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KLINIČKI CENTAR UNIVERZITETA SARAJEVO

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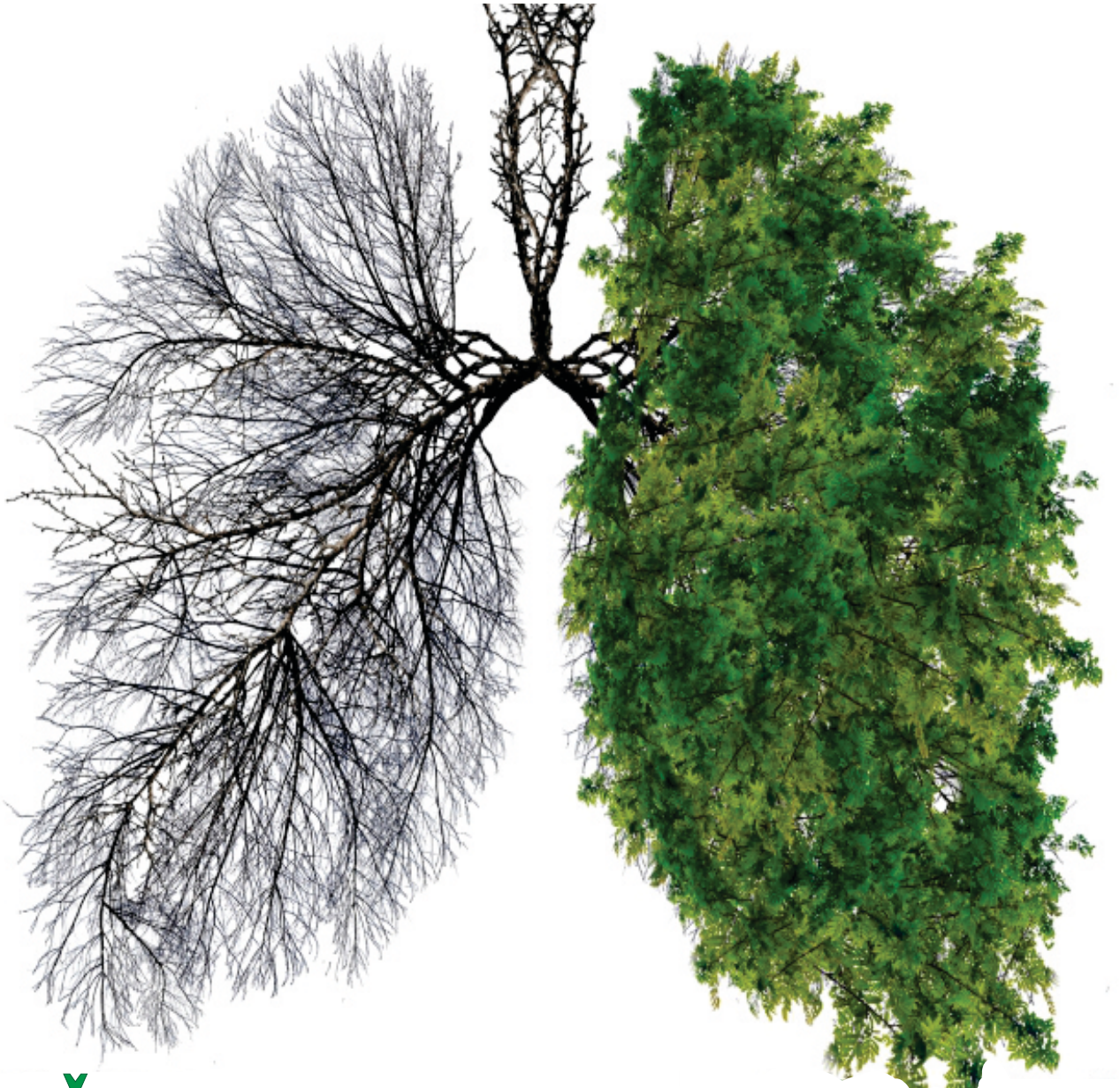

ČUVAJTE SVOJE ZDRAVLJE!

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 !

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Croatia	Germany *	Spain *
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Estonia	Romania	Turkey

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

Novi Evropski vodič za prevenciju tromboembolizma kod A Fib

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

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

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

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

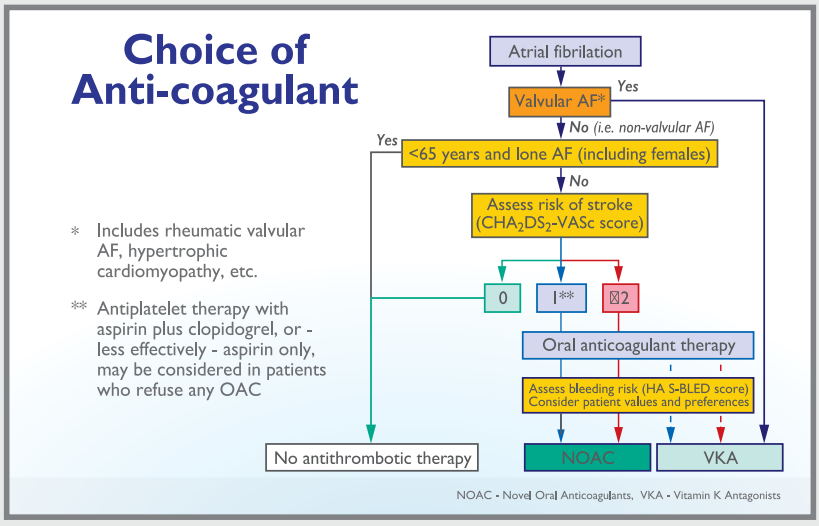
Major i non-major riziko fakori za procjenu tromboembolizma kod A Fib!

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

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

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

Algoritam antikoagulantne terapije nakon procjene CHA_2DS_2VASc i major risk faktora!



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AIMS AND SCOPE

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Mean arterial pressure as predictor of outcome in patients with ruptured abdominal aortic aneurysm

Srednji arterijski pritisak kao prediktor ishoda tretmana kod pacijenata sa rupturom aneurizme abdominalne aorte

Amel Hadžimehmedagić*[1,2], Tarik Selimović[1], Damir Kurtagić[1], Ilirijana Haxibeqiri-Karabdić[1], Slavenka Štraus[1,2], Edin Kabil[1,2], Muhamed Djedović[1,2]

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ABSTRACT

Introduction: hypertension stands as an established risk factor for AAA diagnosis. However, evidence on whether controlling blood pressure can reduce AAA growth is lacking. Aim: the variable importance assigned to systolic and diastolic BP in the literature prompted authors to propose the use of mean arterial pressure (MAP) for a more comprehensive assessment. Materials and methods: all 44 patients with an RAAA underwent urgent repair of an RAAA at the Clinic of Cardiovascular Surgery of the Clinical Center University of Sarajevo in the period from January 2021 to November 2022. Results: there was no statistically significant difference between the analyzed groups regarding cerebrovascular comorbidities (p=0.290), cardiac comorbidities (p=0.932), renal insufficiency (p=0.112), lethal outcome (p=0.209), while we have noticed significant difference in inotropic support (p=0.045), and postoperative complications (p=0.025). Conclusion: patients who initially presented with lower mean arterial pressure, as opposed to those subjected to aggressive fluid resuscitation, exhibited improved survival. These findings reaffirm the established tenets regarding the management of blood loss, the potential benefits of controlled inotropic support, and the criticality of mean arterial pressure in shaping patient outcomes.

