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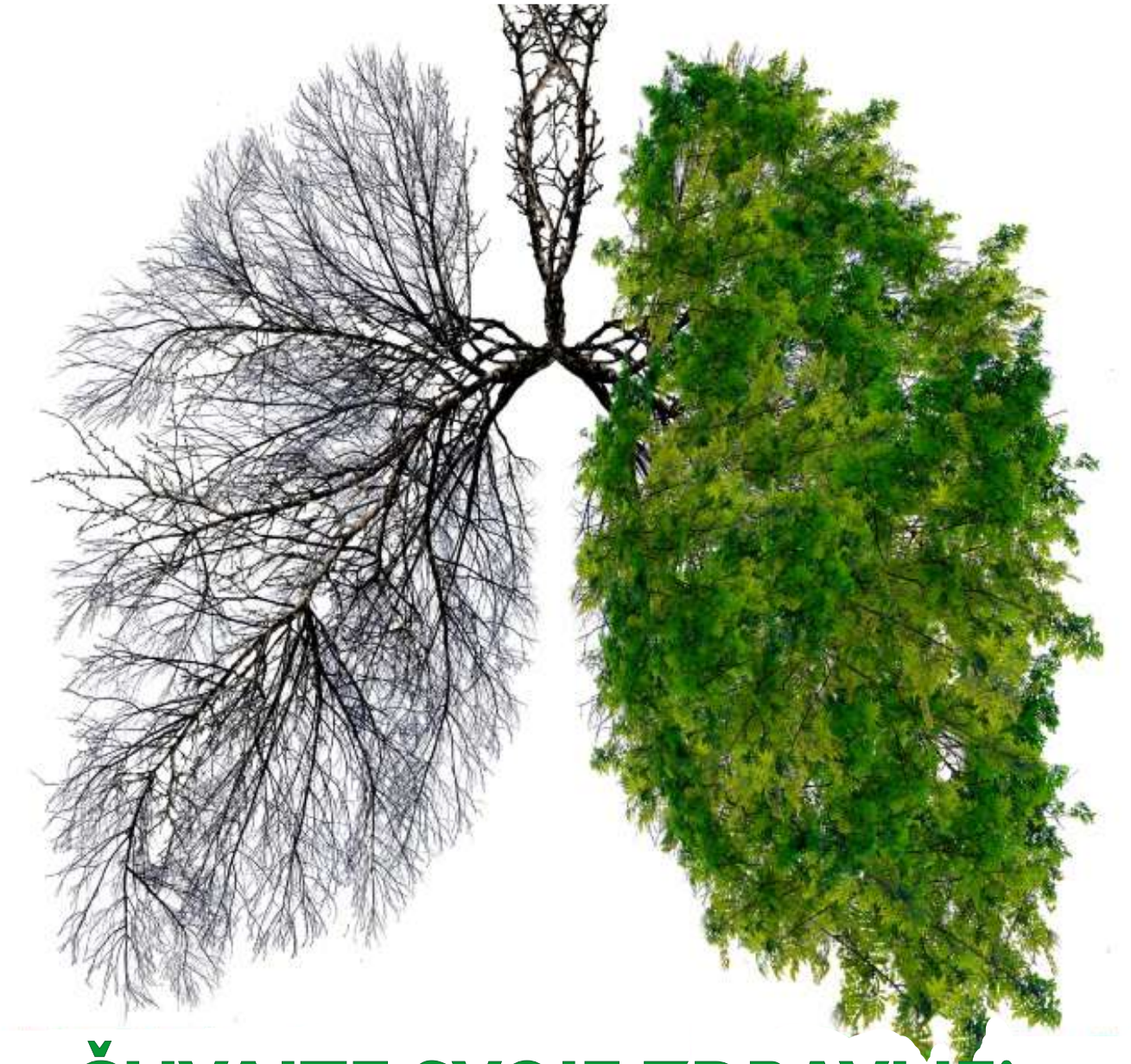

ČUVAJTE SVOJE ZDRAVLJE!

31. maj
Svjetski dan nepušenja

KLINIČKI CENTAR UNIVERZITETA SARAJEVO

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

Bosna i Hercegovina je bila četvrta zemlja u Evropi koja je razvila Nacionalnu verziju HeartScore programa !

Bosnia and Herzegovina version of HeartScore is developed on the languages of the people of Bosnia and Herzegovina i.e. Bosnian, Serbian and Croatian! Program is easy to use and accessible at www.heartscore.org/eu !

Verzija za Bosnu i Hercegovinu razvijena je na jezicima naroda Bosne i Hercegovine, bosanskom, srpskom i hrvatskom! Program je jednostavan za upotrebu preko web stranice www.heartscore.org/eu !

Bosnia Herzegovina	France	Russian Federation
Croatia	Germany *	Spain *
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Novi Centralni medicinski blok - Klinički centar Univerziteta u Sarajevu
New Central Medical Building - Clinical Center University of Sarajevo

Novi Evropski vodič za prevenciju tromboembolizma kod A Fib

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

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

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

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

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

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

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

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

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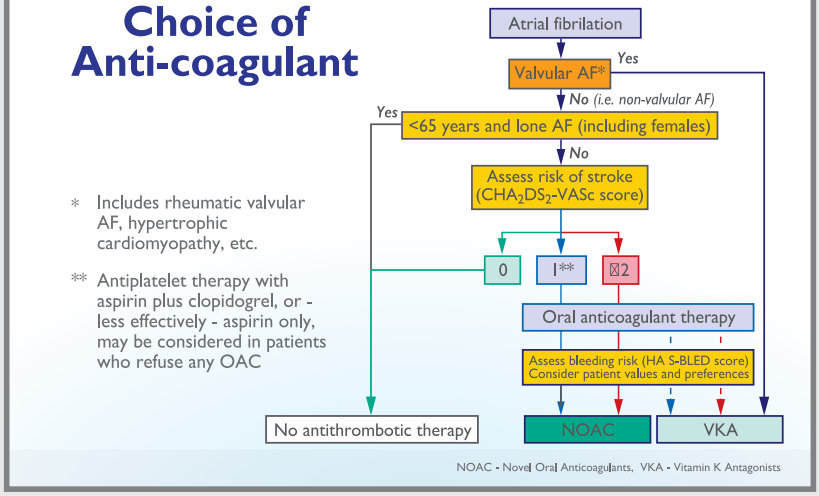
Algoritam antikoagulantne terapije nakon procjene CHA_2DS_2VASc i major risk faktora!

Choice of Anti-coagulant



* Includes rheumatic valvular AF, hypertrophic cardiomyopathy, etc.

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

NOAC - Novel Oral Anticoagulants, VKA - Vitamin K Antagonists

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Case reports

Hypotensive effect of intra-umbilical vein administration oxytocin in the management of retained placenta

Hipotenzivni efekat intraumbilikalne venske aplikacije oksitocina u tretmanu zaostale posteljice

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ABSTRACT

Introduction: retained placenta (RP) affects 0.5% to 3% of women following delivery and it is a major cause of maternal death due to postpartum hemorrhage. Active management of third stage of labor using utero tonics drugs could play an important role in reducing maternal mortality and morbidity. Aim: to compare the hemodynamic parameters and efficacy of the intra-umbilical vein administration of carboprost versus oxytocin in the management of retained placenta by risk factors and doses. Materials and methods: this prospective clinical study with quasi-experimental design (risk factors by medication by doses) was conducted in the period from 2014 to 2016 year at Clinic of Obstetrics and Gynecology, Clinical Center University of Sarajevo. Patients were randomized in 4 groups and 8 subgroups by different medication doses and risk factors. The main outcome variable was expulsion of retained placenta and second outcome variables were: hemodynamic parameters measured 30 minutes after administration of medication and body temperature after expulsion of the placenta, after 12h and 24h. Statistical significance was accepted for p-values, <0.05. Results: the time for placental expulsion was significantly shorter in the intra-umbilical oxytocin groups than in the carboprost groups ($p < 0.001$). The success rates of total expulsion of the placenta by groups were not statistically significant (70% vs. 82% vs. 72% vs. 78%, respectively; $p=0.483$). Oxytocin has a hypotensive effect, and in particular, systolic and diastolic blood pressure were significantly lower in the intra-umbilical oxytocin groups than in carboprost groups at 30 min. after injection ($p<0.001$). Conclusion: oxytocin has a hypotensive effect and carboprost can be used as alternative medication in the management of retained placenta. The success rates of the total expulsion of the placenta are similarly effective comparing intra-umbilical vein administration of carboprost versus oxytocin in the management of retained placenta.

Keywords: retained placenta, oxytocin, carboprost, hemodynamic parameters

SAŽETAK

Uvod: zaostala placenta (ZP) javlja se kod 0,5-3,0% žena koje se porađaju vaginalnim putem i predstavlja veliki uzrok maternalne smrti uzrokujući postporođajnu hemoragiju. Aktivno tretiranje upotrebom uterotonika u trećoj porođajnoj dobi može igrati značajnu ulogu u reduciranju mortaliteta i morbiditeta kod porodilja. Cilj: uporediti hemodinamske parametre i efikasnost intraumbilikalne venske aplikacije različitih terapijskih doza karboprosta i oksitocina u tretmanu zaostale posteljice prema hirurškim i nehirurškimriziko - faktorima. Materijali i metode: sprovedena je prospektivna klinička studija sa kvazi-eksperimentalnim dizajnom (faktor rizika x lijek x doza) u periodu od 2014. - 2016. godine, na Klinici za ginekologiju i porodiljstvo Kliničkog centra Univerziteta u Sarajevu. Pacijentice su randomizirane u 4 grupe i 8 podgrupa prema različitim terapijskim dozama i faktorima rizika. Glavna mjera ishoda je bila ekspulzija zaostale posteljice, te su praćene i zamjenske mjere ishoda: hemodinamski parametri 30 minuta nakon aplikacije lijeka, tjelesna temperatura nakon ekspulzije zaostale posteljice, te nakon 12h i 24h. Prag statističke signifikantnosti postavljen je na konvencionalni nivo $\alpha=0,05$. Rezultati: vrijeme ekspulzije zaostale posteljice je signifikantno kraće kod pacijentica koje su primile oksitocin u poređenju sa karboprostom ($p<0,001$). Ne postoji statistički značajna razlika u stopi uspješnosti totalne ekspulzije zaostale posteljice među grupama: A, B, C i D (70%, 82% 72%, 78%, zaredom; $p=0,483$). Oksitocin ima hipotenzivni efekat i u osnovi, sistolni i dijastolni pritisak je bio signifikantno niži kod ispitanica koje su primile intra-umbilikalnu vensku injekciju oksitocina u poređenju sa karboprostom, 30 minuta nakon aplikacije lijeka ($p<0,001$). Zaključak: oksitocin ima hipotenzivni efekat i karboprost se može koristiti kao alternativni lijek u aktivnom tretmanu zaostale posteljice. Inta-umbilikalna venska aplikacija oksitocina i karboprosta imaju slično efikasne stope uspješnosti totalne ekspulzije posteljice.

Ključne riječi: zaostala posteljica, oksitocin, karboprost, hemodinamski parametri

INTRODUCTION

Obstetric hemorrhage, especially postpartum hemorrhage (PPH), is responsible for more than a quarter of all maternal deaths worldwide (1). One of the main causes of PPH is retained placenta, which affects 0.5% to 3.0% of women following delivery, and a further 15% to 20% of the PPH maternal deaths are due to retained placenta (2,3). It complicates between 0.1 to 2% of births and is usually caused by a failed contraction of the retro placental myometrium (4,5). Established risk factors include prior retained placenta, preterm delivery, prior uterine surgery, previous pregnancy termination, miscarriage or curettage, grand multiparity (greater than five prior deliveries), and congenital uterine anomalies (often unrecognized prior to delivery) (6,7,8,9,10). The term 'retained placenta' is used when the placenta has not been delivered within one hour after the birth of the baby (11). By shortening the time until the expulsion of the adherent placenta, the risk of bleeding and consequent coagulation disorders is reduced with high percentage, with the inestimable value of the non-invasiveness of the intra-umbilical vein injection method. It has been shown that by waiting for up to 30 minutes, spontaneous expulsion of the placenta can be achieved in an additional 42% of cases, and that the percentage of spontaneous expulsion of the placenta after saline infusion is similar to that obtained by waiting (about 40%), therefore saline infusion can be considered a placebo (12). Active management of the third stage of labor involves administration of intravenous oxytocin, early cord clamping, transabdominal manual massage of the uterus, and controlled traction of the umbilical cord. Should this appear insufficient, the next step is usually manual removal of the placenta (13).

Considering the need to find a non-invasive way of treating retained placenta, which would reduce the need for manual lysis, the efforts of researchers are still focused on establishing an effective method of local application of uterotonics, which would achieve adequate contraction of the uterus and expulsion of the placenta.

AIM

This study aimed to compare the hemodynamic parameters and efficacy of the intra-umbilical vein (IUV) administration carboprost versus oxytocin in the management of retained placenta (RP) by risk factors and doses.

MATERIALS AND METHODS

This prospective clinical study with quasi-experimental design 2x2x2 (risk factors by medication by doses) was conducted in the period from 2014 to 2016 year at the Clinic of Obstetrics and Gynecology, Clinical Center University of Sarajevo and included 200 patients. Informed consent was obtained in all cases and risk factors were identified, via a questionnaire, additionally. We studied all the patients prospectively and by computerized randomization. All patients underwent a gynecological sonography with Voluson E6 Ultrasound, General Electric Healthcare (GEHC), upon admission to the clinic. Patients were randomized in 2 groups by surgical risks factors and 8 subgroups by medication and doses. The inclusion criteria were: women beyond 34 weeks of gestation with a singleton living fetus, achieved vaginal delivery, and failed to deliver the placenta after 30 minutes of active management of the third stage of labor (intravenous administration of 5 IU of Syntocinon in the presence of an intact umbilical cord, fundal pressure and controlled cord traction after 5, 10 and 15 minutes) in all patients. The exclusion criteria were: uterine atony and bleeding > 500 ml; maternal hemodynamic instability (pulse ≥ 120 b.p.m., or a decrease in diastolic blood pressure of more than 20mm Hg after delivery, associated medical disorders (e.g., cardiac disease, anemia, hypertension and diabetes), multiple pregnancy. The main outcome variable was expulsion of retained placenta and second outcome variables were: hemodynamic parameters measured 30 minutes after administration of medication, and body temperature after expulsion of the placenta, after 12h and 24 h.

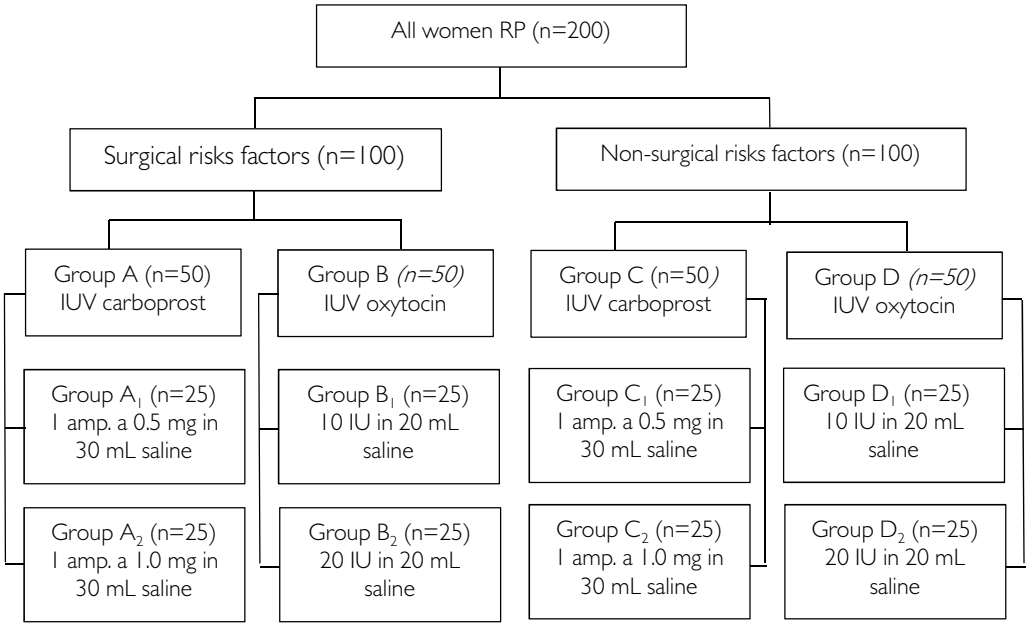

Figure 1 Abbreviations: *RP* retained placenta, *IUV* intra-umbilical vein, *IU* international unit.

A retained placenta was diagnosed when separation did not occur 30 minutes after delivery and UVI is followed. The appropriate solution was injected into the umbilical vein for 15 seconds by type of treatment and the umbilical cord was clamped again. At 5 and 10 minutes after administration of the medication, or in the case of clinical signs of placental separation, an attempt to deliver the placenta was made. If the final attempt to deliver the placenta failed, manual removal was performed by the usual maneuver under general anesthesia.

