematično i strukturno pripremljen i podijeljen u poglavlja i to:

- **UVOD**
- **MATERIJAL I METODE**
- **REZULTATI**
- **DISKUSIJA**
- **ZAKLJUČAK**
- **LITERATURA**

UVOD

Uvod je kratak, koncizan dio rada i u njemu se navodi svrha rada u odnosu na druge objavljene radove sa istom tematikom. Potrebno je navesti glavni problem, cilj istraživanja i/ili glavnu hipotezu koja se provjerava.

MATERIJAL I METODE

Potrebno je da sadrži opis originalnih ili modifikaciju poznatih metoda. Ukoliko se radi o ranije opisanoj metodi dovoljno je dati reference u literaturi. U kliničko-epidemiološkim studijama opisuju se: uzorak, protokol i tip kliničkog istraživanja, mjesto i vrijeme istraživanja. Potrebno je opisati glavne karakteristike istraživanja (npr. randomizacija, dvostruko slijepi pokus, unakrsno testiranje, testiranje s placebom itd.), standardne vrijednosti za testove, vremenski odnos (prospektivna, retrospektivna studija), izbor i broj ispitanika – kriterije za uključivanje i isključivanje u istraživanje.

REZULTATI

Navode se glavni rezultati istraživanja i nivo njihove statističke značajnosti. Rezultati se prikazuju tabelarno, grafički, slikom i direktno se unose u tekst gdje im je mjesto, s rednim brojem i konciznim naslovom. Tabela treba imati najmanje dva stupca s obrazloženjem što prikazuje; slika čista i kontrastna, a grafikon jasan, s vidljivim tekstom i obrazloženjem.

DISKUSIJA

Piše se koncizno i odnosi se prvenstveno na vlastite rezultate, a potom se nastavlja upoređivanje vlastitih rezultata s rezultatima drugih autora, pri čemu se citiranje literature navodi po važećim Vankuverskim pravilima. Diskusija se završava potvrdom zadatog cilja ili hipoteze, odnosno njihovim negiranjem.

ZAKLJUČAK

Treba da bude kratak, da sadrži najbitnije činjenice do kojih se došlo u radu tokom istraživanja i njihovu eventualnu kliničku primjenu, kao i potrebne dodatne studije za potpuniju aplikaciju. Obavezno navesti i afirmativne i negirajuće zaključke.

LITERATURA - Upute za citiranje - pisanje literature

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

Svaku tvrdnju, saznanje ili misao treba potvrditi referencom. Reference u tekstu treba označiti po redoslijedu unošenja arapskim brojevima u zagradi na kraju rečenice. Ukoliko se kasnije u tekstu pozivamo na istu referencu, navodimo broj koji je referenca dobila prilikom prvog unošenja/pominjanja u tekstu. Literatura se popisuje na kraju rada, rednim brojevima pod kojim su reference unesene u tekst (ulazni broj reference), a naslov časopisa se skraćuje po pravilima koje određuje Index Medicus. Ukoliko je citirani rad napisalo više autora, navodi se prvih šest i doda "et al.".

Vrlo je važno ispravno oblikovati reference prema uputama koje se mogu preuzeti na adresama National Library of Medicine Citing Medicine http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=citmed.TOC&depth=2 , ili International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals:

Sample References http://www.nlm.nih.gov/bsd/uniform_requirements.html.