Keywords: mean arterial pressure; abdominal aortic aneurysm rupture

SAŽETAK

Hipertenzija je utvrđeni faktor rizika za dijagnozu AAA. Međutim, nedostaju dokazi o tome može li kontrola krvnog pritiska smanjiti rast AAA. Cilj: relativni značaj koji se u literaturi pripisuje sistolnom i dijastolnom krvnom pritisku podstakao je autore da predlože upotrebu srednjeg arterijskog pritiska (MAP) za sveobuhvatniju procjenu. Materijali i metode: od januara 2021. do novembra 2022. godine kod svih 44 pacijenata sa RAAA izvršena je hitna sanacija RAAA u Klinici za kardiovaskularnu hirurgiju Kliničkog centra Univerziteta u Sarajevu. Rezultati: nije bilo statistički značajne razlike između analiziranih grupa u pogledu cerebrovaskularnih komorbiditeta (p=0,290), srčanih komorbiditeta (p=0,932), bubrežne insuficijencije (p=0,112), te smrtnih ishoda (p=0,209), dok smo uočili značajnu razliku u inotropnoj podršci (p=0,045) i postoperativnim komplikacijama (p=0,025). Zaključak: Pacijenti koji su u početku imali niži srednji arterijski pritisak, za razliku od onih koji su bili podvrgnuti agresivnoj tečnoj reanimaciji, pokazali su poboljšano preživljavanje. Ovi nalazi reafirmišu utvrđene principe u vezi sa upravljanjem gubitkom krvi, potencijalnim prednostima kontrolisane inotropne podrške i kritičnosti srednjeg arterijskog pritiska u oblikovanju ishoda oporavka pacijenata.

Ključne riječi: srednji arterijski pritisak, ruptura aneurizme abdominalne aorte

INTRODUCTION

Hypertension stands as an established risk factor for abdominal aortic aneurysm (AAA) diagnosis. Defined by the World Health Organization (WHO) as systolic blood pressure (SBP) equal to or above 130 mmHg, and/or diastolic blood pressure (DBP) equal to or above 80 mmHg, hypertension's prevalence is projected to rise due to aging, population growth, and changes in behavioral risk factors. However, evidence on whether controlling blood pressure can reduce AAA growth is lacking. Hemodynamic factors, such as peak wall stress associated with AAA growth and rupture, depend on systemic blood pressure, suggesting that blood pressure could be an important target to limit AAA progression. Past clinical trials testing blood pressure-lowering medications reported no effect on AAA growth, with conflicting findings in prospective studies regarding the association between blood

pressure or hypertension and AAA. Current guidelines recommend maintaining blood pressure less than or equal to 130/80 mmHg in people diagnosed with AAA to reduce the risk of cardiovascular events (1-7).

Aneurysm, a term denoting the localized and enduring dilation of a blood vessel with a diameter exceeding 50% of its normal dimensions, distinguishes itself from ectasia (a permanent dilation that falls short of the 50% threshold) and arteriomegaly (a diffuse and enduring enlargement of a blood vessel). Within this spectrum, AAA is referred to as the pathological enlargement of the abdominal aorta, commonly exceeding 30 mm, primarily affecting the infrarenal segment due to its inherent lower elastin concentration and vasa vasorum, with a tendency for gradual expansion (averaging 0.2/0.3 cm annually) and a concomitant risk of rupture (1).

The pathogenesis of abdominal aortic aneurysm (AAA) represents a complex, multifactorial degenerative process influenced by a variety of etiological elements. Risk factors for the development of AAA include older age, male gender, Caucasian race, family history of the disorder, atherosclerotic disease and smoking the latter being considered the primary modifiable risk factor. Other potential risk factors include diabetes mellitus (DM), which has been shown to be negatively associated with AAA, greater height and low fruit and vegetable consumption. They also include connective tissue disorders (Ehlers-Danlos and Marfan syndromes) (2), medial cystic necrosis, tuberous sclerosis, trauma, infections, arteritis, endomechanical variables, and "nonspecific" aneurysms devoid of a specific cause (3). While atherosclerosis was once widely acknowledged as a causal factor, its association with AAA remains the subject of ongoing research, evoking controversy (4,5,6). Despite shared risk factors and a correlation between plaque location and aneurysm size expansion the majority of patients with atherosclerotic occlusive disease do not concurrently present with aneurysms.

While both systolic and diastolic measurements remain essential for diagnosis and treatment, clinical research suggests that in patients above 50 years old, systolic BP may be a more important predictor of adverse events, whereas in patients under 50 years old, diastolic BP may be slightly more predictive. Different studies suggests that hypertension increases the risk of developing AAA by 66% (7). The variable importance assigned to systolic and diastolic BP in the literature prompted authors to propose the use of mean arterial pressure (MAP) for a more comprehensive assessment. MAP, calculated as the average of arterial blood pressure throughout one cardiac cycle, has shown enhanced diagnostic and statistical efficacy compared to separate systolic and diastolic BP measurements. This approach becomes particularly relevant in examining the association of blood pressure with potential causative factors and in improving the detection of mild cases of hypertension. MAP is influenced by cardiac output and systemic vascular resistance, each of which is influenced by several variables. Additionally, MAP offers a practical means of calculation using the formula: $MAP = DP + 1/3 (SP - DP)$ or $MAP = DP + 1/3(PP)$, where DP is the diastolic blood pressure, SP is the systolic blood pressure, and PP is the pulse pressure (8,9).

A decreased risk of a composite of all-cause mortality and readmission to hospital was linked to a higher MAP. For individuals with heart failure, maintaining a comparatively higher MAP may improve the clinical outcome (8,23). Other results indicate that for physical function assessments and related comprehensive fall risk assessments, as well as for weakness, slowness, and poorer balance in older Americans, mean arterial pressure and pulse pressure should be taken into consideration (8-24).

Furthermore, the risk of rupture in AAA is multifactorial, involving geometric configuration, vessel tortuosity, and the presence of intraluminal pathology. Fluid-structure interaction (FSI) simulations have demonstrated increasing wall stresses from normal to pathological cases, with intraluminal thrombus (ILT) potentially exerting a protective effect. Notably, MAP has proven valuable in FSI simulations, contributing to an improved understanding of wall stresses in ruptured aneurysms (10).

Aggressive fluid resuscitation has long been considered the cornerstone in the management of haemorrhagic shock and is widely taught at a basic level. The evidence for this approach originated historically from a canine model of haemorrhagic shock, where hypotension was maintained for several hours by controlled haemorrhage and arterial pressure was restored by the infusion of shed blood. Subsequent research demonstrated that crystalloid infusion equivalent to 2-3 times that of the volume of blood lost could adequately restore blood pressure and many pre-hospital and hospital professionals have employed this technique in the resuscitation of patients with ruptured abdominal aortic aneurysm (AAA). However, unlike the animal models, haemorrhage is not controlled before surgery in patients with ruptured AAA and there is considerable evidence that vigorous fluid replacement may exacerbate bleeding by causing dilutional and hypothermic coagulopathy associated with infusing large volumes of cold fluids; and secondary clot disruption from increased blood flow, increased perfusion pressure and decreased blood viscosity. In 1918 Cannon introduced the concept of deliberate hypotension in the treatment of wounds to the torso with the intent of minimising internal bleeding (11,22).

The mortality for ruptured abdominal aortic aneurysm (RAAA) remains high, with approximately 5.6-17.5 per 100,000 person-years in Western countries and the overall mortality rate of patients with an RAAA is approximately 80% (12).

Understanding the complex etiology, risk factors, and hemodynamic considerations in AAA is crucial for effective management and prevention of adverse events such as rupture. The multifaceted nature of AAA necessitates a comprehensive approach, considering factors such as blood pressure dynamics, MAP, and the intricate interplay of geometric and intraluminal factors contributing to the risk of rupture. Advances in these areas contribute to refining diagnostic and therapeutic strategies, ultimately improving patient outcomes.

AIM

The primary goal of this study was to elucidate the two-year incidence of abdominal aortic aneurysm rupture, examine the gender and demographic composition of affected individuals, assess perioperative mortality risk resulting from hemorrhage, and scrutinize patient outcomes in cases of ruptured abdominal aortic aneurysm, with a specific focus on low mean arterial pressure as a predictive determinant of patient prognosis.