Statistical analysis

The results are presented as the means and standard deviations (±SD) for numerical variables and as numbers and percentages for categorical variables. Statistical significance for differences was analyzed using the One-Way ANOVA, One -Way ANCOVA, Kruskal Wallis H test. Post-hoc analysis was performed using Independent Sample T test or Mann Whitney U test with Bonferroni correction for multiple testing. Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS Release 19.0; SPSS Inc., Chicago, Illinois, United States of America) software. Statistical significance was accepted for p-values< 0.05.

RESULTS

The demographic and obstetric data of the study groups were comparable, except for the level of education ($p<0.05$) and term or preterm delivery ($p<0.01$). The level of education was higher in group D compared with group A (30% vs.6%, respectively). The frequency of preterm delivery was higher in group A compared with groups B and D (14% vs. 0% vs. 0%, respectively).

Table 1 **Clinical characteristics of patients.**

	Surgical risk factors		Non – surgical risk factors		
	Group A (n=50) UVI carboprost	Group B *(n=50)* UVI oxytocin	Group C (n=50) UVI carboprost	Group D *(n=50)* UVI oxytocin	P-value
Maternal age (y)[a]	27.7±3.7	26.5±4.7	28.7±5.2	26.2±5.4	*>0.05*
Gestational age (weeks)[a]	38.4±3.1	39.0±1.0	38.8±1.4	*39.0±1.0*	*>0.05*
Birth length (cm)[c]	52.0 (50 to 53)	52.0 (51 to 53)	52.0 (52 to 53)	51.0 (50 to 53)	*>0.05*
Birth weight (grams)[c]	3400 (3000 to 3825)	3500 (3175 to 3.862)	3425 (2987 to 3912)	*3700 (3200 to 3950)*	*>0.05*

Data were presented as follows: [a] mean±SD, [b] number or percentage (%), [c] median (IQR).

The time for placental expulsion was significantly shorter in the intra-umbilical oxytocin groups than in the carboprost groups ($p<0.001$). The success rates of total expulsion of the placenta by groups were not statistically significant (70% vs. 82% vs. 72% vs. 78%, respectively; $p=0.483$) (Table 2).

Table 2 **The results for the main outcome of the study and success rates by groups.**

	Surgical risk factors		Non – surgical risk factors		
	Group A (n=50) UVI carboprost	Group B *(n=50)* UVI oxytocin	Group C (n=50) UVI carboprost	Group D *(n=50)* UVI oxytocin	P-value
Placental expulsion (min)[a] *(years)*[a]	8.5 (7.0 to 9.0)	6.0 (4.9 to 7.0)	8.0 (6.5 to 9.0)	6.0 (4.5 to 8.0)	*<0.001*
Placenta expelled spontaneously[b]	35 70.0	41 82.0	36 72.0	39 78.0	>0.05
Success rate (%)	70.0	82.0	72.0	78.0	>0.05

Data were presented as follows: [a] median (IQR), [b] number or percentage (%)

Oxytocin has a hypotensive effect, and in particular, systolic BP was significantly lower in the intra-umbilical oxytocin groups than in carboprost groups at 30 min. after injection, F(3,195)=44.977, p<0.001, partial η^2=0.409. The systolic BP was lower in the group B (M=111.2±0.6), compared with groups: A (M=119.3±0.6; p<0.001), C (M=118.5±0.6; p<0.001) and D (M=113.9; p<0.001). The systolic BP was lower in the group D compared with groups: A (p<0.001) and C (p<0.001) (Figure 1).

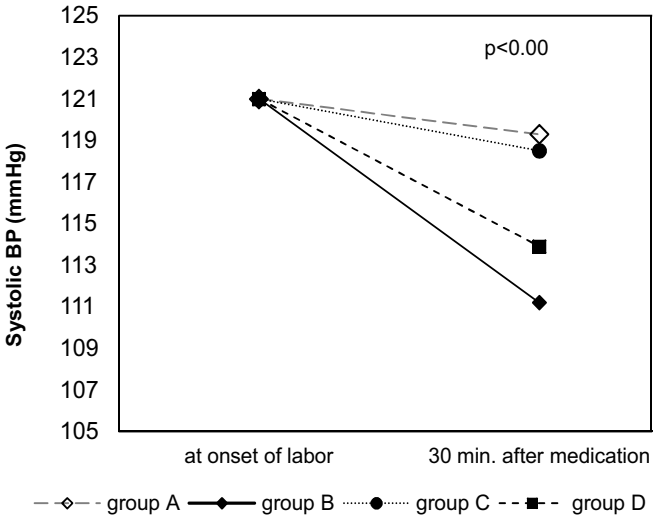

Figure 2 **Adjusted means for 30 min. after medication systolic BP (mmHg)) with systolic BP at onset of labor as a covariate (p<0.001).**

Table 3 **Adjusted and unadjusted means and variability for systolic BP measured 30 min. after medication (mmHg) with systolic BP at onset of labor as a covariate by subgroups (p<0.001).**

Groups	Adjusted means		Unadjusted means		$F_{7,191}$	p	η^2_p
	M	SE	M	SE			
A_1	120.6	1.1	119.4	0.8			
A_2	120.4	1.0	119.2	0.8			
B_1	111.0	1.2	110.4	0.8			
B_2	115.6	1.1	112.1	0.8	19.445	<0.001	0.416
C_1	118.0	1.1	118.5	0.8			
C_2	114.4	1.2	118.4	0.8			
D_1	112.4	1.0	113.7	0.8			
D_2	113.6	1.0	114.2	0.8			

M – mean; SE – standard error; F – value of test; η^2_p –effect size.

Similarly, the diastolic BP was significantly lower in the intra-umbilical oxytocin groups than in carboprost groups at 30 min. after injection, F (3.195)=17.985, p<0.001, partial η^2=0.217. The diastolic BP was lower in the group B (M=77.8±0.3), compared with groups: A (M=79.7±0.3; p<0.001) and C (M=80.4±0.3; p<0.001). The diastolic BP was lower in the group D (M=78.7±0.3), compared with groups: A (p=0.041) and C (p<0.001) (Figure 3).

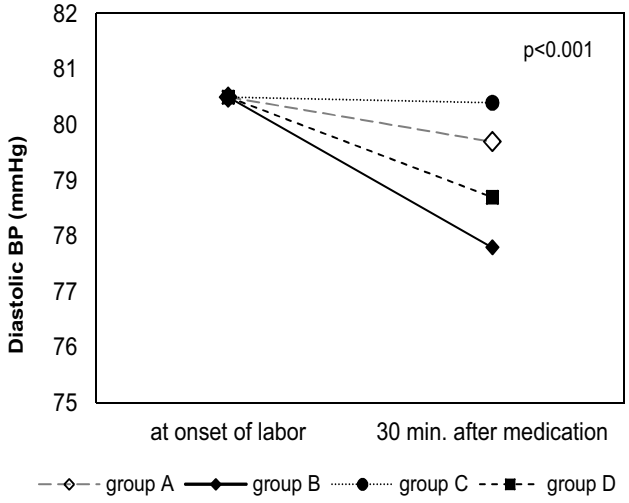

Figure 3 **Adjusted means for 30 min. after medication diastolic BP (mmHg)) with diastolic BP at onset of labor as a covariate (p<0.001).**

Table 4 **Adjusted and unadjusted means and variability for diastolic BP measured 30 min. after medication (mmHg) with diastolic BP at onset of labor as a covariate by subgroups (p<0.001).**

Groups	Adjusted means		Unadjusted means		$F_{7,191}$	p	η^2_p
	M	SE	M	SE			
A_1	80.4	0.5	80.0	0.4			
A_2	81.0	0.4	79.4	0.4			
B_1	80.4	0.4	77.9	0.4			
B_2	80.2	0.6	77.8	0.4	9.091	<0.001	0.250
C_1	77.5	0.5	80.2	0.4			
C_2	76.4	0.5	80.6	0.4			
D_1	78.5	0.4	78.1	0.4			
D_2	78.9	0.6	79.4	0.4			

M – mean; SE – standard error; F – value of test; η^2_p –effect size.

After adjustment for body temperature at onset of labor, there was not a statistically significant difference in body temperature after expulsion of the placenta (p>0.05), after 12h (p>0.05), and 24h (p>0.05) between the groups.

DISCUSSION

This study compared the hemodynamic parameters and efficacy of the intra-umbilical vein administration carboprost versus oxytocin in the management of retained placenta by surgical and non-surgical risk factors and different doses of medication. In placenta adherens, oxytocics have been used to contract the retro-placental myometrium. However, if injected locally through the umbilical vein, they bypass the myometrium and perfuse directly into the venous system (14). In the meta-analysis by Mori R, et al., which included 1,118 subjects, there is also no recommendation for the routine use of oxytocin or other uterotonics through the umbilical vein until new evidence is available (15). The hemodynamic effects of oxytocin have been shown to cause systemic vasodilatation with hypotension, tachycardia with increased cardiac output, resulting in hypotension (16,17). It is shown that chlorobutanol, the one of the excipients in the oxytocin solution, affect the cardiovascular system and produce peripheral vasodilatation and reduced cardiac contractility (18,19). Previous studies have shown that oxytocin and carbetocin have hemodynamic side effects of comparable magnitude and duration, whereas the uterotonic effect of carbetocin is documented to be significantly longer than that of oxytocin (20). Oxytocin had a vasodilatory effect on small and peripheral arteries and increased the left cardiac ventricular ejection time (21).

In the randomized clinical study of Elfayomy AK, systolic blood pressure was significantly lower in the intra-umbilical oxytocin group at 30 and 60 min after injection (22). Nonetheless, diastolic blood pressure was significantly lower in the intra-umbilical oxytocin group than in the carbetocin group at 30 min. In our study, systolic and diastolic blood pressure was significantly lower in the intra-umbilical oxytocin groups than in carboprost groups at 30 min. after injection, also.

In the study of Habek, et al, the success rate when using the Pg F2**α** analogue of carboprost (0.5 mg, 20 ml of saline) was 86%, comparing with oxytocin (20 IU) 80% (23). In the study of Harara et al., placental separation was achieved in 80% of cases with the use of 0.8 mg of misoprostol in 30 ml of saline, comparing with 73% in group of 20 IU of oxytocin (24). The time to separation of the placenta was almost twice as short in the prostaglandin group comparing with oxytocin group (7 min. vs. 13 min.). Delayed expulsion of 30 min was considered as retained placenta, after the birth of the fetus.

In our study, the subgroups that received oxytocin 20 IU in 20 ml saline, with both surgical and non-surgical risk factors, had the highest frequency of placental expulsion (80-88%) compared to the groups that received carboprost with doses 0.5 mg or 1.0 mg in 30 ml saline (68-76%). However, the difference did not reach the level of statistical significance. In our study, after adjustment for body temperature at onset of labor, there was not a statistically significant difference in body temperature after expulsion of the placenta, after 12h, and 24h between the groups.

In a recent review of the Cochrane meta-analysis of the effectiveness of umbilical vein injection, Nardin, et al., indicate that there is a need and justification for further research in this area (12).

CONCLUSION

Oxytocin has a hypotensive effect and carboprost can be used as alternative medication in the management of retained placenta. The success rates of the total expulsion of the placenta are similarly effective comparing intra - umbilical vein administration carboprost versus oxytocin in the management of retained placenta.

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Evaluation of preferred primary and secundary surgical procedures in the pressure sores reconstruction

Evaluacija preferiranih primarnih i sekundarnih hirurških procedura u rekonstrukciji dekubitalnih ulceracija

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ABSTRACT

Introduction: pressure sores represent the complex reconstructive problem. Successful treatment has to be clearly defined by clinical guidelines in the selection of the most optimal procedures, with long-term benefit, and the possibility of alternative secondary procedures for potential relapses. Hypothesis: fasciomyocutaneous flaps are preferred method in primary and secondary pressure sores reconstruction. Aim: establish the algorithm of preferred surgical procedures for pressure sores reconstruction and potential relapses. Materials and methods: retrospective-descriptive clinical study was used to evaluate the modalities of preferred pressure sores reconstruction in primary and secondary procedures in 37 cases of different localizations, treated at the Clinic of Reconstructive and Plastic Surgery, Clinical Center University of Sarajevo, in the period from 2018 to 2021, with the evaluation of gender and age distribution, pressure sores localization and indicated surgical procedures Results: statistically significant difference was evaluated in gender distribution, with a higher male representation, (73.0%); the mean age was 52.8±15.5 years. Statistically significant correlation was confirmed between pressure sores localization and primary reconstruction modality $\chi2=139,120$; $p=0,005$. $\chi2$-test and correlation analysis confirmed no statistically significant correlation between the type of secondary procedure and relapse occurrence, $\chi2=10,833$; $p=0,979$, and also between the type of secondary procedure and relapse localization $\chi2=21,083$; $p=0,716$. Conclusion: fasciomyocutaneous flaps are the preferred method of pressure sores reconstruction in primary and secondary surgical procedures, with the possibility of providing adequate soft tissue cover for defects from different predilection sites. Defining the algorithm of available fasciocutaneous flaps for every potential predilection site, and alternative simpler procedures as an important clinical guidelines in everyday practice.

Keywords: pressure sores, reconstruction, relapse, algorithm

SAŽETAK

Uvod: dekubitalne ulceracije predstavljaju složen rekonstruktivni problem. Uspješno liječenje mora biti jasno definirano kliničkim smjernicama u odabiru najoptimalnijih rekonstruktivnih procedura, sa dugoročnim benefitima i mogućnošću primjene alternativnih hirurških procedura u slučajevima recidiva. Hipoteza: fasciomiokutani režnjevi su preferirani metod u primarnim i sekundarnim rekonstrukcijama dekubitalnih ulceracija. Cilj: utvrditi algoritam preferiranih hirurških procedura u tretmana dekubitalnih ulceracija u odnosu na primarnu lokalizaciju i potencijalnu pojavu recidiva. Materijal i metode: retrospektivno-deskripitiva klinička studija je primjenjena u cilju evaluacije modaliteta preferirane rekonstrukcije dekubitalnih ulceracija u primarnim i sekundarnim procedurama na 37 slučajeva različitih primarnih lokalizacija, tretiranih na Klinici za rekonstruktivnu i plastičnu hirurgiju Kliničkog centra Univerziteta u Sarajevu, u periodu od 2018. do 2021. godine, sa evaluacijom polne i dobne distribucije, lokalizacije dekubitalnih ulceracija i primjenjenih hirurških modaliteta pri primarnoj i sekundarnoj rekonstrukciji. Rezultati: utvrđena je statistički značajna razlika u spolnoj distribuciji, sa većom zastupljenošću muškaraca (73,0 %); Prosječna dob bila je 52,8±15,5 godina. Potvrđena je statistički značajna korelacija između lokalizacije dekubitusa i modaliteta primarne rekonstrukcije $\chi2=139,120$; $p=0,005$. $\chi2$-test i analiza korelacije potvrdili su da nema statistički značajne korelacije između tipe sekundarne hirurške procedure i pojave relapsa, $\chi2=10,833$; $p=0,979$, kao ni statistički značajne razlike između tipa rekonstruktivne hirurške procedure i lokalizacije recidiva, $\chi2=21,083$; $p=0,716$. Zaključak: fasciomiokutani režnjevi su prefirana metoda rekonstrukcije dekubitalnih ulceracija u primarnim i sekundarnim hirurškim procedurama, sa mogućnošću obezbjeđenja adekvatnog mekotkivnog pokrova za dekubitalne ulceracija sa različitih predilekcionih mjesta. Definiranje algoritma dostupnih režnjeva sa svako predilakcijsko mjesto i alternativnih jednostavnijih procedura je značajna klinička smjernica u svakodnevnoj kliničkoj praksi.

Ključne riječi: dekubitalna ulceracija, rekonstrukcija, recidiv, algoritam

INTRODUCTION

The occurrence of pressure sores is one of the ultimate signs of hospital health care quality, so this complex clinical entity should be observed whenever possible from the standpoint of prevention, due to the fact that appropriate prophylaxis avoids potential complications and improves the quality of life (1,2). This is especially important for patients with comorbidities and severe general conditions, which often makes planned reconstructive surgery impossible, EPUAP (European Pressure Ulcer Advisory Panel) classification system defines pressure sores as soft tissue defects resulting from the simultaneous action of pressure, shear, or friction at predilection sites (3,4,5). Pressure sores are classified to the depth of tissue infiltration into stages, which determine the treatment plan and expected outcomes (6). Conservative treatment is the method of choice for the early stages of pressure sores, with a tendency to spontaneous healing during the adequately applied supportive measures (7). Pressure sores of the third and fourth stages, with infiltration of deeper anatomical layers, rarely have a tendency to spontaneous healing, and surgical treatment is considered as preferred method (8). There is a whole range of available reconstructive procedures for pressure sores of different localizations, which donor site and proper design have to provide the space for the alternative reconstructive options in cases of relapses (9,10). Fasciomyocutaneous flaps are the golden rule of pressure sores reconstruction because these types of tissue defects of minimal dimensions on the skin surface can be associated with the involvement of deeper anatomical structures, which requires a serious approach in primary, as well as secondary reconstructive procedures (11,12).

AIM

Establish the algorithm of preferred primary and secondary reconstructive procedures depending on the pressure sores primary localization and available secondary reconstructive procedures in cases of relapses as a guide in clinical practice.

MATERIALS AND METHODS

We assessed 37 patients with pressure sores of different localization treated at the Clinic of Reconstructive and Plastic Surgery, Clinical Center University of Sarajevo, in the period from 2018 to 2021, with the evaluation of the primary pressure sores localization, gender and age distribution, type of primary surgical procedures, occurrence of the relapses and types of secondary surgical procedures. Statistical data processing was done through IBM SPSS Version 25.0. Results were presented in form of tables and charts as the total number of cases, percentage, mean with standard deviation and range, depending on the data type. The analysis of differences between observed groups was conducted using the χ2-square test, while the possible influence of independent variables was tested using the Spearman rank correlation and linear regression model. The results of all tests were considered statistically significant at the confidence level of 95%.

Study inclusion criteria: patients of all ages and genders with pressure sores of different primary localization, patients with indication for primary pressure sores reconstruction, patients with relapses after primary reconstruction, and patients with indication for secondary procedures.

Study exclusion criteria from the study: patients primarily treated in other hospital facilities, patients with pressure sores treated with conservative methods, patients without the possibility of postoperative evaluation.

RESULTS

The research included 37 patients who met the criteria for inclusion in the study. Out of the total number of estimated cases in this research, 27 (73.0%) were male and 10 (27, 0%) were female (Table 1). Analysis of gender representation showed a statistically significant difference ($p < 0.05$) in terms of higher male representation in patients with pressure sores.

Table 1 **Gender distribution of the estimated group with pressure sores.**

Gender		
	N	%
Male	27	73,0
Female	10	27,0
Total	37	100,0

The mean age of the patients in the sample was 52.8 ± 15.5 years with the youngest patient at the age of 29 and the oldest at the age of 84 years, standard deviation (SD) was 15,472 (Table 2, Figure 1).

Table 2 **Representation of age distribution.**

$\bar{x}$	52.78
SD	15.47
Minimum	29
Maximum	84

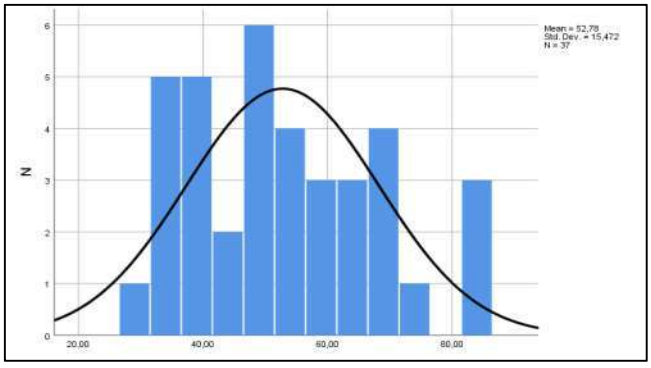

Figure 1 **The average age of the evaluated group.**

Assessment of the indicated primary reconstructive procedures in patients with pressure sores of different primary localizations (Table 3, Figure 2) evaluated that gluteus maximus fasciomyocutanous flap has been used in the majority of cases for sacral (6 cases, 40%) and ishiadic pressure sores (6 cases, 40%).), and in 2 cases (13.3%) for gluteal reconstruction. This type of

reconstruction was indicated in 1 case (6.7%) for combined ischial/gluetal pressure sores. Tensor fascie latae (TFL) myocutaneous flap was indicated in 3 cases for pressure sores reconstruction on the trochanter (60%), which is the method of choice for this anatomical localization, and in 2 cases (40%) for ischial pressure sores reconstruction. Biceps femoris fasciomyocutaneous flap was indicated in the highest percentage for the ischial pressure sores (4, cases, 80%), which is also the method of choice for this anatomical region, and in 1 case (20%) for the reconstruction combined ischial/gluteal localization. V-Y fasciomyocutaneous flap was used in 1 case (33.3%) for the trochanter, ischial, and combined ischial/gluteal pressure sores. Combined fasciomyocutaneous flaps were indicated for complex and combined pressure sores of different anatomical localizations, TFL / gluteus maximus fasciomyocutaneous flap indicated in 2 cases for the trochanter/sacral pressure sores reconstruction (66.7%), and in 1 case (33.3%)) for the ischial/sacral reconstruction. The other types of combined fasciomyocutenous flaps, biceps femoris/gluteus maximus, and TFL / quadriceps femoris were used only in 1 case for the ischial, and trochanter/ischial reconstruction.

Primary closure, otherwise contraindicated in pressure sore reconstruction due to complexity and potential infiltration of deeper anatomical structures, indicated in 1 case for the superficial gluteal pressure sore. Skin transplantation, reconstruction modality, used in 3 cases, heel pressure sores (2 cases; 66.7%), and in 1 case (33.3%) for the reconstruction of superficial ischial pressure sore.

χ2-square test and correlation analysis confirmed a statistically significant correlation between surgical procedure and pressure sores localization ($p < 0.05$).

Table 3 **Correlation between pressure sore localization and primary reconstruction modality.**

			Primary reconstruction									
			Gluteus max. flap	TFL flap	Biceps femoris flap	V-Y flap	TFL/gluteus max. fap	Bic.fem/gl.max flap	TFL/quadr. femoris flap	Primary closure	Skin grafting	Total
Localization	Sacrum	N	6	0	0	0	0	0	0	0	0	6
		%	40.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	16.2
	Tro chanter	N	0	3	0	1	0	0	0	0	0	4
		%	0.0	60.0	0.0	33..3	0.0	0,0	0,0	0,0	0,0	10.8
	Gluteus	N	2	0	0	0	0	0	0	1	0	3
		%	13.3	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	8.1
	Ischium	N	6	2	4	1	0	1	0	0	1	15
		%	40.0	40.0	80.0	33.3	0.0	100.0	0.0	0.0	33.3	40.5
	Heel	N	0	0	0	0	0	0	0	0	2	2
		%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	66.7	5.4
	Ischium/gluteus	N	1	0	1	1	0	0	0	0	0	3
		%	6.7	0.0	20.0	33.3	0.0	0.0	0.0	0.0	0.0	8.1
	Tro chanter/ischium	N	0	0	0	0	0	0	1	0	0	1
		%	0.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0	0.0	2.7
	Ischium/sacrum	N	0	0	0	0	1	0	0	0	0	1
		%	0.0	0.0	0.0	0.0	33.3	0.0	0.0	0.0	0.0	2.7
	Trochanter/sacrum	N	0	0	0	0	2	0	0	0	0	2
		%	0.0	0.0	0.0	0.0	66.7	0.0	0.0	0.0	0.0	5.4
Total		N	15	5	5	3	3	1	1	1	3	37
		%	40.5	13.5	13.5	8.1	8.1	2.7	2.7	2.7	8.1	100.0

χ2=139,120; df=64; p=0.0001; r=0.456; p=0.005.

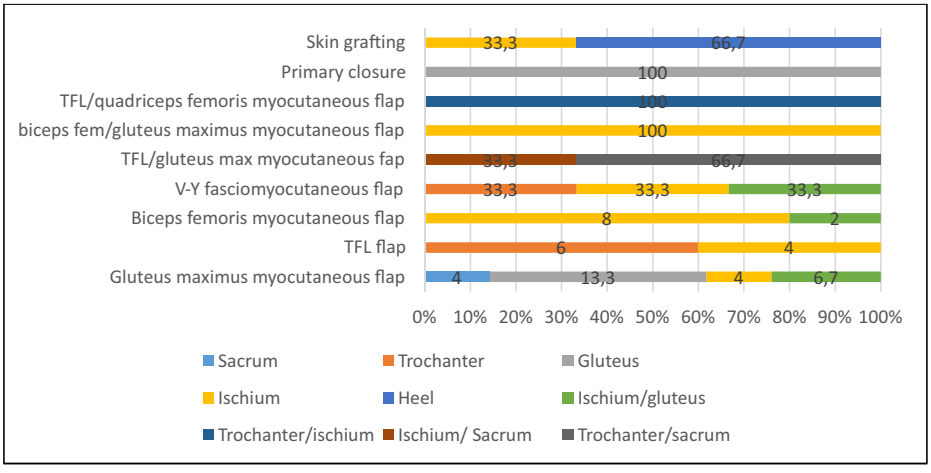

Figure 2 **Percentage distribution of primary surgical procedures.**

Assessment of the relapses after a primary surgical procedure of the pressure sores (Table 4, Figure 3), evaluated the highest percentage after reconstruction with TFL and biceps femoris fasciomyocutaneous flaps, 3 cases each (60.0%). In 2 cases we evaluated relapse after pressure sores reconstruction with gluteus maximus fasciomyocutaneous flap (13.3%), compared to the total of 15 patients (40.5%) operated with this method. After V-Y fasciomyocutaneous flap reconstruction the relapse were evaluated in 2 cases (66.7%) The occurrence of relapse was also observed in 1 case (33.3%) after pressure sores reconstruction with skin grafting. In our study group of 37 cases, relapses were assessed in 11 cases (29.7%).

χ2-test and correlation analysis confirmed no statistically significant correlation between the type of primary reconstruction and relapse after primary procedure.

Table 4 **Relapse distribution to the type of primary surgical procedure.**

			Relapse		Total
			Yes	No	
Surgical modality	Gluteus max.	N	2	13	15
	fasciomyocutaneous flap	%	13.3	86.,7	40.5
	TFL myocutaneous flap	N	3	2	5
		%	60.0	30.0	13.5
	Biceps femoris fasciomyocutaneous	N	3	2	5
	Flap	%	60.0	30.0	13.5
	V-Y fasciomyocutaneous flap	N	2	1	3
		%	66.7	33.3	8.1
	TFL/gluteus maximus fasciomyocutaneous flap	N	0	3	3
		%	0,0	100.0	8.1
	Biceps femoris/gluteus maxims	N	0	1	1
	Fasciomyocutaneous flap	%	0.0	100.0	2.7
	TFL/quadriceps myocutaneous	N	0	1	1
	Flap	%	0.0	100.0	2.7
	Primary closure	N	0	1	1
		%	0.0	100.0	2.7
	Skin grafting	N	1	2	3
		%	33.3	66.7	8.1
Total		N	11	26	37
		%	29.7	70.3	100.0

χ2=10.833; df=8; p=0.211; r=0.004; p=0.979.

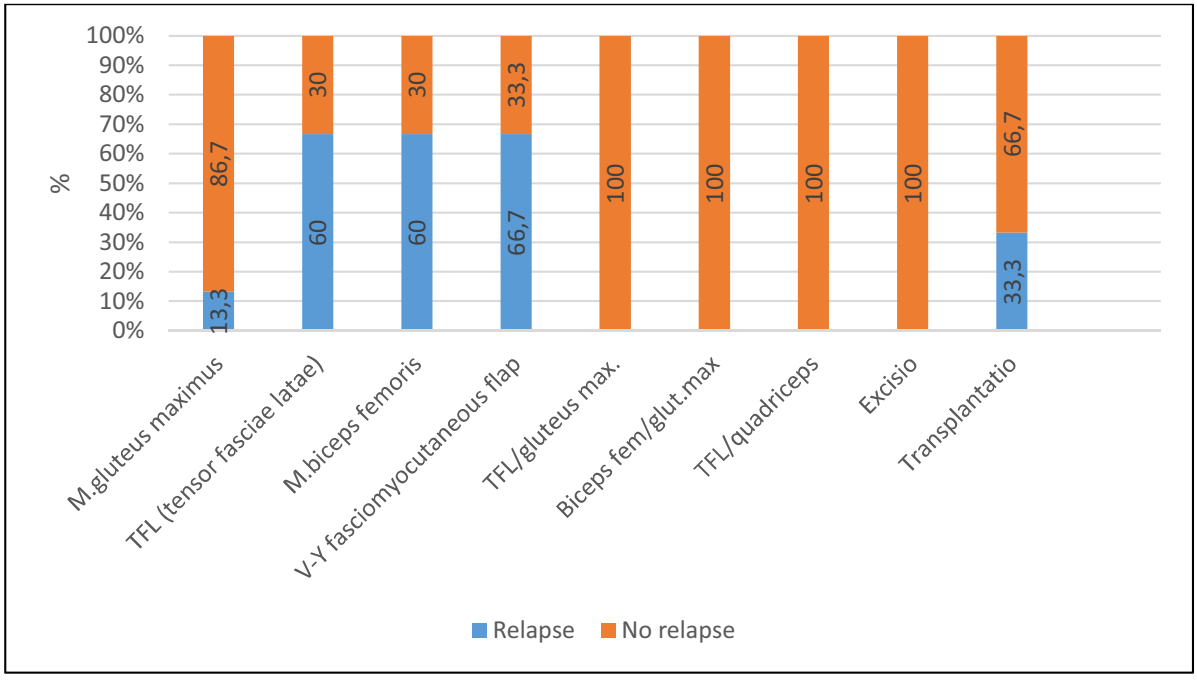

Figure 3 **Percentage distribution of relapses.**

Secondary surgical procedures were presented by evaluation of 11 cases of relapse (Table 5, Figure 4) (Table 5, Figure 4). Biceps femoris fasciomyocutaneous flap was used in most cases (3 patients), for the trochanter, gluteal, and ischial pressure sores reconstruction (1 case, 33.3%, for each anatomical localization). Gluteus maximus fasciomyocutaneous flap was indicated in two cases for the secondary pressure sores reconstruction, ischial and combined ischial/gluteal anatomical localization (1 case, 50.0% each). Rotation fasciocutaneous flap was used in 2 cases for sacral and ischial pressure sores (1 case each, 50.0%). The other surgical modalities for the secondary pressure sores reconstruction were indicated in a small number of cases, V-Y fasciomyocutaneous flap and necrectomy/capsulectomy, for ischial reconstruction. TFL/quadriceps femoris flap was indicated for trochanter reconstruction. Direct reconstruction, as a more simple procedure, was indicated for the ischial/gluteal area.

χ^2-test and correlation analysis confirmed no statistically significant correlation between the type of secondary reconstruction procedure and pressure sores relapse localization. Cross tabulation with gender and comparison of mean age to relapse also did not show significant correlations.

Table 5 **Evaluation of secondary reconstruction procedure to pressure sores localization.**

			Secondary procedure							Total
			Biceps femoris flap	Guteus max flap	V-Y fflap	Rotation flap	Nercretomy/capsulectomy	TFL/quadr. fem.flap	Direct reconstruction	
Localization	Sacrum	N	0	0	0	1	0	0	0	1
		%	0.0	0.0	0.0	50.0	0.0	0.0	0.0	9.1
	Trochanter	N	1	0	0	0	0	1	0	2
		%	33.3	0.0	0.0	0.0	0.0	100.0	0.0	18.2
	Gluteus	N	1	0	0	0	0	0	0	1
		%	33.3	0.0	0.0	0.0	0.0	0.0	0.0	9.1
	Ischium	N	1	1	1	1	1	0	0	5
		%	33.3	50.0	100.0	50.0	100.0	0.0	0.0	45.5
	Ischium/gluteus	N	0	1	0	0	0	0	1	2
		%	0.0	50.0	0.0	0.0	0.0	0.0	100.0	18.2
Total		N	3	2	1	2	1	1	1	11
		%								100.0

χ^2=21.083; df=24; p=0.634; r=0.124; p=0.716.

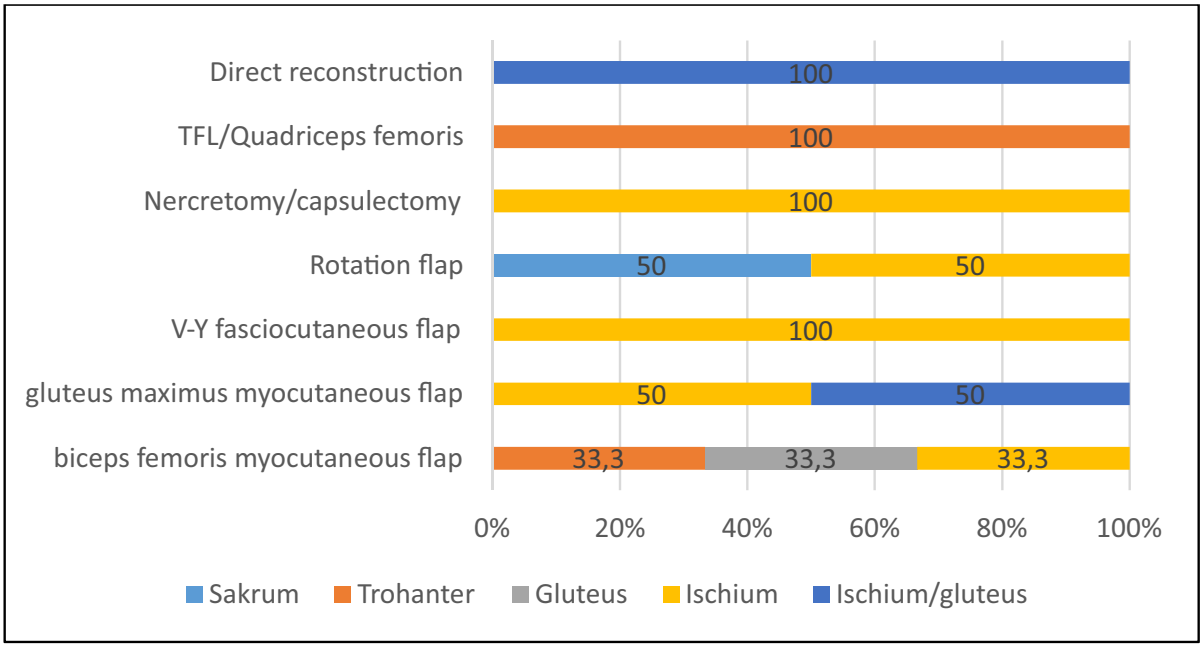

Figure 5 **Percentage distribution of secondary surgical procedures to localization.**

Preferred surgical techniques in the primary and secondary pressure sores reconstruction of decubitus to predilection sites according to our clinical experience were presented by the algorithm (Figure 6).