MATERIALS AND METHODS

This retrospective cross-sectional investigation was conducted in the period from January 2021 to November 2022 at the Clinic of Cardiovascular Surgery of the Clinical Center University of

Sarajevo. The protocol included admission under emergency conditions, emergency surgery, postoperative treatment in the intensive care unit, and ambulatory supervision for a month after discharge. The study considered demographic data and all parameters related to the clinical course, objective calculation of the loss of circulating volume due to bleeding, degree of development of hemorrhagic shock, and duration of acute preoperative symptomatology. Additionally acknowledged were the relevant laboratory analyses related to the degree of renal function impairment. All data excluded from medical documentation was stored in a unique database that represents research material and the basis for statistical processing. The research focused on the meticulous review of medical records pertaining to a cohort of 43 patients. It is noteworthy that this study garnered the necessary prior authorization and endorsement from the Ethics Committee of the Clinical Center University of Sarajevo, thereby ensuring its ethical soundness. The study adhered unwaveringly to the successive revisions of the Helsinki Declaration as delineated in the study protocol. The exclusion criteria encompassed the following: patients who, of their own volition, declined surgical intervention and departed the clinical setting, as well as patients who regrettably succumbed prior to the initiation of the scheduled surgical procedure.

Statistical analysis

The MAP values were calculated from the obtained data and using the general formula: MAP = DP + 1/3(SP – DP) or MAP = DP + 1/3(PP), where DP is the diastolic blood pressure, SP is the systolic blood pressure, and PP is the pulse pressure. The collected data underwent a systematic arrangement and underwent statistical analysis, a process executed using version 27.0 of the Statistical Package for the Social Sciences (SPSS). Data that exhibited a normal distribution were presented through the expression of frequencies, percentages, and the mean value accompanied by its standard deviation, while data that deviated from a normal distribution were represented as the median along with the respective 25th and 75th percentiles. Descriptive statistical techniques were employed to elucidate the characteristics of the data, with a particular focus on the presentation of data trends over the course of a three-year timeframe within the various groups. The threshold for statistical significance was predefined at $p<0.05$.

RESULTS

All 44 patients with an RAAA underwent urgent repair of an RAAA at the Clinic of Cardiovascular Surgery of the Clinical Center University of Sarajevo. Out of 44 patients, 37 (86%) were male and 7 (14%) were female with a median age of 71 +/- 7.404. 16 out of 44 patients had a history of underlying or previous cardiac disease, while the majority of patients, 86% of them had renal insufficiency (Tables 1,2). Other comorbidities present in patient included: type 2 diabetes mellitus in 10 (22.7%) cases, hyperlipidemia in 12 (27.3%) cases, chronic obstructive pulmonary disease in 5 (11.3%) cases.

Table 1 **Cardiac comorbidities.**

	Frequency	Percent	Valid Percent
No	27	62.8	62.8
Yes	16	37.2	37.2
Total	43	100.0	100.0

Table 2 **Renal insufficiency.**

	Frequency	Percent	Valid Percent
No	6	14.0	14.0
Yes	37	86.0	86.0
Total	43	100.0	100.0

Table 3 **Hemoragic shock.**

	Frequency	Percent	Valid Percent
No	13	30.2	30.2
Yes	30	69.8	69.8
Total	43	100.0	100.0

It was noted that 30 patients had signs of hemorrhagic shock (Table 3.). On average, patients perioperatively lost 1654.4±757.1 ml of blood, with a minimum of 450 ml and a maximum of 3200 ml.

Perioperative inotropic support was administered to 25 (56.8%) patients (Table 4). The statistical analysis showed that there was a significant correlation in values of mean arterial pressure and requirement for inotropic support ($p<0.05$), but there was no statistically significant correlation between usage of inotropic support and mortality (Table 5).

Table 4 **Inotropic support.**

	Frequency	Percent	Valid Percent
No	18	41.9	41.9
Yes	25	58.1	58.1
Total	43	100.0	100.0

Table 5 **Correlation between Inotropic support and lethal outcome.**

		Inotropic support
Lethal outcome	Pearson Correlation	.244
	Sig. (2-tailed)	.115
	N	43

Postoperative complications included: peripheral vascular ischemia, amputation of the lower limb, prolonged mechanical

ventilation, newly onset renal, cardiac, and neurological incidents, etc. In total postoperative complications were observed in 29 out of 43 patients (Table 6.). A statistically significant correlation was found between the occurrence of postoperative complications and the incidence of mortality (Table 7).

Table 6 **Postoperative complications.**

	Frequency	Percent	Valid Percent
No	14	32.6	32.6
Yes	29	67.4	67.4
Total	43	100.0	100.0

Table 7 **Correlation between postoperative complications and lethal outcome.**

		Postoperative complications
Lethal outcome	Pearson Correlation	-.675
	Sig. (2-tailed)	<.001
	N	43

With regard to mean arterial pressure, it was found that there was a statistically significant correlation between low mean arterial pressure and occurrence of postoperative complications ($p<0.05$), as well the need for inotropic support ($p<0.05$) (Table 8, Figure 1). No statistically significant correlation between MAP and mortality was found. It has to be mentioned that much better survival prognosis was noted in patients who had controlled hypotension with low mean arterial pressure of 60±10 mmHg compared to patients who received aggresive fluid comepnsation with mean arterial pressure of 80±10mmHg , although patient sample was small so it did not reach statistical significance (Figure 1).

Table 8 **Correlations of MAP with preoperative comorbidities, perioperative and postoperative.**

data		Mean arterial pressure
Cerebrovascular comorbidities	Pearson Correlation	-.165
	Sig. (2-tailed)	.290
	N	43
Cardiac comorbidities	Pearson Correlation	.013
	Sig. (2-tailed)	.932
	N	43
Renal insufficiency	Pearson Correlation	-.246
	Sig. (2-tailed)	.112
	N	43
Lethal outcome	Pearson Correlation	-.195
	Sig. (2-tailed)	.209
	N	43
Inotropic support	Pearson Correlation	-.308
	Sig. (2-tailed)	.045
	N	43
Postoperative complications	Pearson Correlation	.341
	Sig. (2-tailed)	.025
	N	43

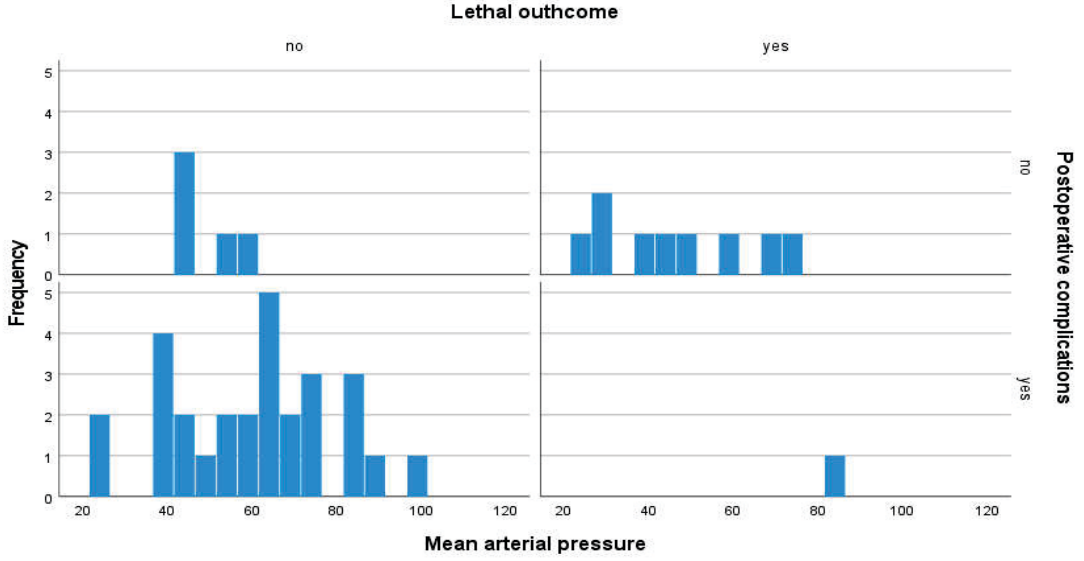

Figure 1 **Correlation of mean arterial pressure, postoperative complications and mortality.**

DISCUSSION

To the best of our knowledge, this study represents the first research effort within Bosnia and Herzegovina aimed at determining low mean arterial pressure as a predictor of the ultimate outcome in patients afflicted with abdominal aortic aneurysm rupture. In addition to elucidating the advantages and repercussions associated with resuscitation strategies, this inquiry sheds light on their potential implications, thereby extending valuable insights into the domain. Furthermore, it provides a comprehensive account of the prevailing prevalence of abdominal aortic aneurysm ruptures, taking into consideration their concomitant comorbidities and other vascular-related ailments. The study cohort predominantly consisted of male individuals, who presented with a spectrum of medical conditions including hypertension, heart failure, type 2 diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, and renal insufficiency.