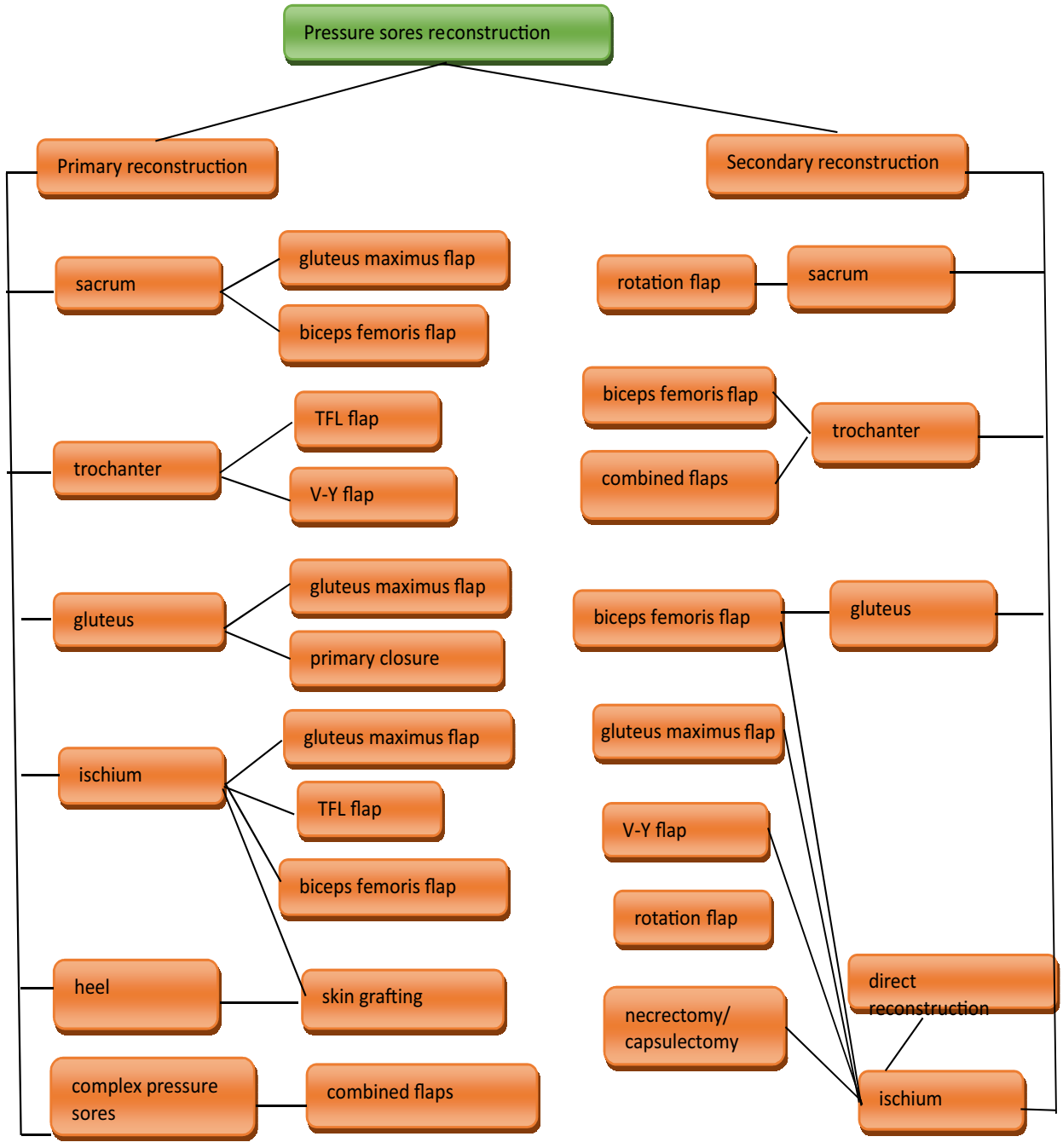

Figure 6 Scheme of the preferred modalities of pressure sores reconstruction.

DISCUSSION

Although the pressure sores prophylaxis is very important considering the overall issue and quality of health care (13), surgical treatment is crucial for success in indicated cases for successful recovery (14), but conservative methods, which referred to the application of vacuum and light therapy, or alginate dressings, are generally indicated for defects of different etiology, such as diabetic foot or venous ulcers, with satisfactory outcome in treatment (15,16). Surgical procedures, with providing sufficient soft tissue cover by properly designed flaps, are the most optimal for treatment of the pressure sores of third and fourth-degree, with preoperative successive necrectomies and control of bacterial contamination (17). Fasciomyocutaneous flaps have to be always considered as one of the best options, which adequate preoperative assessment and correct decision making in primary and secondary reconstructions (18). More simplex procedures, such as primary closure or skin grafting, are generally indicated for superficial defects in the early stages of postoperative wound dehiscence, considering the fact that skin grafting is a method that does not provide adequate soft tissue cover quality, especially in predilection areas exposed to various external factors (19). The success of the reconstructive procedure is correlated with the general condition of the patient, as well as potential comorbidities (20) that affect the quality of postoperative recovery (21), and possible postoperative complications (22). The selection of the secondary reconstructive procedure also has to be conditioned to the anatomical localization of the relapse and also to the availability of the quality of surrounding tissue (23). These complex clinical problems represent the extensive pressure sores ulceration, with accompanying infiltration of adjacent anatomical structures, which we presented in this study. Complex cases were mainly treated by combined fasciomyocutaneous flaps in primary reconstruction, with providing quality cover and satisfactory postoperative results in the cases of temporary or long-term immobility (24).

CONCLUSION

Pressure sores are an important segment of reconstructive plastic surgery, and are very often a challenge in the treatment of clinically complex cases with associated diseases. Although the prophylaxis measures are the result of health care quality at all levels, the occurrence of pressure sores is an inevitable concomitant problem of severe clinical cases. Determination of the most optimal algorithm for preoperative decision-making, based on many years of our experience, is an important guideline in clinical practice. Evaluation of the general condition, the assessment of the accurate localization and potential presence of multiple pressure sores, as well as the quality of the soft tissue cover, are factors of appropriate surgical treatment. Each anatomical localization is related to a defined spectrum of available faciomyocutaneous flaps, for the primary and possible secondary reconstructions, as variants of the first, second, or third choice. The algorithm is guided by principles of our postoperative results based on the assessment of all relevant clinical factors and expected outcomes.

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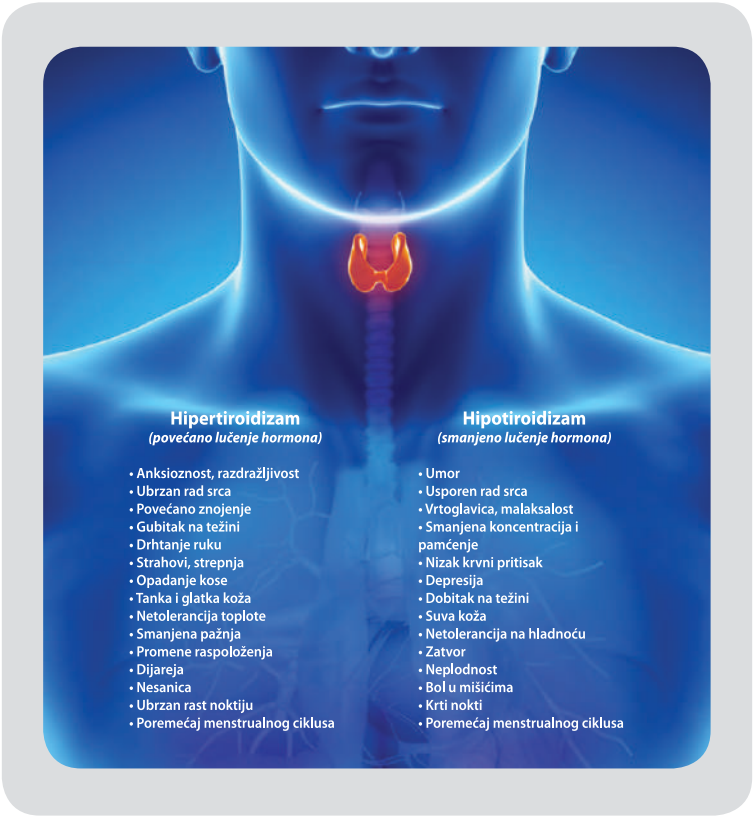

Correlations of uPA-PAi-1 complex values in the serum of patients with different molecular subtypes of early invasive breast cancer and status of axillary lymph nodes

Korelacije vrijednosti uPA-PAi-1 kompleksa u serumu pacijentica sa različitim molekularnim podtipovima ranog invazivnog karcinoma dojke i statusa aksilarnih limfnih čvorova

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ABSTRACT

Introduction: high values of the urokinase plasminogen activator (uPA) complex and its plasminogen-1 activator inhibitor (PAI-1) determined from tumor tissue are associated with a poor prognosis in breast cancer. Aim: to determine whether the values of serum uPA/PAI-1 complex in patients with early invasive breast cancer can serve to assess the axillary lymph nodes of molecular subtypes of cancers. Materials and methods: the study prospectively included 166 patients with early invasive breast cancer (IUCC: pT1-3, pN0-2, M0 / stage: 0 - IIIA), divided into the group without axillary metastases and the group with axillary metastases. Surgical treatment was performed at the Clinic of General and Abdominal Surgery of the Clinical Center University of Sarajevo (CCUS). The laboratory part of the research was done at the Clinical Biochemistry with Immunology of the CCUS. Pathohistological analysis of surgical resect was performed on Clinical Pathology, Cytology and Human Genetics of the CCUS. Statistical anaysis was made in the IBM SPSS Statistics v. 21.0 for Windows, and the most important results are presented in the form of tables and figures. Results: analysis of differences by Mann-Whitney U test shows that there isn't statistically significant difference in the value of uPA/PAI-1 complex in serum between the examined groups without and with metastases in axillary lymph nodes (Z=-0.283; p=0.777). Analysis of the presence of luminal type A in the group without metastases in axillary lymph nodes shows that there is a statistically significant difference compared to the presence of other types ($\chi2$=49.959; p <0.0001) as well as in the group with metastases in axillary lymph nodes ($\chi2$=14.866; p=0.005). Conclusion: we didn't find a statistically significant correlation between the value of uPA/PAI-1 complex concentration in serum and molecular subtype of breast carcinoma regardless of axillary node status nor a statistically significant correlation with classical clinical-pathological parameters.

Keywords: breast cancer, surgery, prognosis, biomarkers

SAŽETAK

Uvod: visoke vrijednosti kompleksa aktivatora plazminogena (uPA) urokinaze i njegovog inhibitora aktivatora plazminogena-1 (PAI-1) određene iz tumorskog tkiva povezane su s lošom prognozom karcinoma dojke. Cilj: utvrditi mogu li vrijednosti kompleksa uPA/PAI-1 u serumu u bolesnika s ranim invazivnim rakom dojke poslužiti za procjenu aksilarnih limfnih čvorova molekularnih podtipova karcinoma. Materijali i metode: U istraživanje je prospektivno uključeno 166 pacijentica s ranim invazivnim karcinomom dojke (IUCC: pT1-3, pN0-2, M0 / stadij: 0 - IIIA), podijeljenih u skupinu bez aksilarnih metastaza i skupinu s aksilarnim metastazama. Operativno liječenje obavljeno je na Klinici za opštu i abdominalnu hirurgiju Kliničkog centra Univerziteta u Sarajevu (KCUS). Laboratorijski dio istraživanja rađen je na Kliničkoj biohemiji sa imunologijom KCUS-a. Patohistološka analiza hirurškog resektata rađena je na Kliničkoj patologiji, citologiji i humanoj genetici KCUS-a. Statistička analiza rađena je u IBM SPSS Statistics v. 21.0 for Windows, a najvažniji rezultati prikazani su u obliku tabela i grafikona. Rezultati: analiza razlika Mann-Whitney U testom pokazuje da ne postoji statistički značajna razlika u vrijednosti kompleksa uPA/PAI-1 u serumu između ispitivanih skupina bez i sa metastazama u aksilarnim limfnim čvorovima (Z=-0,283; p=0,777). Analiza prisutnosti luminalnog tipa A u skupini bez metastaza u aksilarnim limfnim čvorovima pokazuje da postoji statistički značajna razlika u odnosu na prisutnost ostalih tipova ($\chi2$=49,959; p<0,0001) kao i u skupini s metastazama u aksilarnih limfnih čvorova ($\chi2$=14,866; p=0,005). Zaključak: nismo pronašli statistički značajnu korelaciju između vrijednosti koncentracije uPA/PAI-1 kompleksa u serumu i molekularnog podtipa karcinoma dojke bez obzira na status aksilarnih limfnih čvorova niti statistički značajnu korelaciju s klasičnim kliničko-patološkim parametrima.

Ključne riječi: karcinom dojke, hirurgija, prognoza, biomarkeri

INTRODUCTION

Breast cancer is the most common malignant tumor in women and the fifth cause of death caused by cancer (1,2).

According to the molecular classification of breast cancer, based on immunochemical (IH) expression of estrogen (ER) and progesterone (PR), human epidermal growth factor (HER-2 protein) and Ki-67 proliferation index, all breast cancers can be divided into 4 molecular subtypes:

a) luminal A,
b) luminal B (HER-2 + and HER-2 -),
c) HER-2 positive and
d) basaloid or triple negative (3).

Luminal A is the most common molecular subtype, and accounts for more than 50% of all breast cancers (4-6).

Prognostic and predictive factors for breast cancer include patient-related variables (age, ethnicity, race), tumor-related clinicopathological variables (tumor size, histological type and grade, axillary lymph node status) and biological factors, called biomarkers, such as ER and PR receptor status, HER-2 status, etc.

The status of the axillary lymph nodes is still one of the most important morphological prognostic factors in breast cancer. The appearance of metastases in the axillary lymph nodes is associated with a shortening of the disease-free survival (DFS) and overall survival (OS) (7-9).

The issue of correlation of certain molecular subtypes of early invasive breast cancer and serum values of the uPA-PAI-1 complex in relation to the status of axillary lymph nodes hasn't yet been fully investigated.

AIM

The aim of the study was to determine whether the values of the uPA/PAI-1 complex in the serum of patients with early invasive breast cancer can be used to assess axillary lymph nodes in different molecular subtypes of cancer.

MATERIALS AND METHODS

This retrospective, descriptive-analytical study included 166 female patients, aged 18 to 80, surgically treated at the Clinic of General and Abdominal Surgery of the Clinical Center University of Sarajevo (CCUS), in the period from September 2015 to February 2017 in which early invasive breast cancer was pathohistologically verified by preoperative CORE ultrasound control biopsy.

Laboratory tests were performed at the Clinic for Clinical Biochemistry and Immunology of CCUS. The ELISA method (Enzyme Linked Immunosorbent Assay) was used for the quantitative determination of uPA and PAI-1 complexes in the serum of patients. The concentration of the complex in serum according to the manufacturer's instructions (Innovative Research, Inc., 4630 Pearly Court, Novi, MI 48377, USA, Human PAI-1 Upa Complex ELISA Kit) was in the range of 0.1 to 100 ng/ml (10). The surgical treatment of all patients was carried out at the Clinic for General and Abdominal Surgery of CCUS in the form of a radical or sparing operation on the breast, with complete or sparing dissection of the ipsilateral axillary lymph nodes. Pathohistological analysis of surgical resected breasts with tumor and axillary lymph nodes of patients was performed at the Clinic of Clinical Pathology, Cytology and Human Genetics of the CCUS.

Postoperatively, all patients were monitored on an outpatient basis according to valid protocols.

Statistical analysis was made in the IBM SPSS Statistics v. 21.0 for Windows, and the most important results are presented in the form of tables and figures. The data were processed using the descriptive and analytical statistical methods, and we used the Hi-square test to prove the correlation between the variables. The Mann-Whitney U test was used to examine differences in the median values of groups. The statistical significance threshold was set at the conventional level ($p < 0.05$).