One of the notable demographic aspects of our patient cohort was the predominance of male patients, with a male-to-female ratio of approximately 6:1. This skewed gender distribution is consistent with previous literature on aortic aneurysms, suggesting a higher incidence of aneurysmal disease in men. Intriguingly, our study revealed that males had a statistically significantly higher chance of lethal outcomes ($p=0.04$) than their female counterparts, which is different than in other studies that we have found (13-16). This gender-based discrepancy in RAAA outcomes merits further investigation.

Renal insufficiency was a prevalent comorbidity in our patient cohort, affecting the majority of individuals. Our findings indicate that patients with previous renal disease had a higher chance of mortality ($p=0.04$). Given the substantial renal complications associated with RAAA repair, including acute kidney injury, our results underscore the importance of proactive renal assessment and management in this population.

Concordant with prior investigations, a consistent focus has been directed towards the pivotal role of blood loss in determining surgical outcomes. Literature has consistently posited that excessive intraoperative blood loss engenders an elevated risk of postoperative complications, including mortality. In alignment with these established paradigms, our findings demonstrate a significantly less perioperative blood loss among patients who ultimately survived (14). In the realm of cardiovascular surgery, the utilization of inotropic support has remained an area of perpetual interest. An assortment of studies has probed the impacts of inotropic agents on cardiac function and patient outcomes. Although there was no statistically significant correlation between inotropes usage and mortality, our study identified more stable mean arterial pressure in patients receiving inotropic support thereby underscoring the potential advantages of such interventions (17).

Various studies, like the one from have reported that in the context of suspected rupture of an abdominal aortic aneurysm (AAA), fundamental principle of management is the practice of hypotensive hemostasis, which can be achieved through the implementation of permissive hypovolemia or controlled hypotension (18). According to some research this concept has also been incorporated into the treatment algorithm for ruptured abdominal aortic aneurysms (RAAA) at the University Hospital of Zurich (19). To elaborate, in cases where there is suspicion or confirmation of bleeding from a RAAA, it is recommended to deliberately lower the systolic blood pressure (SBP) within the range of 70-90 mmHg. If the patient exhibits hemodynamic instability, treatment options include catecholamine therapy or fluid resuscitation (18). The underlying rationale for this approach lies in the reduction of blood loss at the site of rupture, thereby decreasing the requirement for transfusions and diminishing the risk of coagulopathy and the impending threat of abdominal compartment syndrome. Ultimately, this strategy contributes to an overall reduction in perioperative mortality (18,19).

The interplay between mean arterial pressure and patient outcomes has been the subject of scrutiny across several studies. A diminished mean arterial pressure may culminate in insufficient tissue perfusion, potentially leading to certain organ dysfunction. Our study's observation that patients with lower mean arterial pressure, in contrast to those who underwent aggressive fluid resuscitation, exhibited superior prognostic outcomes in terms of survival., but also exhibited more postoperative non lethal complications. This aligns with the overarching concept that maintaining hemodynamic stability is of paramount significance for less postoperative complications (18,20).

While this study does not directly delve into the comparison of surgical approaches such as open surgery versus minimally invasive techniques, the broader domain of cardiovascular surgery research has witnessed investigations into the merits and demerits of varying surgical methodologies. Future research endeavors may consider exploring the implications of surgical approach specifically within the context of abdominal aortic aneurysm rupture cases (21).

Nonetheless, our study harbors certain limitations. Primarily, it was confined to a solitary cardiovascular surgical center within the country, necessitating the inclusion of data from all cardiovascular surgical centers nationwide in future research to provide a more comprehensive perspective. Additionally, our it did not encompass patients who necessitated a conversion from one surgical technique to another during the operative procedure. Subsequent studies should encompass this subgroup to appraise operative complications, the success rates in completing minimally invasive cardiac surgery procedures, and potential enhancements in both preoperative and postoperative strategies aimed at mitigating such occurrences. Furthermore, forthcoming research should contemplate the incorporation of a postoperative doctor-patient questionnaire to evaluate patients' subjective experiences subsequent to these procedures.

CONCLUSION

In summary, the findings of this study resonate with the broader body of research within the domain of cardiovascular surgery and perioperative care. Patients who initially presented with lower mean arterial pressure, as opposed to those subjected to aggressive fluid resuscitation, exhibited improved survival. These findings reaffirm the established tenets regarding the management of blood loss, the potential benefits of controlled inotropic support, and the criticality of mean arterial pressure in shaping patient outcomes. This contribution enriches the expanding body of evidence that informs clinical practice, underscoring the need for tailored, multidisciplinary approaches to optimize patient care. Future studies may leverage these insights to augment patient outcomes in the arena of cardiovascular surgery

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Elevated C-reactive protein could be useful as predictive factor for the severity of the COVID-19 infection and potential invasive mechanical ventilation

Povišeni C-reaktivni protein može biti koristan kao prediktivni faktor za procijenu težine COVID-19 infekcije i potencijalnu invazivnu mehaničku ventilaciju

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ABSTRACT

Introduction: a systematic inflammatory response has been observed in Coronavirus disease-19 (COVID-19). C-reactive protein (CRP is well established as a marker of systemic inflammation and severe bacterial infection. Elevated CRP concentrations have also been reported in severe viral infections, including H1N1 influenza pneumonia and recently SARS-CoV-2 infection. Aim: to determine whether C-reactive protein level in COVID-19 patients upon admission to the hospital might be a biomarker for early prediction of invasive mechanical ventilation, i.e. intubation. Materials and methods: a retrospective, single centre study was conducted and comprised 136 surviving patients with COVID-19 infection, who were admitted to the Clinical Centre University of Sarajevo in the period from March to May 2021. Results: serum CRP concentration in intubated COVID-19 patients (189.1 ± 71.4 mg/L) was statistically significantly higher ($p<0.001$) than serum CRP concentration in non-intubated COVID-19 patients (70.2 ± 65.2 mg/L). The sensitivity and specificity of CRP in assessing the need for intubation in COVID-19 patients was investigated by Receiver operating characteristic (ROC) analysis. In differentiating intubated from non-Intubated COVID-19 patients; areas under the curve (AUC) for CRP was 0.910, with 95% CI of 0.85 - 0.966 ($p < 0.001$); the optimal cut-off value was 113.5 mg/L with 90.9% sensitivity and 85.7% specificity. Conclusion: the results imply that CRP testing could be useful as predictive factor of COVID-19 severity and potential intubation.

Keywords: COVID-19, inflammatory markers, serum C-reactive protein

SAŽETAK

Uvod: uočen je sistemski upalni odgovor kod bolesti Coronavirus-19 (COVID-19). C-reaktivni protein (CRP) dobro je poznat kao marker sistemske upale i teške bakterijske infekcije. Povišene koncentracije CRP-a zabilježene su i kod teških virusnih infekcija, uključujući upalu pluća uzrokovanu gripom H1N1, a od nedavno i kod infekcije SARS-CoV-2. Cilj: odrediti da li bi nivo C-reaktivnog proteina kod COVID-19 pacijenata pri prijemu u bolnicu mogao biti biomarker za rano predviđanje invazivne mehaničke ventilacije, tj. intubacije. Materijali i metode: provedena je retrospektivna studija jednog centra i obuhvatila je 136 preživjelih pacijenata s COVID-19 infekcijom, a koji su primljeni u Klinički centar Univerziteta u Sarajevu u periodu od marta do maja 2021. godine. Rezultati: koncentracija CRP u serumu intubiranih pacijenata s COVID-19 (189,1 ± 71,4 mg/L) bila je statistički značajno viša ($p<0,001$) od koncentracije CRP u serumu neintubiranih pacijenata s COVID-19 (70,2 ± 65,2 mg/L). Osjetljivost i specifičnost CRP-a u procjeni potrebe za intubacijom kod pacijenata s COVID-19 ispitana je analizom operativnih karakteristika prijemnika (ROC). U razlikovanju intubiranih od neintubiranih pacijenata s COVID-19; areas under the curve (AUC) za CRP bio je 0,910, s 95% CI od 0,85 - 0,966 ($p < 0,001$); optimalna granična vrijednost bila je 113,5 mg/L s 90,9% osjetljivošću i 85,7% specifičnošću. Zaključak: rezultati impliciraju da bi CRP testiranje moglo biti korisno kao prediktivni faktor težine COVID-19 infekcije i potencijalne intubacije.