RESULTS

The research included 166 patients, the youngest being 31 and the oldest 88. The average age of the patients was 61.2 years, with a standard deviation of 11.4 years. The values of the uPA/PAI-1 complex in the patient's serum ranged from 0.0554 ng/ml to 7.2660 ng/ml, median value 1.4275 ng/ml (interquartile range from 1.0705 ng/ml to 1 .9490 ng/ml). In 80 (48.2%) patients, the tumor size was up to 1.99 cm, and in 86 (51.8%) patients, the tumor was ≥2.0 cm in diameter (Table 1). 20 (12.0%) patients had well-differentiated carcinomas (grade 1), 81 (48.8%) patients had medium-differentiated carcinomas (grade 2), while poorly differentiated carcinomas (grade 3) were noted in 65 (39.2%) patients (Table 1). Lymphovascular invasion by cancer cells wasn't noted in 85 (51.2%) patients, and lymphovascular invasion was found in 81 (48.8%) patients; no perineural invasion by cancer cells was noted in 108 (65.1%) patients, while perineural invasion was noted in 58 (48.8%) patients (Table 1). Expression of estrogen receptors in the tumor was negative in 27 (16.3%) patients, while positive expression was noted in 139 (83.7%) patients. Progesterone receptors were negative in 53 (31.9%) patients, and positive in 113 (68.1%) patients (Table 1). HER-2 protein expression in cancer was negative in 132 (79.5%) patients, and positive in 34 (20.5%) patients (Table 1). A low Ki-67 proliferation index was noted in 133 (80.1%) patients, while a high proliferation index was noted in 33 (19.9%) patients (Table 1). Luminal A molecular subtype was present in 98 (59.0%) patients, Luminal B (HER-2 negative) subtype of cancer was noted in 16 (9.6%) patients, and Luminal B (HER-2 positive) in 25 (15.1%) female patients. HER-2 positive molecular subtype was present in 9 (5.4%) patients. Triple negative molecular subtype was present in 18 (10.8%) patients (Table 1).

Table 1 **Demographic-pathological data of 166 patients included in the study.**

Parameters	Number (No)	Percentage (%)
Age (years)		
≤ 40	6	3,6
41-50	29	17.5
51-60	40	24.1
61-70	59	35.5
71-80	25	15.1
≥ 81	7	4.2
uPA/PAI-1 complex (ng/ml)		
< 0,99	35	21.1
1,00-1,99	93	56.0
2,00-2,99	33	19.9
≥ 3	5	3.0
Tumor size (cm)		
< 2	80	48.2
≥ 2	86	51.8
Histological grade of the tumor		
G1	20	12.0
G2	81	48.8
G3	65	39,2
Lymphovascular tumor invasion		
Negative	85	51.2
Positive	81	48.8
Perineural tumor invasion		
Negative	108	65.1
Positive	58	34.9
Expression of estrogen		
Negative	27	16.3
Positive	139	83.7
Expression of progesterone receptors in the tumor		
Negative	53	31.9
Pozitive	113	68.1
Expression of HER-2 protein in		
Negative	132	79.5
Positive	34	20.5
Ki-67 (%) tumor proliferation index		
≤14 (low)	133	80.1
>14 (high)	33	19.9
Molecular subtype of breast		
Luminal-A	98	59.0
Luminal-B/HER2-	16	9.6
Luminal-B/HER2+	25	15.1
HER 2 +	9	5.4
Triple-negative	18	10.8

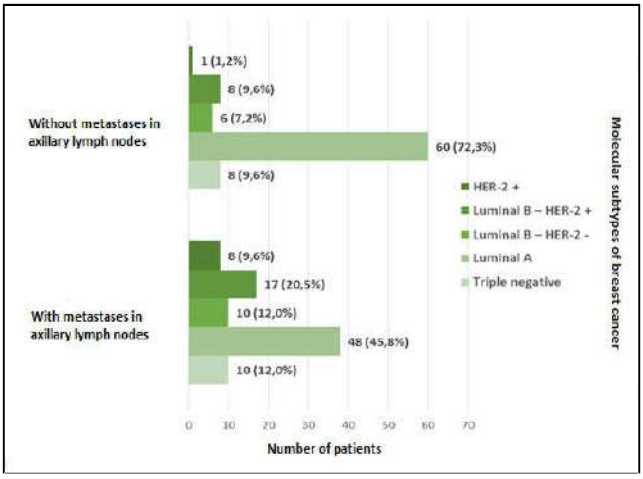

Figure 1 **Molecular subtypes of breast cancer of 166 patients divided into two groups - with and without metastases in the axillary lymph nodes.**

In the group of patients without metastases in the axillary lymph nodes, 60 (72.3%) cancers were of the luminal A type, and in the group of patients with metastases in the axillary lymph nodes, 38 (45.8%) cancers were of the luminal A molecular subtype (Figure 1). Analysis of the representation of luminal type A in the group without metastases in the axillary lymph nodes shows that there is a statistically significant difference compared to the representation of other types ($\chi 2=49.959$; $p<0.0001$). Analysis of the representation of luminal type A in the group with metastases in axillary lymph nodes shows that there is a statistically significant difference compared to the representation of other types ($\chi 2=14.866$; $p=0.005$). Statistical analysis of the differences between the examined groups shows a statistically significant difference ($\chi 2=14.845$; $p=0.005$).

Table 2 **Correlation of uPA/PAI-1 complex (ng/ml) in serum (median and interquartile range) and molecular subtypes of early invasive breast cancer in 166 patients with early invasive breast cancer, divided into two groups - with and without metastases in axillary lymph nodes.**

Parametres	Axillary lymph nodes status					
	No metastases in the axillary lymph nodes			With metastases in the axillary lymph nodes		
	N (%)	Values of uPA/PAI-1 complex (ng/ml) in serum	P	N (%)	Values of uPA/PAI-1 complex (ng/ml) in serum	P
Molecular subtype of breast cancer						
Luminal A	8(54.4)	1.583 (1.063-2.005)		10(55.6)	1.352 (1.000-2.078)	
Luminal B – HER-2 -	60(67.2)	1.293 (1.086-2.871)		38(38.8)	1.535 (1.227-1.899)	
Luminal B – HER-2 +	6(37.5)	1.165 (0.868-1.687)	P=0,526	10(62.5)	1.293 (1.117-1.939)	P=0.942
HER-2 +	8(32.0)	1.629 (1.629-1.629)		17(68.0)	1.381 (1.008-1.743)	
Triple-negative	1(11.1)	1.253 (0.920-1.576)		8 (88.9)	1.425 (1.082-2.180)	

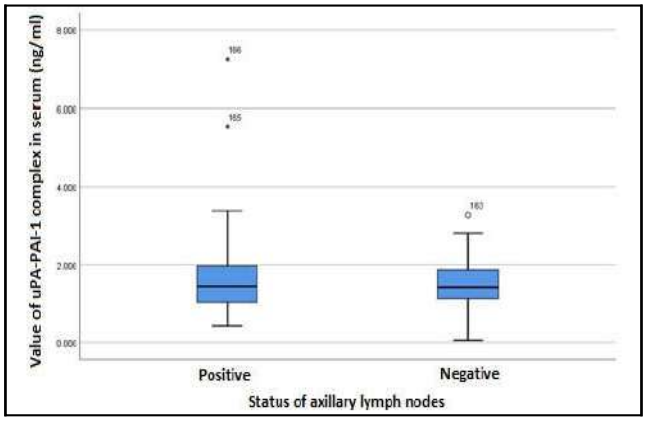

Figure 2 **Values of the uPA/PAI-1 complex in the serum of 166 patients with early invasive breast cancer divided into two groups - with and without metastases in the axillary lymph nodes.**

In the group of patients without metastases in the axillary lymph nodes, the median value of the concentration of the uPA/PAI-1 complex in the serum was 1.433 ng/mL (Figure 2). In the group of patients with metastases in the axillary lymph nodes, the median concentration of the uPA/PAI-1 complex in the serum was 1,410 ng/mL (Figure 2). Analysis of differences using the Mann-Whitney U test shows that there is no statistically significant difference in the value of the uPA/PAI-1 complex in the serum between the examined groups (Z=-0.021; p=0.983).

DISCUSSION

Numerous studies have examined the role that the uPA/PAI-1 complex and/or its components have in the process of the formation, development and spread of tumors in breast cancer (11-17).

In our study, in both groups of patients, the most common molecular subtype of cancer was luminal A, which was statistically significant, compared to other molecular subtypes (Figure 1). The obtained results are consistent with the results of the author's research who investigated the representation of certain molecular subtypes of breast cancer in Bosnia and Herzegovina, as well as other studies that dealt with similar issues (18-21).

Upon further analysis of the study data, we found no statistically significant difference in the value of the uPA/PAI-1 complex in the serum of individual groups of patients, in relation to the status of the axillary lymph nodes.

Namely, it would be expected that in the group with positive lymph nodes of different molecular types the serum values were elevated compared to the group with negative axillary lymph nodes, according to the results of most studies, but in our study this was not the case. (21,22).

In this regard, it should be noted that the largest number of studies investigating the prognostic value of the uPA-PAI-1 complex analysed the values of the complex in tumor tissue and not in serum, as is the case in our study (22-25).

In relation to the mentioned studies, our study evaluated the value of the uPA-PAI-1 complex in the serum of patients with early invasive breast cancer, which most likely explains our results, which correspond to the results of the study that consider that the values of the uPA-PAI-1 complex in the serum don't can be taken as relevant indicators for assessing prognosis and prediction in early invasive breast cancer (26).

CONCLUSION

Based on the above, we can conclude that the serum values of the uPA-PAI-1 complex cannot be taken as a separate, clear and precise prognostic factor when assessing the malignant potential of different molecular subtypes of breast cancer. Also, we have to take into account the limitation of the study in terms of the number of patients and the duration of the study. When assessing the malignant potential of different molecular subtypes of breast cancer, the standard clinical-pathological factor alone and/or in combination with newer prognostic-predictive factors must still be taken into account.

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Results of the analysis of surveillance cultures of patients in intensive care units and their significance in the prevention and control of hospital-acquired infections

Rezultati analize nadzornih kultura pacijenata u jedinicama intenzivne njege i njihov značaj u prevenciji i kontroli bolničkih infekcija

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ABSTRACT

Introduction: the occurrence of a hospital-acquired infection is usually preceded by colonization with some of the hospital pathogens. In patients hospitalized in intensive care units, surveillance testing is recommended to detect colonization on admission and during hospitalization, and also for the reason that colonized patients are a potential reservoir and source of multidrug-resistant microorganisms. Aim of the study: to show the importance of screening through the results of surveillance cultures according to defined intervals and in relation to the type of sample, the most frequently isolated causative agents, and the frequency of causative agents based on the type of samples. Materials and methods: this retrospective study included samples of patients hospitalized at the Clinic of Anesthesia and Reanimation of the Clinical Center University of Sarajevo (CCUS) in the period from September 2021 to May 2022. Swabs of the throat or tube, nose, axilla, groin, rectum and tracheal aspirate from patients on mechanical ventilation were used as samples at the following time intervals: on admission and on each third and seventh day of hospitalization. Results: the research included 900 samples/60 patients, of whom 58.3% were male and 41.7% female, with an average age of 58.02 +/- 15.78 years. Out of 900 samples, 186 (20.7%) were positive, and 714 (79.3%) were negative. In relation to the defined intervals the majority of positive results were reported on Day 7 of the screening, slightly less on Day 3, while the least positive results were reported on admission to intensive care. The most common isolated pathogens were: *Acinetobacter baumannii* (32%), *Klebsiella pneumoniae* CPE (20%), *Methicillin-sensitive Staphylococcus aureus* (10.7%) and *Pseudomonas aeruginosa* (10.2%). In relation to the type of sample, the majority of positive results were found in the throat/tube swab, and slightly less in the nose and rectal swab. Conclusion: patients who had negative screening smears upon admission and stayed in the intensive care unit for three or more days became colonized with hospital pathogens. Colonization/infection of patients in the intensive care unit was mainly caused by multidrug-resistant microorganisms.

Keywords: intensive care, screening tests, hospital pathogens

SAŽETAK

Uvod: pojavi bolničke infekcije u pravilu prethodi kolonizacija nekim od bolničkih patogena. Kod pacjenata koji se smještaju u jedinice intenzivne njege, nadzorni brisevi se preporučuju u detekciji kolonizacije na prijemu i u toku hospitalizacije, a iz razloga što su kolonizirani bolesnici potencijalni rezervoar i izvor multiplorezistentnih mikroorganizama. Cilj rada: prikazati značaj skrininga kroz rezultate nadzornih kultura prema definisanim intervalima i u odnosu na vrstu uzorka, najčešće izolovane uzročnike, kao i učestalost uzročnika prema vrsti uzoraka. Materijali i metode: ova retrospektivna studija je obuhavtila uzorke pacijenata hospitaliziranih na Klinici za anesteziju i reanimaciju Kliničkog centra Univerziteta u Sarajevu (KCUS) u periodu septembar 2021-maj 2022.godine. Kao uzorci su korišteni brisevi guše ili tubusa, nosa, aksile, prepone, anusa i trahealni aspirat kod pacijenata na mehaničkoj ventilaciji u vremenskim intervalima po prijemu, te trećeg i svakog sedmog dana hospitalizacije, Rezultati: Istraživanjem je obuhvaćeno 900 uzoraka /60 pacijenta, 58.3% muškaraca i 41.7% žena, prosječne starosti 58.02 +/- 15.78 godina. Od 900 uzoraka 186 (20.7%) je pozitivno, a 714 (79.3%) negativno. Najviše pozitivnih rezultata u odnosu na definisane intervale bilo je na skriningu 7. dan, nešto manje na 3. dan, a najmanje na prijemu u intenzivnu njegu. Najčešći izolovani uzročnici su: *Acinetobacter baumannii* (32%), *Klebsiella pneumoniae* CPE (20%), *Methicilin senzitivni Staphylococcus aureus* (10,7%) i *Pseudomonas aeruginosa* (10,2%). Najviše pozitivnih rezultata u odnosu na vrstu uzorka bilo je u brisu grla/tubusa, nešto manje u brisu nosa i brisu anusa. Zaključak: pacijenti koji su pri prijemu imali negativne skrining briseve, a boravili su u jedinici intenzivne njege tri i više dana kolonizirali su se bolničkim patogenima. Kolonizacija/infekcija pacijenata u jedinici intenzivne njege najčešće je izazvana multiplorezistentnim mikroorganizmima.

Ključne riječi: intenzivna njega, skrining brisevi, bolnički patogeni

INTRODUCTION

Patients treated in intensive care units have a high risk of hospital infection, both due to the application of a series of invasive diagnostic and therapeutic procedures, and also due to the patient's condition itself. Infections in intensive care units can be exogenous and endogenous in their origin, and the former can be primary and secondary. Primary exogenous infection is an infection caused by the direct transfer of a microorganism from the environment to the tissues causing inflammation, and a secondary exogenous infection is an infection with the previous mucous membranes colonization and subsequent spreading of the microorganism into the blood and organs.

Such infections are often caused by the transmission of infection through aerosols, hospital staff hands, direct entry during invasive procedures, via patient hygiene accessories, etc. (1). Endogenous infections occur when bacteria, commensals from its own organism (most often the intestines), penetrate sterile and other mucous membranes or into the blood causing an inflammatory reaction. Such infections are more common in immunocompromised patients (1) and occur in the first days of their hospitalization in the intensive care unit.

The occurrence of a hospital infection is usually preceded by colonization with some of the hospital pathogens. The mucous membrane of the nose, pharynx and trachea, the surface of the skin, the mucous membrane of the urinary bladder and digestive tract (stomach and intestine), surgical and decubitus wounds in patients with prolonged hospitalization in the intensive care unit are often colonized with hospital microorganisms. Foreign materials used and kept in the body for a long time, such as endotracheal tubes, tracheal cannulas, arterial, venous and urinary catheters, over time become contaminated with hospital pathogens, very often with multidrug-resistant microorganisms (2,3).

In patients admitted to intensive care units, surveillance testing is recommended to detect colonization on admission and during hospitalization given that colonized patients are a potential reservoir and source of multidrug-resistant microorganisms for the hospital environment (4,5). In addition to detecting colonization and germs in newly admitted patients, nowadays, surveillance swabs also serve for the control of nursing medical care, primarily in terms of monitoring the level of cleanliness of the patient (regular washing and bathing, local skin disinfection before performing invasive procedures, oral hygiene).

In addition, by taking and analyzing surveillance swabs, we also get information on the success of decolonization measures and suppression of pathogens spreading, given that contact isolation and decolonization measures are taken for those with isolated pathogenic bacteria isolated from skin samples.

AIM

The aim of the study was to show the importance of screening through the results of surveillance cultures according to defined intervals and in relation to the type of sample, the most frequently isolated causative agents, and the frequency of causative agents based on the type of samples.

MATERIALS AND METHODS

This retrospective study included samples of patients hospitalized at the Clinic of Anesthesia and Reanimation of the Clinical Center University of Sarajevo (CCUS) in the period from September 2021 to May 2022. Microbiological analysis of the samples was carried out in the Laboratory for Hospital Infection Control, Clinical Microbiology of the CCUS.

Swabs of the throat or tube, nose, axilla, groin, rectum and tracheal aspirate from patients on mechanical ventilation were used as samples at the following time intervals: on admission and on each third and seventh day of hospitalization. The samples were immediately transported to Laboratory for Hospital Infection Control of the Clinical Microbiology. Data on the gender and age of the patient were taken from the laboratory protocol, and data on previous hospitalization and potential risk factors for hospital colonization or infection were taken from the medical history.

Isolation and identification of the causative agent was done using standard microbiological methods: suitable chromogenic media were used for isolation in culture, which enable the rapid identification of some Gram-negative and Gram-positive bacteria based on the different colors of the colonies produced by the reaction of genera - or species-specific enzymes with two chromogenic substrates (ISO13485:2003). The identification of the causative agent was carried out on the basis of the characteristic appearance of the colonies, by examining physiological and biochemical properties, and by the automated VITEK 2 Compact system method (bioMérieux, Marcy l'Étoile, Francuska). Antimicrobial susceptibility was tested using the disk-diffusion method and the automated VITEK 2 Compact system (bioMérieux, Marcy l'Étoile, France) in accordance with the instructions of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

A strain of bacteria resistant to one antibiotic in three or more groups was considered multiresistant, and a bacterial isolate sensitive to only one or two groups of antibiotics was considered extremely resistant.

IBM SPSS Ver. 21 was used for statistical analysis and data processing (SPSS Inc, Chicago, Illinois, USA). Data processing involved descriptive statistics and non-parametric significance tests. Differences in frequencies were examined with the Chi-square (X^2) test. Statistically significant values for all tests were considered at $p<0.05$.

RESULTS

The study included 900 samples taken from 60 patients, of which 35 (58.3%) were men and 25 (41.7%) women with an average age of 58.02 +/- 15.78 years. The youngest respondent was 20, and the oldest was 82 years of age. Out of 900 samples included in the study, 186 (20.7%) were positive for the presence of certain agents of infection or colonization, whereas 714 (79.3%) were negative.

Out of the total number of tested patients, the majority of positive results in relation to the defined intervals were recorded on the 7th day of the screening, slightly less on the 3rd day, and the least positive results were recorded on admission to intensive care.

Based on the X^2 test, there was a statistically significant difference in the frequency of positive/negative survaillance cultures in relation to the mentioned intervals, $p=0.001$ (Table 1).

Table 1 **Results of surveillance cultures according to defined sampling intervals.**

Defined interval	Evaluation of findings		Total
	Pozitive	Negative	
Admission	43 (14.3%)	258 (85.7%)	301 (100.0%)
3rd day	63 (21.1%)	236 (78.9%)	299 (100.0%)
7th day	80 (26.7%)	220 (73.3%)	300 (100.0%)

Pearson Chi-Square = 14.092; p = 0.001

Out of 186 (100%) samples positive for the presence of the causative infection or colonization agent, 153 (82.3%) were positive for one, and 33 (17.7%) for several causative agents at the same time. Table 2 shows all types of pathogens isolated from positive surveillance cultures in this study, and their frequency of occurrence as a cause of colonization or infection. Samples with multiple causative agents were broken down into individual causative agents, and individual causative agents appeared 225 times as the cause of infection or colonization.

Table 2 **Total frequency of infectious agents in positive survaillance culture samples.**

Cause of infection/ colonization	Observed N (%)	Expected N	Residual/ rest
Acinetobacter baumannii	72 (32%)	17.3	54.7
Klebsiella pneumoniae	8 (3.6%)	17.3	-9.3
Klebsiella pneumoniae ESBL	16 (7.1%)	17.3	-1.3
Klebsiella pneumoniae CPE	45 (20%)	17.3	27.7
Meticilin rezistentni S. aureus	1 (0.4%)	17.3	-16.3
Meticilin senzitivni S. aureus	24 (10.7%)	17.3	6.7
Pseudomonas aeruginosa	23 (10.2%)	17.3	5.7
Proteus mirabilis	9 (4%)	17.3	-8.3
Vankomicin rezistentni Enterococcus	11 (4.9%)	17.3	-6.3
Serratia marcescens	3 (1.3%)	17.3	-14.3
Enterobacter cloacae	8 (3.6%)	17.3	-9.3
Escherichia coli ESBL	4 (1.8%)	17.3	-13.3
KNS	1 (0.4%)	17.3	-16.3
Total	225(100%)		

Chi-Square = 290.782; p < 0.001

The most common isolated pathogen in positive surveillance culture samples was *Acinetobacter baumannii* (32%), followed by *Klebsiella pneumoniae* CPE (20%). Methicillin-sensitive *Staphylococcus aureus* and *Pseudomonas aeruginosa* were the next isolates in terms of frequency with 10.7% and 10.4%, respectively. The least represented isolated causative agents were *methicillin-resistant Staphylococcus aureus* and *coagulase-negative staphylococci* (CNS) with 0.4% each. There was a statistically significant difference in the frequency of occurrence between the mentioned causes of infection/colonization (p<0.001).

The types of samples from which individual causative agents were isolated were: throat/tube swab, nasal swab, axilla swab, groin swab and rectal swab. Out of the total number of tested samples, the most positive results in relation to the type of sample were in throat/tube swabs, somewhat less in nasal and rectal swabs, and the least in groin and axilla swabs (Table 3). Based on the X^2 test, there was a statistically significant difference in the frequency of positive/negative surveillance cultures in relation to the mentioned type of sample, p<0.001.

Table 3 **Results of surveillance cultures in relation to sample type.**

Type of sample	Evaluation of findings		Total
	Positive N/%	Negative N/%	
Throat/tube swab	61 (33.3%)	119 (66.1%)	180 (100%)
Nasal swab	49 (27.2%)	131 (72.8%)	180 (100%)
Axillary smear	12 (6.7%)	168 (93.3%)	180 (100%)
Groin swab	22 (12.3%)	158 (87.8%)	180 (100%)
Bris anusa	42 (23.6%)	138 (76.7%)	180 (100%)

Pearson Chi-Square = 52.735; p < 0.001

In 186 (100%) different samples positive for the presence of infection or colonization causative agent, the total frequency of occurrence of the causative agent was 225. Table 4 shows the frequency of occurrence of certain colonization or infection agents according to the type of sample examined. The types of isolated causative agents statistically significantly (p<0.001) differ in the throat/tube and nasal swab samples. *Acinetobacter baumannii* was the most common pathogen isolated from the throat/tubal and nasal samples. In the groin and rectal swab samples there was a statistically significant difference (p<0.001) in the type of proven causative agent, where *Klebsiella pneumoniae* CPE was the statistically significantly proven isolates (p<0.001). The type of pathogen causing colonization did not differ significantly in axilla swab samples (p=0.467).

Table 4 **Total frequency of infectious agents by type of positive samples.**

Cause of infection/ colonization	Throat/tube swab	Nasal swab	Axilla swab	Groin swab	Rectal swab
Acinetobacter baumannii	36 (48%)	21 (32.8%)	3 (20.0%)	7 (28.0%)	5 (10.9%)
Klebsiella pneumoniae	4 (5.3%)	1 (1.6%)	0 (0%)	1 (4.0%)	2 (4.3%)
Klebsiella pneumoniae ESBL	6 (8.0%)	5 (7.8%)	1 (6.7%)	0 (0%)	4 (8.7%)
Klebsiella pneumoniae CPE	7 (9.3%)	7 (10.9%)	5 (33.3%)	9 (36.0%)	17 (37.0%)
Meticilin rezistentni S. aureus	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Meticilin senzitivni S. aureus	8 (10.7%)	13 (20.3%)	3 (20.0%)	0 (0%)	0 (0%)
Pseudomonas aeruginosa	8 (10.7%)	11 (17.2%)	2 (13.3%)	2 (8.0%)	0 (0%)
Proteus mirabilis	1 (1.3%)	2 (3.1%)	0 (0%)	4 (16.0%)	2 (4.3%)
Vankomicin rezistentni Enterococcus	0 (0%)	0 (0%)	0 (00%)	0 (%0)	11 (23.9%)
Serratia marcescens	1 (1.3%)	2 (3.1%)	0 (0%)	0 (0%)	0 (0%)
Enterobacter cloacae	2 (2.7%)	2 (3.1%)	1 (6.7%)	1 (4.0%)	2 (4.3%)
Escherichia coli ESBL	0 (0%)	0 (0%)	0 (0%)	1 (4.0%)	3 (6.5%)
Coagulase negative Staphylococcus (CNS)	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	75 (100%)	64 (100%)	15 (100%)	25 (100%)	46 (100%)
Chi-Square	**149.840**	**51.031**	**4.600**	**17.840**	**36.087**
p	**<0.001**	**<0.001**	**0.467**	**0.007**	**<0.001**

DISCUSSION

Each day of hospitalization in the intensive care unit increases the duration of exposure to invasive diagnostic and therapeutic methods, crucial for life maintaining, but it also increases the risk of infections and clinical complications (6).

Unrecognized colonization and infection can lead to the spread of nosocomial infections in a healthcare facility. Therefore, it is important to introduce surveillance cultures as part of the routine control of all newly admitted patients, as well as those hospitalized for more than four days due to the greater possibility of colonization with hospital pathogens. Control swabs are also indicators of the quality of nursing care and patients' contact with pathogens (7). Microbiological diagnosis of infections occurring during treatment in intensive care units is extremely important due to the timely application of appropriate treatment methods, i.e. antimicrobial drugs and other methods contributing to the infection treatment (8).

Our study included 900 samples taken from 60 patients, of whom 35 (58.3%) were male and 25 (41.7%) female with an average age 58.02 +/- 15.78 years. In the study conducted by Zarb P, et al., the respondents were older (median age was 65, ranging from 54 to 74 years), and they stayed in the intensive care unit for more than nine days, which is significantly longer compared to the average number of hospitalization days, which is five days (9).

Prolonged hospitalization in the intensive care unit exposes patients to an increased risk of colonization or infection with nosocomial pathogens. If the patient, who was not colonized or infected on admission to the intensive care unit, stays in that environment for a longer time (more than two or four days), he/she will be exposed to an increased risk of colonization or infection (1). In our study, out of the total number of tested samples, the majority of positive results in relation to the defined intervals were on the 7th day of screening, i.e. 80/300 (26.7%). In the study conducted by Alberti C, et al., 31.5% of patients were positive immediately after admission, and 68.4% became colonized/infected during their hospitalization in the intensive care unit (10).

We had a total of 186 (20.7%) samples positive for the presence of the causative infection or colonization agent, of which 153 (82.3%) were positive for one, and 33 (17.7%) for multiple causative agents simultaneously.

The most frequently isolated causative agents in srvaillance cultures were: *Acinetobacter baumannii* (32%), followed by *Klebsiella*

pneumoniae CPE (20%), Methicillin-resistant *Staphylococcus aureus* (10.7%) and *Pseudomonas aeruginosa* (10.4%). This indicates that the colonization/infection is most often caused by resistant hospital pathogens.

The data about the causative agent of hospital colonization/infection is different in different areas of the world (it varies from country to country). There are differences between hospital departments, between different ICUs, it also depends on some characteristics of the patient (severity of the patient's clinical condition, site of infection) and the surveillance and prevention strategy (11).

In a retrospective four-year analysis conducted by Zah Bogović T, et al., *Acinetobacter baumannii* was also the most frequently isolated causative agent, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* (12,13).

The results of our study showed that there was a statistically significant difference ($p<0.001$) in the type of isolated causative agents in the samples of throat/tube and nasal swabs. *Acinetobacter baumannii* was the most common pathogen isolated from throat/tubal and nasal samples. *Klebsiella pneumoniae* CPE ($p<0.001$) was statistically significantly more prevalent in the groin and rectal swab samples, and vancomycin-resistant enterococcus (VRE) was also prevalent in the rectal swab. In several studies Lee BY, et al., have proven that the throat and nose swabs samplimg can be a cost-effective means of controlling methicillin-resistant *Staphylococcus aureus* (MRSA) (14-17). In epidemics, it is also useful to take a screening of the rectal and colostomy site swab in order to detect hospital strains. Since the digestive system is a reservoir of enterobacteria, the best clinical samples for detecting carbapenemase-producing enterobacteria are stool or rectal swab (18).

CONCLUSION

Patients who stayed in the intensive care unit for three or more days became colonized with hospital pathogens. In addition to the early detection of patients colonized/infected with hospital pathogens, screening upon admission is extremely important for making decisions about rational and targeted antimicrobial therapy and application of other methods contributing to the infection prevention and control.

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A gigantic nodular goiter with retrosternal propagation: case report

Gigantska nodozna retrosternalna struma štitne žlijezde: prikaz slučaja

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ABSTRACT

Introduction: retrosternal extension of nodular goiter is rare but challenging disease which in most cases requires surgical treatment. Nodular goiter is the most common thyroid gland disease. However retrosternal extensions are rare. Aim: to present a case of surgically treated patient with pathologically verified gigantic nodular goiter. Case report: in this report we present a 69 years old female patient who was surgically treated because of a gigantic retrosternal nodular goiter. Conclusion: surgical treatment of gigantic nodular goiters with retrosternal extension associated with other symptoms remains a golden standard of care for such patients.

Keywords: nodular goiter, surgical treatment, sternotomy

SAŽETAK

Uvod: retrosternalna struma štitne žlijezde predstavlja rijetko ali istovremeno i izazovnu bolest koja zahtijeva hirurški tretman. Nodozno izmijenjena struma štitne žlijezde predstavlja najzastupljenije oboljenje štitnjače. Retrosternalna propagacija iste predstavlja rijedak slučaj. Cilj: predstaviti slučaj hirurški tretirane pacijentice sa patohistološki verificiranom nodoznom strumom štitne žlijezde. Prikaz slučaja: u ovom prikazu slučaja predstavit ćemo 69-godišnju pacijenticu koja je operativno tretirana zbog gigantske retrosternalne nodozne strume štitne žlijezde. Zaključak: hirurški tretman gigantske nodozne strume štitne žlijezde sa retrosternalnom propagacijom, povezana sa propratnim simptomima osnovne bolesti I dalje predstavlja zlatni standard njege kod ovakvih pacijenata.

Ključne riječi: nodozna struma, hirurški tretman, sternotomija

INTRODUCTION

Retrosternal extension of nodular goiter is rare but challenging disease which in most cases requires surgical treatment. Retrosternal goiter (RSG) is most commonly defined as one that either descends below the thoracic inlet, or has more than 50% of its volume below this level (1). Mediastinal extension is more common in huge goiters with a peak incidence in 5th to 6th decade (2). The incidence of substernal goiters among patients with thyroid goiters is reported to range from approximately 5-15% (3). It was previously perceived that all retrosternally positioned nodular goiters were an absolute indication for surgical treatment. With the advancements in diagnostic procedures which are in everyday use, the incidence of these patients is becoming higher and the indication for surgical treatment is reserved for patients who are developing symptoms related to retrosternal goiter. Dyspnea, sleep disturbance, dysphagia and hoarseness are the most common symptoms described in the literature (4).

AIM

The aim of this study was to present a case of surgically treated patient with pathologically verified gigantic nodular goiter.

CASE REPORT

A 69 years old female patient was admitted via emergency center with the symptoms of dyspnea, transient loss of consciousness, general weakness. General examination was insignificant. Local examination revealed a discrete swelling of left lobe of thyroid gland. Radiological examination was done. Computed tomography of chest and neck revealed 10 x 8 cm retrosternal mediastinal mass arising from left lobe of thyroid with tracheal compression (trachea compressed to 7 mm in width) as well as dislocation to the right end side. Esophageal compression in its proximal third was also CT confirmed. Laboratory tests revealed that she was in euthyroid condition (TSH 0.56 uIU/mL, FT3 3.2 pmol/L, FT4 15.6 pmol/L, T3 1.2 nmol/L, T4 81 nmol/L. Medical history revealed that she was

advised to consult surgeon in order to be surgically treated which she declined. Preoperative counseling was performed and she was induced into general anesthesia. Skin incision extended from sternal manubrium to mid neck region. Strap musculature was divided, left thyroid lobe was exposed and excised, followed by full sternotomy which exposed the anterior mediastinum and the tumor mass was completely excised. Homeostasis was achieved. Drain was kept and closure was done in layers. Having in mind patient's age, general condition and the fact that right lobe showed no pathological masses, we decided to preserve it. Drainage suction was removed on a fourth postoperative day. Postoperative chest x-ray confirmed lung reexpansion. Postoperative of values of serum calcium were within the physiological range. On the sixth postoperative day she was discharged from the hospital. Pathological review of the excised specimen revealed that it was nodular goiter of the thyroid gland.