Ključne riječi: COVID-19, upalni markeri, serumski C-reaktivni protein

INTRODUCTION

Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is a highly transmissible and pathogenic coronavirus that emerged in late 2019 and has caused a pandemic of acute respiratory disease, named 'coronavirus disease 2019' (COVID-19), which threatens human health and public safety (1).

According to WHO guidance, the clinical manifestations of COVID-19 disease are heterogeneous, including severe and non-severe forms (2,3).

This severe respiratory illness, termed coronavirus disease 2019 (COVID-19) pneumonia, typically develops 8 days after symptom onset, and when it does not respond to non-invasive respiratory support, it requires advanced respiratory support, including high concentrations of inspired oxygen and mechanical ventilation (4).

Therefore, it is important to identify and treat this subset of patients early to reduce disease severity and improve the outcomes of COVID-19. Clinical studies demonstrated that altered levels of some blood markers might be linked with the degree of severity and mortality of patients with COVID-19 (5).

There has been insufficient data to help predict the need for intubation in COVID-19 (6).

C-reactive protein (CRP) is an acute-phase reactant that is produced by the liver in response to inflammation. It is commonly secreted under the influence of cytokines such as interleukin-6 and tumor necrosis factor-alpha (7).

Critical patients with COVID-19 presented higher plasma levels of cytokines, suggesting the involvement of an inflammatory storm in the pathogenesis of disease progression. C-reactive protein (CRP), a routinely measured inflammatory marker, was increased in most patients with COVID-19 and associated with disease severity (8).

Therefore, the current study aims to evaluate the correlation between CRP levels upon hospital admission and disease progression requiring intubation and mechanical ventilation in patients with COVID-19 infection.

MATERIALS AND METHODS

A retrospective, single centre study that included 136 surviving patients with COVID-19 infection, previously admitted to the Intensive care unit of the Clinical Centre of the University of Sarajevo, was conducted in the period from March to May 2021.

We included only the laboratory confirmed cases, as the diagnosis was performed by a real-time reverse-transcriptase polymerase-chain reaction (RT-PCR) assay to test nasal and pharyngeal swab specimens according to the WHO guidance (9).

In other words, all patients with clinical respiratory symptoms, chest X-ray COVID pneumonia and laboratory-confirmed (positive nasopharyngeal/throat swab specimens by reverse transcription-polymerase chain reaction (RT-PCR) for COVID-19 infection, while suspected cases with similar clinical symptoms and negative RT-PCR for COVID-19 infection were excluded.

Patients younger than 18 years were not included in the study.

Data collection

Patient medical records were reviewed by an experienced team of clinicians of the Clinical Centre of the University Sarajevo. The data on epidemiological, clinical, laboratory, radiological findings and outcomes were collected using a data collection checklist from electronic medical records. Moreover, recorded patient data, such as demographic characteristics, past medical history (PMH), underlying medical conditions, symptoms and signs, were collected.

Statistical analysis

Continuous variables were reported as means ± standard deviation (SD), while categorical variables were presented as numbers (n) and percentages (%). The differences between two continuous variables were analyzed using independent samples Student's t-test. Categorical variables were compared using Pearson's chi-square ($\chi 2$) test or Fisher's exact probability test. To determine the accuracy and optimal cut-off values of C reactive protein in distinguishing between intubated and non-intubated COVID-19 patients, Receiver Operating Characteristic (ROC) analysis was performed. Areas under the curve (AUC) and diagnostic accuracy measures were calculated with a 95% confidence interval (CI). Statistical analyses were conducted using SPSS software version 16.0 (SPSS, Inc., Chicago, IL). A significance level of $p<0.05$ was considered statistically significant.

RESULTS

Our study included 136 patients with COVID-19 pneumonia hospitalized in the Intensive Care Unit in the period from March to May 2021. 66 of them were intubated on controlled mechanical ventilation, and 70 patients required non-invasive mechanical ventilation. The demographic and clinical characteristics of the patients are summarized in Table 1. Most patients were male, 79 (58.1); of whom 44 (62.9) were not intubated and 35 (53.0) were intubated. The female population was 57 (41.9), and 26 (37.1) were not intubated, while 31 (47.0) were intubated (p-value 0.246). The mean age was 63.1 ± 12.8. The average age was higher in the severe group that was intubated than in the group of patients that were not intubated (p-value 0.511).

Moreover, most patients had comorbidities such as diabetes (27.9%), cardiomyopathies (16.9%), hypertension (54.4%), ischemic cerebrovascular disease (6.6%), chronic obstructive pulmonary disease (COPD) (6.6%), pulmonary thromboembolism (PTE) (3.7%), ischemic renal disease (7.4%) (Table 1).

Table I **Demographic characteristics and comorbidities of the patients with COVID-19.**

Variables	Total cohort (n=136)	Non Intubated (n=70)	Intubated (n=66)	p-value
Age (years)	63.1 ± 12.8	62.4 ± 14.0	63.8 ± 11.4	0.511
Gender, n (%)				
Female	57 (41.9)	26 (37.1)	31 (47.0)	0.246
Male	79 (58.1)	44 (62.9)	35 (53.0)	
Comorbidities n (%)				
Diabetes mellitus	38 (27.9)	17 (24.3)	21 (31.8)	0.328
Hypertension	74 (54.4)	38 (54.3)	36 (54.5)	0.976
ICVD	9 (6.6)	4 (5.7)	5 (7.6)	0.663
Cardiomyopathies	23 (16.9)	11 (15.7)	12 (18.2)	0.701
Ischemic heart disease	3 (2.2)	2 (2.9)	1 (1.5)	0.594
Hypo-Hyperthyroidism	6 (4.4)	1 (1.4)	5 (7.6)	0.081
Cancer	5 (3.7)	2 (2.9)	3 (4.5)	0.601
COPD	9 (6.6)	4 (5.7)	5 (7.6)	0.663
PTE	5 (3.7)	0 (0.0)	5 (7.6)	**0.019**
IRD	10 (7.4)	6 (8.6)	4 (6.1)	0.575
Other comorbidities	87 (64.0)	44 (62.9)	43 (65.2)	0.781

Data are expressed as number (n) and %, mean ± standard deviation (SD); ICV - Ischemic cerebrovascular disease; COPD - Chronic obstructive pulmonary disease; PTE - pulmonary thromboembolism; IRD - Ischemic renal disease; p - probability.

Serum CRP concentration in intubated COVID-19 patients (189.1 ± 71.4 mg/L) was statistically significantly higher ($p<0.001$) than serum CRP concentration in non-intubated COVID-19 patients (70.2 ± 65.2 mg/L) (Figure 1).

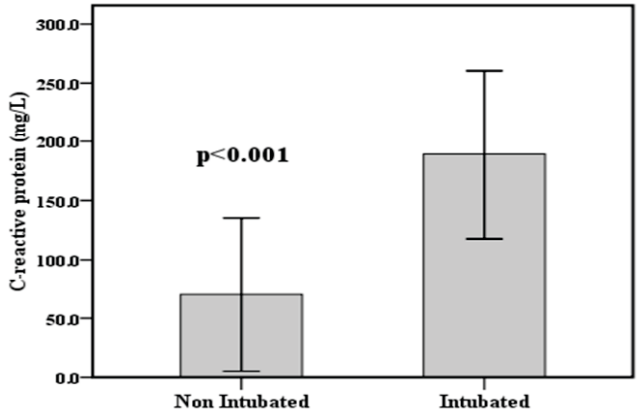

Figure 1 **Serum C-reactive protein concentration (mg/L) in non-Intubated and intubated COVID-19 patients.**

The sensitivity and specificity of CRP in assessing the need for intubation in COVID-19 patients were investigated by Receiver operating characteristic (ROC) analysis. In differentiating intubated from non-intubated COVID-19 patients, AUC for CRP was 0.910, with 95% CI of 0.85 - 0.966 ($p < 0.001$); the optimal cut-off value was 113.5 mg/L with 90.9% sensitivity and 85.7% specificity (Figure 2).

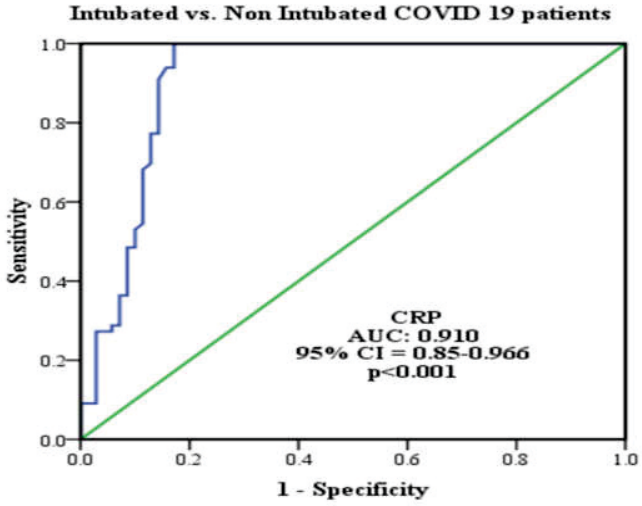

Figure 2 **The Receiver operating characteristic (ROC) analysis of CRP values in differentiating intubated with non-intubated COVID-19 patients.**

DISCUSSION

Since December 2019, Coronavirus Disease 2019 (COVID-19) has been spreading around the world. On 11 March 2020, the World Health Organization (WHO) declared the outbreak of COVID-19 a pandemic. As of 7 July 2021, there were more than 180 million COVID-19 cases and over 3 million deaths worldwide, posing a tremendous burden on the health care systems.

COVID-19 patients can range from mild to critical illness according to their clinical status (10,11).

Abnormalities in several hematological, biochemical and inflammatory biomarkers have been observed in COVID-19 patients with serious illness compared with a mild disease, which provide clinicians with justification for inclusion of these biomarkers in risk stratification models. These biomarkers act as an important tool to detect patients who are on the verge of developing severe disease even before the manifestation of clinical symptoms in those epidemic areas which have limited health resources to carry out expensive laboratory and radiological examinations on COVID-19 patients (12).

Since the early phase of the SARS-CoV-2 pandemic, many studies have pointed out how elevated C-reactive protein (CRP) concentrations in serum were highly prevalent in individuals affected by COVID-19 disease, also correlating the entity of elevations with disease severity and patient outcome. Pooled prevalence rates of elevated CRP in COVID-19 patients varied in different publications between 60 and 80 %, with some individual studies showing increases in more than 90 % of patients (13).

C-reactive protein is well established as a marker of systemic inflammation and severe infection. As an acute-phase reactant, CRP binds to phosphocholine in pathogens and membranes of host cells and acts as an opsonin to enhance phagocytosis and facilitate clearance. Ligand-bound CRP also efficiently activates the classical pathway of the complement system, an important component of innate host defence. Prior to the COVID-19 global pandemic, up to 90% of all marked elevations in CRP concentration were attributed to an infectious aetiology, most often from bacterial pathogens. Elevated CRP concentrations have also been reported in severe viral infections, including H1N1 influenza pneumonia, and recently in SARS-CoV-2 infection (14).

In this retrospective single-center study, 136 hospitalized patients with COVID-19 pneumonia were included within the specified time frame. We analyzed CRP values upon admission to the Intensive care unit (ICU) and compared them between patients who were intubated and those who were not intubated.

The sensitivity and specificity of CRP in assessing the need for intubation in COVID-19 patients was investigated by receiver operating characteristic (ROC) analysis. In differentiating intubated from non-Intubated COVID-19 patients, AUC for CRP was 0.910, with 95% CI of 0.85 - 0.966 ($p < 0.001$); the optimal cut-off value was 113.5 mg/L with 90.9% sensitivity and 85.7% specificity (Figure 2).

Kumar S, et al. analyzed 663 patients hospitalized with COVID-19. 125 patients were intubated, with a median time to intubation of 43.4 hours. Only the initial CRP level (> 92.2 mg/L) was associated with overall, early, and late intubation ($p¼0.003$, $p¼0.03$, $p¼0.0002$, respectively). They also concluded that for patients admitted with COVID-19 who are not intubated within 48 hours of admission, the admission CRP value may help clinicians identify patients still at significant risk for respiratory decompensation and predict the need for intubation during hospitalization (6).

In their study, Basina B, et al. analyzed CRP at hospital admission in 85 patients who were hospitalized with confirmed COVID-19 pneumonia. The aim was to evaluate the diagnostic and prognostic role of CRP at admission in hospitalized patients with confirmed COVID-19 pneumonia. They concluded that a significant increase in CRP greater than 100 mg/l at the admission of a patient with COVID-19 pneumonia is associated with a critical course of the disease and could itself be a parameter for hospitalization in intensive care (15).

Herold T, et al. included 89 patients in their study with the aim of identifying and prospectively validating biomarkers that allow the identification of patients in need of impending mechanical ventilation. Their findings show that the maximal IL-6 level before intubation showed the strongest association with the need for mechanical ventilation, followed by the maximal CRP level. The respective AUC values for IL-6 and CRP levels in the evaluation cohort were 0.97 and 0.86, and they were similar in the validation cohort (0.90 and 0.83, respectively). The calculated optimal cut-off values during the course of disease from the evaluation cohort (IL-6 level > 80 pg/mL and CRP level > 97 mg/L) both correctly classified 80% of patients in the validation cohort regarding their risk of respiratory failure [16].

Osawa EA, et al. performed a retrospective cohort study with patients with COVID-19 pneumonia. They compared three subgroups: non-intensive care unit (ICU) admission, ICU admission without receiving invasive mechanical ventilation (IMV) and IMV requirement. They found that the main serum biomarkers differed among study subgroups. Furthermore, good predictive performance was observed with CRP, LDH, and LCR levels obtained at hospital admission. Their study supports the findings reported by other investigators with regards to the pattern of laboratory biomarker derangements. Elevated CRP levels were associated with greater disease severity in observational cohorts (17).

CONCLUSION

A reliable prognostic marker is C-reactive protein. Our findings suggest that a CRP reading of 113 mg/L or higher at admission may indicate a more severe case of the illness and a higher chance of intubation. This implies that CRP testing could be useful as a predictive factor of disease severity of COVID-19 infection and potential intubation.

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Declaration of patient consent: the authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given their consent for their images and other clinical information to be reported in the journal.
Authors Contributions: AK-M, JM-P, BP, AMA, BK and AM-A gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author had role in article drafting and in process of revision. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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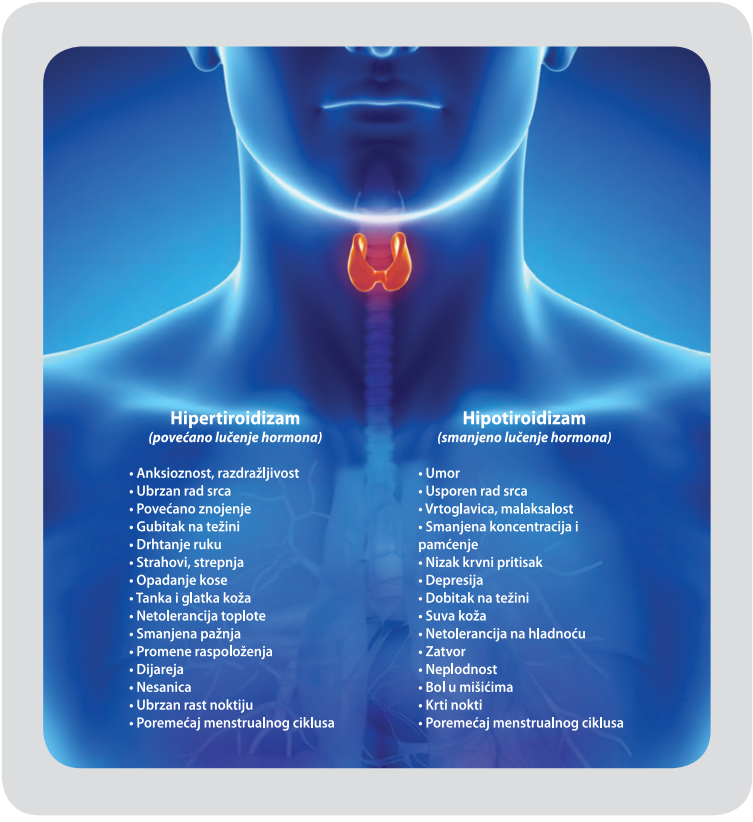