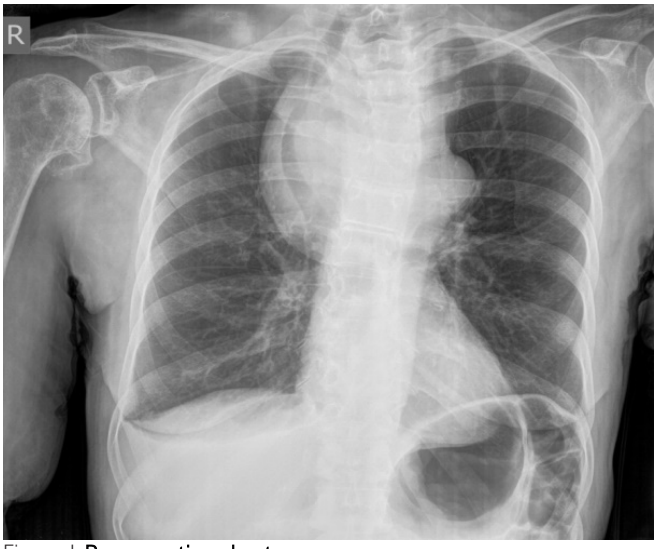

Figure 1 **Preoperative chest x-ray**.

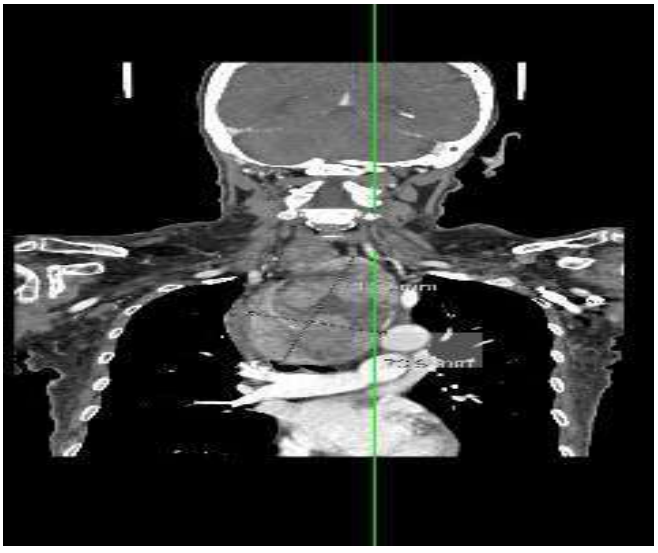

Figure 2 **Preoperative axial CT scan.**

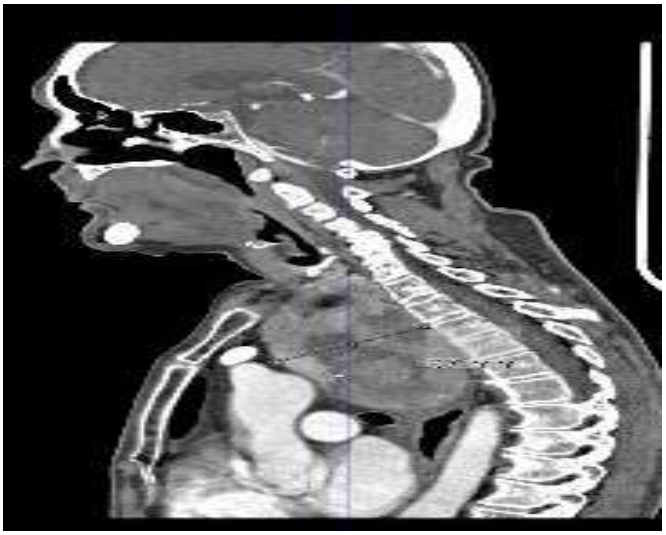

Figure 3 **Preoperative coronal CT scan.**

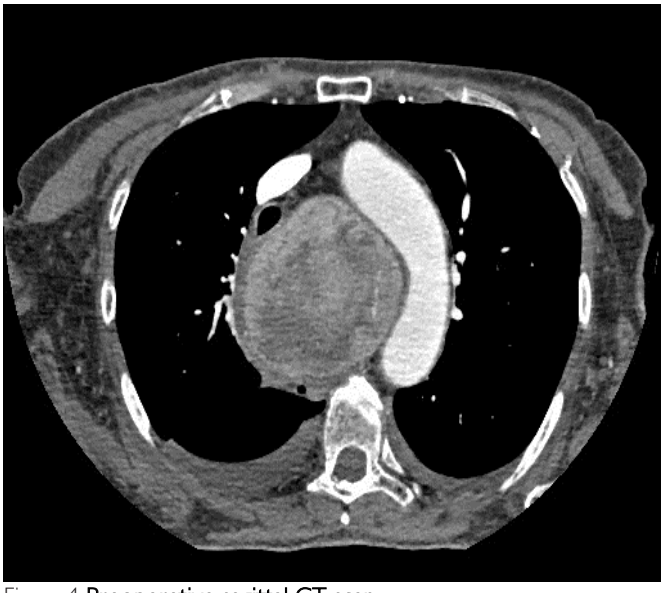

Figure 4 **Preoperative sagittal CT scan.**

DISCUSSION

Retrosternal nodular goiter is a condition in which a part of a thyroid gland is situated beneath the upper thoracic outlet. In most cases this condition is treatable via cervical approach (5). Factors as propagation below aortic arch or posterior mediastinum, dumb-bell shaped goiter and a thoracic goiter component wider than the thoracic inlet are all indicators for sternotomy (6). In our case, all the factors were positive so the indication for the sternotomy was justified.

Regarding preoperative management, patient underwent a routine preoperative work-up, including ultrasonography, hormonal status, lymph scintigraphy and a chest and neck CT. In a decision making process whether to perform a sternotomy or not, diagnostic value of computed tomography was shown as invaluable and can be considered a gold standard in treating retrosternal goiter (7).

Symptoms like dyspnea, dysphagia or hoarseness are often linked with such medical condition (4). Notably, symptom mostly represented in our patient was dyspnea, which was completely expected due to the extent of tracheal compression and tracheal deviation and was in accordance with current literature (8).

Surgical procedure mostly used in these cases is thyroidectomy (9). In the case that we reported retrosternal goiter was a continuation of thyroid gland left lobe tissue into the thoracic cavity, with right lobe without any tumor mass which was confirmed by CT scan so our final decision was to preserve it, also as a precautionary measure to avoid any postoperative complication. This type of spread was noted as the most common (7).

Final pathologic result showed that patient was having a follicular adenoma, which is frequently diagnosed condition in such cases (10). Therefore, no further treatment was warranted.

CONCLUSION

Surgical treatment of gigantic nodular goiters with retrosternal extension associated with other symptoms remains a procedure of choice for such patients.

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A case of giant myxoid liposarcoma in a young male: diagnosis and treatment

Slučaj gigantskog miksoidnog liposarkoma kod mladog muškarca: dijagnoza i tretman

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ABSTRACT

Introduction: liposarcoma is the second most commonly diagnosed soft tissue sarcoma. Most patients are adults over 50 complaining of a large, painless, deep-seated mass located proximally in the extremities. Histologic subtypes include well-differentiated liposarcoma, myxoid liposarcoma, round-cell liposarcoma, and pleomorphic liposarcoma. Aim: presentation of clinical findings, diagnosis and treatment protocols for myxoid liposarcoma. Case report: a 29-year old male was presented with a large, painless mass in proximal and middle third of the left femoral adductor region. The mass was progressively increasing in size during the last two years. CT-scans show large tumorous mass in anterior and medial compartment of the left thigh. Intraoperatively, a large solid mass infiltrated m. sartorius and m. vastus medialis, femoral vessels were intact, and the mass was extirpated in toto with infiltrated muscles. Histopathologic result showed myxoid liposarcoma G3. Myxoid liposarcomas generally most often occur in thigh region, but have a tendency to occur in the retroperitoneum. MRI is nonspecific. Similar to most soft-tissue sarcomas, the metastases occur in lungs, but mainly in retroperitoneum, contralateral leg or bone. The treatment is wide local excision. Lung, abdomen and pelvis CT-scans should be included in patient follow-up. Patients with high-grade lesions have a 60% 5-year survival rate. Conclusion: liposarcomas most common occur as a deep-seated lesions in proximal aspect of the extremity, primarily the thigh. Prior to surgery, biopsy is indicated. The main goal of surgery is wide resection.

Keywords: myxoid liposarcoma, thigh region, surgical treatment

SAŽETAK

Uvod: liposarkom je drugi najčešće dijagnosticirani mekotkivni sarkom. Većina pacijenata su stariji od 50. godine života, te se javljaju na pregled zbog veće, bezbolne, duboko smještene mase, locirane u proksimalnom dijelu ekstremiteta. Histološki podtipovi uključuju dobro-diferencirani liposarkom, miksoidni liposarkom, „round-cell" liposarkom i pleomorfni liposarkom. Cilj: prezentacija kliničke slike, dijagnostičkog puta i terapijskih protokola u tretmanu miksoidnog liposarkoma. Prikaz slučaja: dvadesetdevetogodišnji muškarac se javlja na pregled zbog velike, bezbolne tumorske mase locirane u proksimalnoj i srednjoj trećini lijeve femoralne aduktorne regije. Masa je progresivno rasla unazad dvije godine. CT- skenovi pokažu veliku tumorsku masu smještenu u prednjem i medijalnom kompartmentu lijeve natkoljenice. Intraoperativno, velika, solidna masa infiltrira m. sartorius i m. vastus medialis, femoralni krvni sudovi su intaktni, te se tumorska masa ekstirpira u cjelosti sa inflitriranom muskulaturom. Histopatološki nalaz pokaže miksoidni liposarkom G3. Miksoidni liposarkomi se najčešće javljaju u natkoljenoj regiji, ali imaju tendencu da se jave i u retroperitoneumu. MRI je nespecifičan. Kao i većina mekotkivnih sarkoma, metastazira u pluća, ali najčešće u retroperitoneum, kontralateralnu nogu ili kost. Tretman je široka ekscizija tumora. CT-skenovi pluća, abdomena i male zdjelice trebaju biti uključeni u praćenje stepena i razvoja bolesti. Pacijenti sa lezijama visokog gradusa imaju stepen petogodišnjeg preživljavanja oko 60%. Zaključak: liposarkomi se najčešće prezentiraju kao duboko smještene lezije u proksimalnom aspektu ekstremiteta, dominantno natkoljenice. Biopsija je indicirana prije hirurškog tretmana. Glavni cilj operativnog liječenja je široka ekscizija tumora.

Ključne riječi: miksoidni liposarkom, natkoljena regija, hirurški tretman

INTRODUCTION

The word sarcoma originates from the Greek word sark or sarx, which means flesh (1). Liposarcoma is one of the most common soft tissue sarcomas of the adult life, which ranges from 16-18% of all the soft tissue sarcomas (2). It is seen mostly in males between the sixth and seventh decades. Retroperitoneum and the lower extremity locations are the most common sites. They have a tendency to originate from anatomic areas of normal fat, such as perivascular or perineural locations. Well-differentiated, myxoid, round cell and

pleomorphic liposarcomas are variants of liposarcoma. Well-differentiated and myxoid liposarcomas are low grade and have a low risk for metastasis. Conversely, round cell and pleomorphic liposarcomas are high grade and have high risk for metastasis. Most of them are larger than 5 cm and are deep-seated tumors (3). Plain radiographs are usually normal. MRI is nonspecific except for well-differentiated tumors in which fat signal is shown (4). Lipoma and well-differentiated liposarcoma are usually resected marginally. Well-differentiated liposarcoma or atypical lipomatous tumors have a high risk of recurrence (20-25%) and should be followed for the possibility of local recurrence (3). Treatment for other types of liposarcoma is wide resection. Radiation can be used as adjuvant treatment for large tumors for any case in which margins are close. Poor prognostic indicators include high grade, large size, proximal or deep location, and the presence of metastases (4).

CASE REPORT

A 29-year old male was admitted to our clinic with a giant tumor of the left thigh. The mass was painless, progressively increasing in size for the last two years. Physical examination revealed approximately 45/35 cm hard consistency tumor, seated dominantly in adductor region of the left thigh. The mass seamed immobile, palpatory painless, with no evident inguinal lymphadenopathy (Figure 1). ROM in the left hip and the knee was restricted, due to the size and weight of the tumor. No neurovascular compromise was noted and no previous medical conditions and surgeries were registered. Hereditary anamnesis for malignancies was negative.

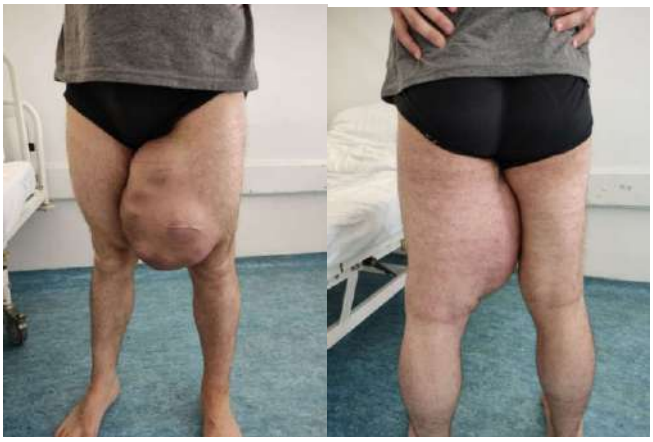

Figure 1 **Giant tumorous mass seated in antero-medial aspect of the left thigh**.

Laboratory findings showed elevated CRP (28.9 mg/L) and mildly elevated LDH (273 U/L). Tumor markers, including Ca 153, CEA, AFP, CA-19-9, PSA and PSA ratio, remained in referent interval. X-rays showed inhomogenous soft tissue enlargement of the left thigh, no bone lesion was notable (Figure 2). CT scans showed extensive tumorous mass, located in anterior and medial compartment of the left thigh (Figure 3). The mass infiltrated sartorius and vastus medialis muscles, and suppressed adductor longus and magnus muscles, and the infiltration of these muscles could not be excluded. Internal, heterogenous, multinodular structure of the lesion suggested myxomatous component and had no hypervascular character, no certain signs of infiltrated femoral vessels (Figure 4). Differential diagnosis included myxoid liposarcoma, myxofibrosarcoma, fibromyxoid sarcoma.

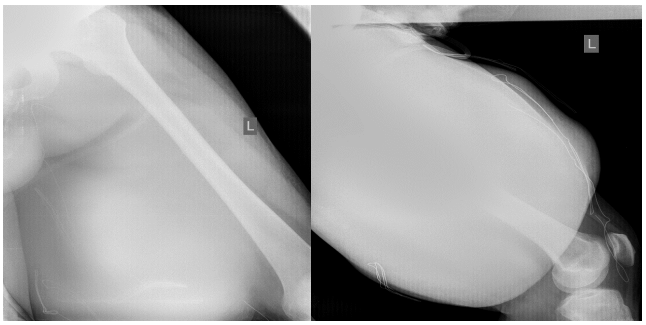

Figure 2 **Left thigh X-rays: Inhomogenous soft tissue enlargement with no bone lesion.**

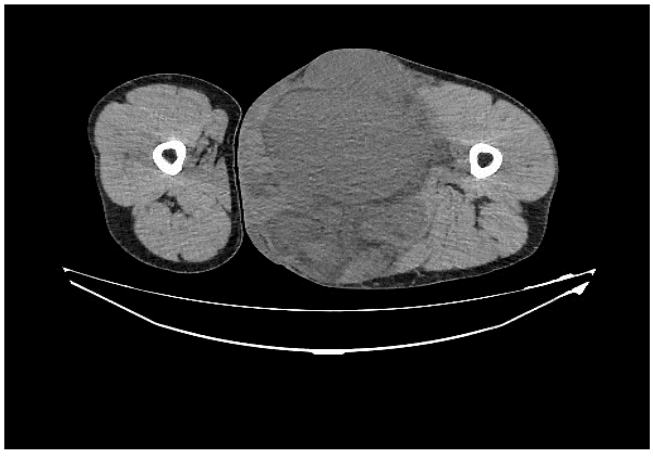

Figure 3 **Axial CT-scans: Large lesion in medial and anterior left thigh compartment.**

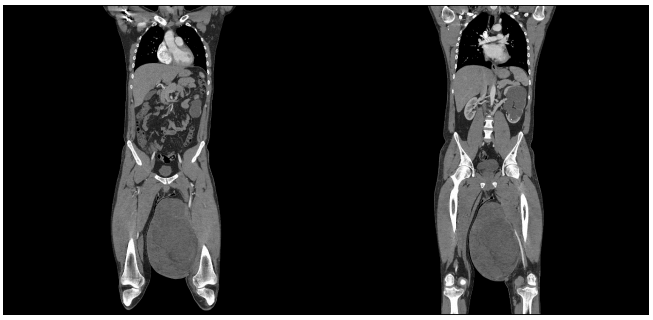

Figure 4 **Coronal CT-angiography scans: no signs of femoral vessels infiltration**.

Core biopsy under the ultrasound control was performed. Pathology examination confirmed myxoid liposarcoma diagnosis. In addition, human citogenetics showed 80% of the cells had DDIT3-gene translocation. The marginal surgical resection was performed (Figure 5 and 6). Tumor was fully extirpated with infiltrated musculature and sent for pathology examination. Neurovascular structures remained intact. The wound healed primarily. The patient was discharged on 12th postoperative day and appointed to oncologic consilium for further treatment.