Management of professional stress among healthcare managers

Profesionalni stres kod menadžera zdravstvene njege

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ABSTRACT

Introduction: the term stress is taken from engineering technology, where this term describes an external force that acts on an object causeing tension, strain and fatigue of the material, as well as structural changes in the object. Aim: to examine the presence of stress in healthcare managers and the conditions that can be associated with stress in the workplace. Results: in 45 or 34.4% of cases respondents felt that they were under constant stress due to their work load, and they believed that poor organization and inadequate interpersonal relationships resulted in stress. Conclusion: correlation analysis determined the influence of the workplace function on the presence of stress, which means that there is a higher probability that head nurses - ward technicians will have a higher level of stress compared to head nurses - clinical technicians.

Keywords: stress, management, health care managers

SAŽETAK

Uvod: pojam stresa preuzet je iz inžinjerske tehnologije, gdje ovaj pojam označava vanjsku silu koja djeluje na neki predmet i izaziva napetost, naprezanje i umor materijala, te strukturalne promjene u predmetu. Cilj: ispitati prisustvo stresa kod menadžera zdravstvene njege i stanja koja se mogu povezati sa stresom na radnom mjestu. Rezultati istraživanja: ispitanici u 45 ili 34,4% slučajeva se osjećaju da su u stalnom stresu zbog obima posla, te smatraju da loša organizacija i neadekvatni međuljudski odnosi dovode do stresa. Zaključak: korelacionom analizom je utvrđen uticaj funkcije na radnom mjestu na prisustvo stresa u smislu da postoji veća vjerovatnoća da će viši nivo stresa imati glavne medicinske sestre - tehničari odjeljenja u odnosu na glavne medicinske sestre - tehničare klinika.

Ključne riječi: stres, menadžment, menadžeri zdravstvene njege

INTRODUCTION

The issue of stress has recently become more and more represented both in everyday life and in psychology. Stress can be divided into good (acute) and harmful (chronic) stress (1). Stress, as a high level of burnout at work and poor lifestyle habits, can result in a serious health deterioration of nurses. On the other hand, the cumulative health risks are increased, given that medical professionals are exposed to viruses, bacteria, complex mixtures of different chemicals and other dangerous agents in the long term (2). External, actual threatening situations are characteristic of acute stress. Internal causes are more related to chronic stressful conditions which occur following longer exposure of an individual to more severe stressful events, which that particular individual can no longer cope with, resulting in permanent feeling of helplessness, guilt and anxiety (3). Physical stressors are related to various external circumstances, such as exposure to loud noise, extreme heat or cold, but also exposure to sensory deprivation, or a situation in which we are stimulated by an insufficient number of stimuli from the environment. These stressors also include severe pain of unknown cause, which alerts the individual to a potential physical disorder (4).

Psychological stressors are conditioned by interpersonal misunderstandings and conflicts. In developed societies, social stressors are among the most common stressors. Misunderstandings and conflicts with family members, friends, colleagues and managers at work are daily stressors which intensity can range from mild misunderstandings to war conflicts of entire nations. These are typical examples of psychological stressors, which are the most common (5).

Psychological reactions to stress can include: increased anxiety, concentration problems, negative emotions, loss of attention, depression, fatigue, burnout syndrome or an increase in suicide rates. The most common behavioural reactions to stress involve: withdrawal and isolation at work or at home, increase in number of accidents, higher consumption of alcohol, tobacco and caffeine, irritability, aggressiveness, sexual dysfunctions, low motivation for work and interpersonal relationships, and increase in violence at

work or at home. Physiological reactions to stress include: an increase in cortisol levels, higher cholesterol values, increased blood pressure, chest pains, insomnia, and development of certain types of cancer, indigestion, headaches, musculoskeletal problems, and impaired immune system functions (6). Stress can be the result of an imbalance between the effort invested and the financial and non-financial incentives received, which can significantly affect employee satisfaction (7).

It is considered that excessive work engagement can be a constant source of stress with negative health consequences. A special source of managerial stress relates to business ethics and ethical behaviour, and problems which solution is in contradiction with the personal experience of moral values and organizational business requirements. In a conceptual sense, ethics is described as a philosophy which determines whether an individual's behaviour is adequate or not (8).

The influence of culture on the sources and experiences of managerial stress is significant. Stress at work has significant consequences for the overall behaviour and life of people, given that over a period of 35-40 years people spend half of their waking hours (9).

AIM

The aim of this study was to examine the presence of stress in health care managers and conditions that could be associated with stress in the workplace.

MATERIALS AND METHODS

The study was conducted among head nurses - technicians employed in public institutions providing hospital health care in the Federation of Bosnia and Herzegovina. The study included 139 nurses - technicians with responsible positions at the workplace. The respondents were selected by the method of random sampling.

The study respected all ethical principles related to the protection of respondents' identity and data obtained through questionnaires/interviews. Data confidentiality was guaranteed by the researcher, the author of this paper. Respondents did not have any financial or other interest in participating in the research.

The study used an author's questionnaire created on the basis of a review of professional and scientific literature and experiences from everyday clinical practice. The questionnaire was created in electronic "Google form", assessable to the respondents by email. The research was conducted in the period from 15 to 30 January 2023. The questionnaire was anonymous and the identity of the respondents remained confidential. The questionnaire used the scientific methods of deduction, compilation, etc. The results were presented in tables and figures through number of cases, percentage, arithmetic mean with standard deviation, standard error of the arithmetic mean and range of values. The chi-square test, Ficher's exact test and Student t test were used for testing possible differences between the examined groups of institutions, and Spearman's rank correlation test was used to test the influence of all parameters on the variable indicators of leadership styles. The level of statistical significance was set at 95% or $p<0.05$. The analysis was performed using the statistical package for sociological research IBM Statistics SPSS v 23.0.

RESULTS

The study included the total of 139 head nurses-technicians of institutions, clinics or departments who filled out the Google online forms in the period from 1 to 15 January 2023.

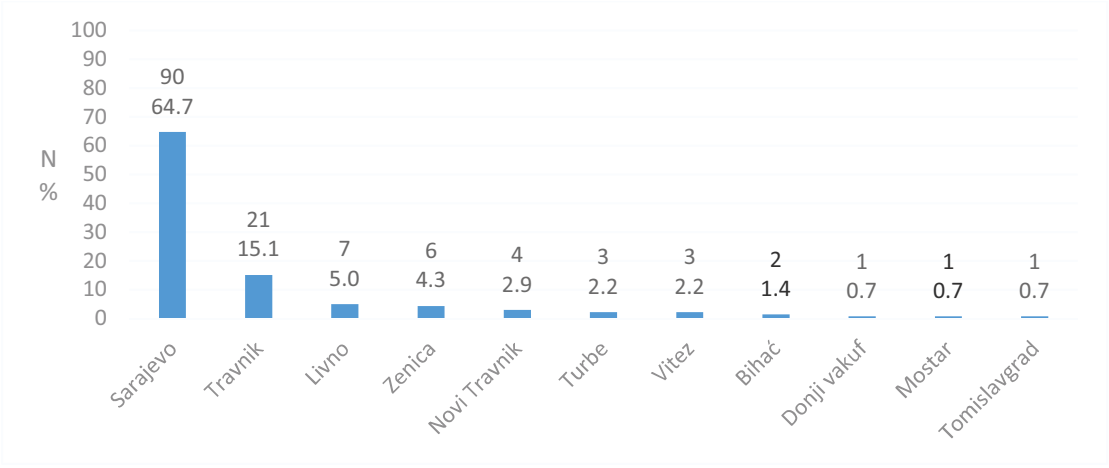


Figure 1 Analysis of respondents' place of residence.