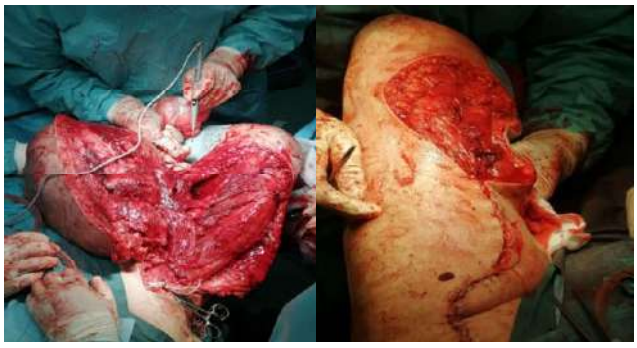

Figure 5 **Intraoperative images.**

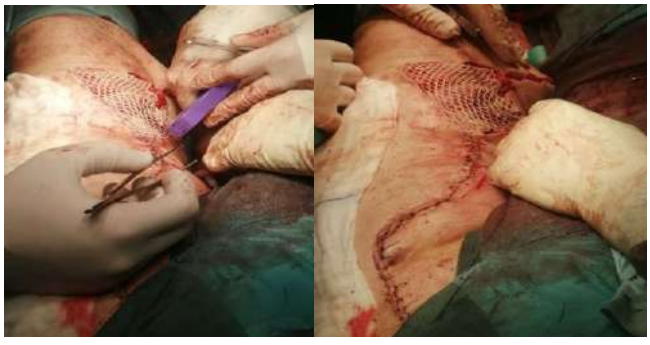

Figure 6 **Intraoperative images.**

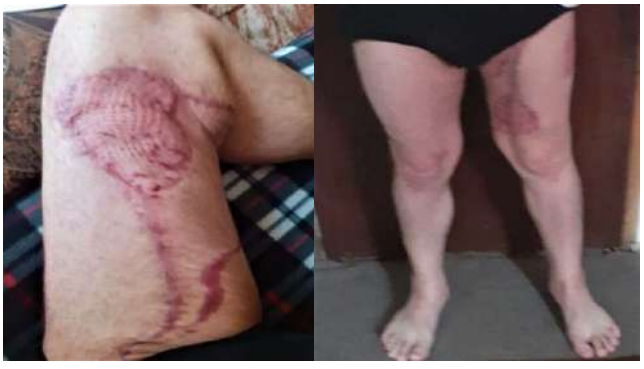

Figure 7 **Postoperative images**.

DISCUSSION

Myxoid liposarcoma is the second most common type of liposarcoma and represents 20%–50% of all liposarcomas (5). Myxoid liposarcomas account for 10% of all soft tissue sarcomas (6). It is seen mostly in males between the fifth and sixth decades (3). Liposarcomas are extraordinarily rare in patients less than 10 years of age (7). However, myxoid liposarcoma is the most common type of liposarcoma to affect children, accounting for 76% of liposarcomatous lesions in patients aged 10-16 years (8). Extremity myxoid liposarcomas are most frequently intermuscular lesions (70% - 80% of cases), and an origin in muscle or subcutaneous. These lesions predominantly affect the lower extremity (75% - 80% of cases), particularly the medial thigh and popliteal regions. Other locations in the lower extremities include the groin, buttock, and calf. The upper extremity accounts for 5% of lesions and the retroperitoneum 8% (9). Histologicaly, myxoid or round cell liposarcomas consist of round, primitive, nonlipogenic mesenchymal cells, and small signet ring lipoblasts in a prominent myxoid stroma. The histologic grade is dependent on the round cell component of the tumor, with greater than 5% being high grade, and is a predictor of worse outcome (1). Our patients histological findings showed myxoid liposarcoma G3; AJCC TNM:pT4, Nx, Mx. Citogenetics showed DDIT3-gene translocation. The clinical symptoms accompanying the diagnosis of soft tissue sarcomas are typically nonspecific (1). The clinical appearance of myxoid liposarcoma is that of a painless, soft-tissue mass. Lesions may be quite large (>15 cm) at presentation, similar to well-differentiated liposarcoma (7). Our patient was a 29-year old male with a progressively growing mass in the left thigh, for the course of over two years, without admitting to general practitioner. Psychosocial and environmental factors, and also indolent symptoms as well, may be the main reasons for the late admittance to GP, especially due to COVID-19 pandemics. Radiographs of myxoid liposarcoma may appear normal or more frequently reveal a nonspecific soft-tissue mass (10). At CT and MR imaging, myxoid liposarcoma often have a pathognomonic appearance. Myxoid liposarcomas are typically large, well-defined, and multilobulated intermuscular lesions. However, the pathognomonic feature is the adipose tissue seen in the mass. MR imaging is superior to CT in this important depiction of fat, owing to its improved contrast resolution (11). Fat also typically constitutes only a small volume of the overall mass size (10% of the lesion) and is often seen in septa, or as subtle small nodules in the lesion. This pathognomonic appearance of fatty septa or small adipose nodules in a myxoid mass has been reported in 42%-78% of cases (12). Prior to surgery, the patient underwent CT scans with angiograms. Intern, heterogenous, multinodular structure suggested possible myxoid liposarcoma. Sartorius and vastus medialis muscles were infiltrated, with possible infiltration of adductor magnus and longus muscles. The lesion had no hypervascular character, femoral artery showed no signs of infiltration. Due to the importance of obtaining an accurate diagnosis, a biopsy is both necessary and appropriate (1). A properly executed surgical resection of the tumor is the most important part of the patient's overall treatment. A wide resection, defined above, is clearly desired and results in the highest likelihood of local control. Unfortunately, this is not always possible due to the location and extent of the tumor. It may be in close proximity to critical structures where obtaining an adequate margin would result in a significant functional deficit. In this situation, adjuvant treatments, such as radiotherapy, can be employed to help achieve local control while maintaining functional limb salvage as an option (1). The majority of patients require radiation therapy with wide resection for the treatment of their disease. When combined with surgery and negative margins, local control rates have been reported to be 90% or greater. The goals of radiotherapy in the management of soft tissue sarcomas are to enhance local control, preserve function, and achieve acceptable cosmetics by contributing to tissue preservation

(13). Adjuvant chemotherapy may also prove beneficial in treatment of myxoid liposarcoma (3). Our surgical team has done marginal tumor resection, due to the size of the tumor and the proximity of the major neurovascular structures. Intraoperatively, infiltrated sections of sartorius, vastus medialis and adductor magnus were found and resected. The adherent skin flap was also resected, and the defect was surgically closed partially by primary suturing and partially by Thiersch skin grafting. Postoperative CT scans of the operative field showed no residual tumor and signs of recurrence. As well, thorax, abdomen and pelvis CT scans showed no signs of metastatic disease. Our patient was admitted to the Clinic of Oncology, and undergone chemotherapy and radiotherapy. The rate of metastatic disease is significantly increased for patients whose myxoid liposarcomas contain a greater proportion of round cell component (14). Pulmonary metastatic disease carries a poor prognosis with a five-year survival rate of approximately 10% (1), although pulmonary involvement is seen in only 6% of patients (3). Unlike the other subtypes of liposarcoma, myxoid lesions have a strong predilection for extrapulmonary metastases. In a study by Pearlstone, et al, 94% of patients with metastatic myxoid liposarcoma also developed metastases in extrapulmonary soft-tissue sites, including the retroperitoneum, thorax and pelvis (15). Current recommendations for surveillance of the soft tissue sarcomas include a clinical exam and chest radiograph or CT scan every 3 months for the first 2 years, every 4 months for the third year, every 6 months for the following 2 years, and annually thereafter. Local recurrence is monitored with physical exams of the surgical site at routine intervals. If the patient is felt to be at high risk for local recurrence or there is concern on physical exam findings, then an ultrasound or MRI with and without gadolinium should be obtained (1). The overall 5-year survival rate for patients with myxoid liposarcoma ranges from 47% to 77% (3).

CONCLUSION

Liposarcomas most common occur as a deep-seated lesions in proximal aspect of the extremity, primarily the thigh. Prior to surgery, biopsy is indicated. The main goal of the surgery is wide resection.

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Severe depressive episode as a consequence of social isolation: case report

Teška depresivna epizoda kao posljedica socijalne izolacije: prikaz slučaja

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ABSTRACT

Introduction: any extreme life situation results in problems with psychological adaptation, mental self-defence mechanisms, and disturbances in the spectrum of anxiety and depressive disorders, which was especially manifested during the COVID-19 pandemic. Aim: to establish possible causal link of social isolation as a "trigger" for the development of a severe depressive episode Case report: the paper describes a case of severe depressive episode which correlates with the beginning of a coronavirus pandemic. The patient's daily routine was disrupted by the imposed restrictions of self-isolation, and by constantly exposing himself to news about the danger and mortality of the virus, she developed fear, anxiety and low mood. After the realized hospitalization, the patient also recorded symptoms from the sphere of depressive illnesses, which were originally treated with noradrenergic and specific serotonergic antidepressants augmented by atypical antipsychotic, which led to her stabilization. Conclusion: social isolation and effects of coronavirus on mental health have not yet been sufficiently investigated. Our research justifies further investigations of this phenomenon.

Keywords: COVID-19, social isolation, mental health

SAŽETAK

Uvod: svaka ekstremna životna situacija za posljedicu ima probleme psihičkog prilagođavanja, mentalnim mehanizmima samoobrambene, te smetnje u spektru anksiozno-depresivnih poremećaja, što se posebno pokazalo tokom pandemije COVID-19. Cilj: da se utvrde moguće uzročne veze socijalne izolacije kao "okidača" za razvoj teške depresivne. Prikaz slučaja: u radu je opisan prikaz slučaja pojave teške depresive epizode, a koja korelira sa početkom pandemije koronavirusa. Pacijentici je nametnutim restrikcijama samoizolacije, socijalnog distanciranja, narušena svakodnevna rutina, te je stalnim izlaganjem vijestima o opasnosti i smrtnosti virusa razvila strah, anksioznost, sniženo osnovno raspoloženje. Po realiziranoj hospitalizaciji, kod pacijentice se evidentiraju simptomi iz kruga depresivnih poremećaja, koji se tretiraju noradrenergičkim i specifičnim serotonergičkim antidepresivom, a potom i augmentacijom atipičnim antipsihotikom, na što dolazi do stabilizacije. Zaključak: socijalna izolacija i posljedice koronavirusa na mentalno zdravlje još uvijek nisu dovoljno ispitane. Naše istraživanje opravdava dalja ispitivanja ovog fenomena.

Ključne riječi: COVID -19, socijalna izolacija, mentalno zdravlje

INTRODUCTION

Any extreme life situation results in problems with psychological adaptation, mental self-defence mechanisms, and disturbances in the spectrum of anxiety and depressive disorders. This was especially manifested during the COVID-19 pandemic. In 2020, the perception of life changed. Restrictive measures instated to reduce exposure to COVID-19 infection and thus disease through social isolation, have led to a disturbance of the overall settings of social relations (1). All of this has led to the appearance of fear, tension, depressive mood, loss of interest and satisfaction in normal activities, sleep and eating disorder. Those symptoms are characteristic of depressive and anxiety disorders (2, 3).

AIM

The aim of the paper was to establish possible causal link of social isolation as a "trigger" for the development of a severe depressive episode.

CASE REPORT

A 64-year-old patient, married, mother of three adult sons, housewife was referred to our Clinic. Changes in the mental and behavioural state occurred in May 2020, two weeks after the restriction measures were imposed due to the COVID-19 pandemic. Those changes manifested in increased nervousness, high concern for her own health and safety, as well as safety of her family. She also reported stomach ache, loss of appetite and insomnia.

She was born in a normal family as the oldest of two children. Her mother's pregnancy and childbirth, as well as her early psychomotor development, went without any complications. She grew up in a stable family environment. She started school in time, finishing only four grades of primary school education. As reported by our patient, her mother had similar mental disorders. She is living with her husband in a harmonious marriage. Her sons left their parents' home and started their own families.

Due to disorders mentioned above, during the year 2020 the patient underwent many lab diagnostics and consultative specialist examinations, which excluded the organic substrate of her illness. She was eventually referred to a psychiatrist. During the first quarter of 2021, the patient was examined several times in the admission department of the Psychiatric Clinic when she verbalized psychiatric disorders in the form of tension, anxiety, overall reduction of her functionality along with stomach pain. A diagnosis of mixed anxiety-depressive disorder was given. Therapy, which included selective serotonin reuptake inhibitor (SSRI) paroxetine and first-generation antipsychotic sulpiride was administered at a dose that achieves an antidepressant effect while reducing mentioned somatic symptoms. The patient was pessimistic about the therapy. She was not motivated to accept hospital treatment and insisted on outpatient treatment and correction of therapy. However, the patient reacted slowly and insufficiently to the prescribed psychopharmacotherapy and, after three weeks, she voluntarily agreed to hospital treatment.

At admission, the patient was tested and evaluated with HAM-D 25, HAM-A 22, CGI-I 6.

During the hospital treatment, standard laboratory tests (blood tests, hormonal status of the thyroid gland) were performed, which were in reference values, as well as neurocranium CT, which was normal, and the patient was also psychologically evaluated.

The therapy which was given in the time prior to hospitalization was adjusted in terms of gradual reduction and discontinuation, with titration of antidepressant mirtazapine from the NaSSA (Noradrenergic and specific serotonergic antidepressants) group in a total daily dose of 15 mg in the evening, and as augmentation therapy we introduced atypical antipsychotic aripiprazole in the total daily dose of 10 mg in the morning.

During the next two weeks, the patient became more relaxed, less worried, the facial expression was brighter and an increase in vital capacities was recorded. Sleep was regulated. The patient started to eat normally, gradual increase in body weight was noticed along with reduction of disorders related to somatic problems and the patient started to gradually get involved in social contacts, and the overall mental state showed a clear tendency to improve.

Satisfactory cooperation of the patient was achieved in terms of accepting the necessity of hospitalization, anxiety was in withdrawal, the mood was improved and interest in social contacts grew. At discharge, the assessment of HAM-D was 12, HAM-A 15, CGI-I 2. The patient is undergoing regular follow-up outpatient examinations and is active in psychotherapeutic therapy settings. Improvement of voluntary-instinctual dynamisms and mood, adequate social and work functionality indicated a favourable psychopharmacological outcome.

DISCUSSION

The pandemic caused by COVID-19 infection consequently reflected on all aspects of people's functionality, including changes in the mental state and general efficiency, as recorded in our case. This correlates with the results of research conducted during the COVID-19 pandemic within the lockdown measures. Consequent reduction of social contacts with reflection on mental health was recorded (5).

A study conducted on a sample of 843 people from 51 Turkish cities indicated a cause-and-effect relationship between social isolation and psychological adjustment/maladaptation of examinees in relation to the occurrence of stress, anxiety and depression (6).

A survey conducted on a national Internet sample in March 2020 on 435 adult examinees in the United States tried to answer the question of whether the imposed measures (social distancing and the need to stay at home) are associated with the development of symptoms of acute stress, depression, generalized anxiety disorder (GAD) and insomnia. A subsample of 118 participants who completed a survey which was measuring the presence of the above symptoms at the beginning of the pandemic (February 2020), showed an increase in the number of patients with symptoms of depression and GAD during February and March. Prolonged time of pandemic and imposed measures including social distancing was linked with an increase in the presence of these mental disorders (7).

A study of 3,005 adults aged 57-85 with symptoms of depression and anxiety showed that social isolation was a predictor of the development of more severe clinical cases of depression and anxiety (9).

Genetic determinants, environmental factors, such as stressful life events, are known to increase the risk of developing psychiatric disorders, as well as the risk of relapses. The imposed measures and the consequent social isolation are leading to increased secretion of cortisol, the so-called stress hormone. General adaptation syndrome (GAS) describes the process your body goes through when you are exposed to any kind of stress, positive or negative. It has three stages: alarm, resistance, and exhaustion. The alarm reaction stage is the body's initial response to stress. This stage is also referred to as the fight-or-flight response. During this stage, the body's sympathetic nervous system is activated by the sudden release of hormones (such as cortisol, adrenaline and noradrenaline). The resistance stage is when body tries to repair itself after the initial shock of stress. If the stressful situation is no longer present than everything will start to return to prestress levels during this stage. However, if the stressful situation continues for a long time, body will never receive a clear signal to return to normal functioning levels. This means it will continue to secrete the stress hormones. Prolonged or chronic stress leads to the last stage of exhaustion. Enduring stressors without relief drains physical, emotional, and mental resources to the point where body is no longer able to cope with stress (8). Excessive cortisol secretion has a number of detrimental effects on the body (9) and given the importance of its role, future research is expected to significantly improve knowledge about the role of steroid hormones in psycho-immunological studies.

CONCLUSION

The measures imposed during the pandemic caused by SARS COV-2 infection resulted in significant changes in the mental health and affected all parts of general efficiency of the individuals. It is possible to establish a causal link between stress, social isolation, a generally altered way of functioning on one side, with the development of a depressive/anxiety disorders on the other side, especially in a vulnerable group of individuals burdened with heritability for psychiatric disorders. We believe that planning and implementation of future initiatives and projects in the field of public health, involving the wider community, through information on possible risk factors for mental health, would significantly contribute to prevention of its consequences.

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