The largest number of respondents was from the Sarajevo Canton, 90 or 64.7% of them.

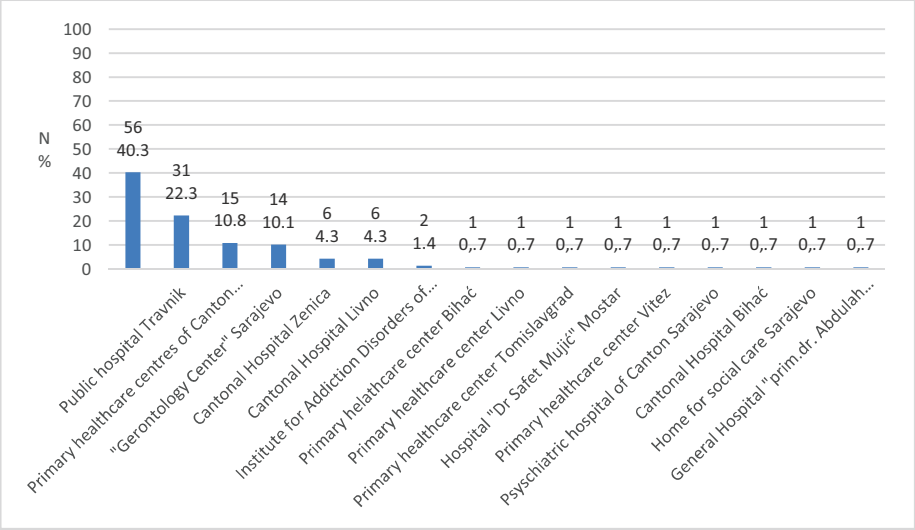


Figure 2 Analysis of health institutions in which the respondents worked.

Based on the institutions ratio, the largest number of respondents was employed in the Clinical Center University of Sarajevo (56 or 40.3%), followed by respondents employed in the Travnik Hospital (31 or 22.3%) and the Primary Healthcare Centres of the Canton Sarajevo (15 or 10.8%).

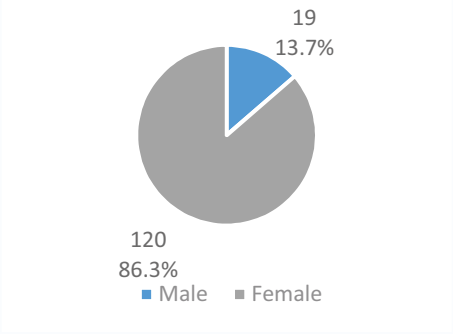


Figure 3 Analysis of the respondents' gender structure.

In relation to gender structure, there was significantly higher number of women (120 or 56.3%) than men (19 or 13.7%).

In relation to education, the largest number of respondents had university education (41.0%), followed by the respondents with high school (39.6%) master degree, professors or medical doctors (14.4%), and 5.0% of respondents was with higher medical school diploma.

Table 1 **Overview of functions at the workplace.**

		N	%
Function at workplace	Head nurse-technician of the institution/clinic	27	19.4
	Head nurse-technician of the ward	112	80.6
	Total	139	100.0

In relation to the workplace function, 112 or 80.6% of the respondents were head nurse-technicians of the departments, and 27 or 19.4% were head nurse-technicians of a clinic or institution. The largest number of respondents was with 21-30 years of work experience (60 or 43.2%).

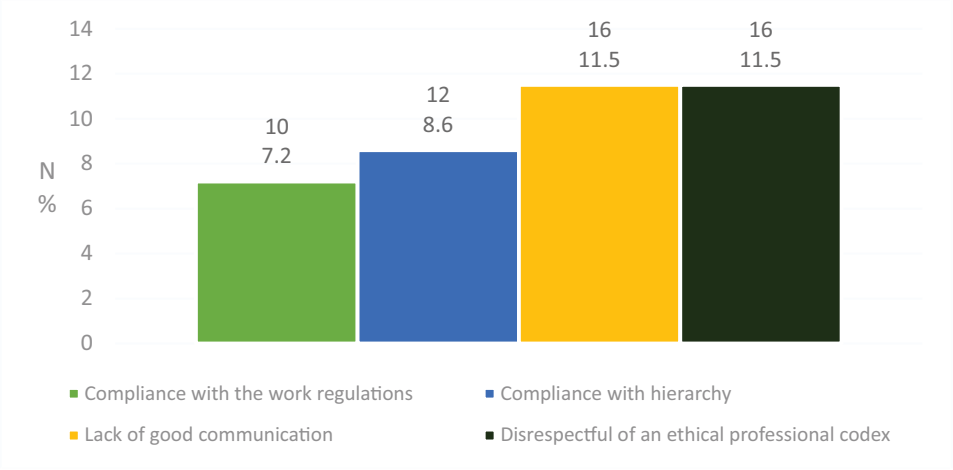
Table 2 **Overview of the average rating of respondents' satisfaction with work environment parameters.**

	Technical equipment	The relationship between subordinates and superiors	Team work	Quality of work environment (atmosphere at work)	Monthly income
Mean	3.01	3.41	3.41	3.27	2.88
SD	1.25	1.23	1.26	1.28	1.26
SEM	0.11	0.10	0.11	0.11	0.11
Minimum	1.00	1.00	1.00	1.00	1.00
Maximum	5.00	5.00	5.00	5.00	5.00

The analysis of the average rating of respondents' satisfaction with the work environment parameters showed that the highest degree of satisfaction was expressed for teamwork, with an average rating of 3.41±1.26 and the relationship between subordinates and superiors with an average rating of 3.41±1.23.

The average rating of satisfaction with the work environment quality was 3.27±1.28, with technical equipment 3.01±1.25 and the lowest satisfaction was expressed for the amount of monthly income, 2.88±1.26.

Table 3 **Overview of the reasons for dissatisfaction with the work of subordinates.**



As the reasons for dissatisfaction with the work of subordinates, respondents most often cited the following: lack of good communication and disrespect for the ethical professional codex (11.5%), followed by compliance with hierarchy (8.6%) and compliance with the work regulations (7.2%).

Based on the responses, conflicts between employees in their respectful work institutions where often occasional (61.2%), extremely rare (33.1%) and very frequent affecting the work (5.8%).

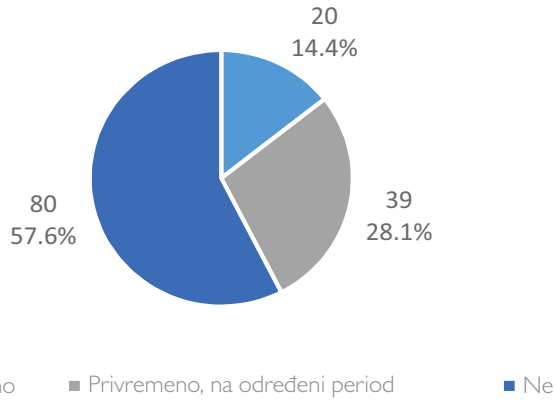
Table 4 **Overview of the work presence and causes of stress.**

	N	%
At work I feel full of energy and work makes me happy	52	37.4
I feel that I am under constant stress due to work overload	45	32.4
I believe that my work is not difficult, but that the superiors produce stress	26	18.7
I believe that poor organization results in stress	50	36.0
I think I'm under stress because of inadequate interpersonal relationships	31	22.3
I'm thinking of changing my work as I feel professionally burnt out	16	11.5

Respondents most often stated that they were full of energy and that their work made them happy (37.4%), but also they believed that poor organization resulted in stress (36.0%), and they felt to be under constant stress due to work overload (32.4%).

Out of the total number of respondents, 22.3% believed that they were under stress due to inadequate interpersonal relationships, and 11.5% of them considered work replacement options as they felt to be professionally burned out.

Table 5 **Overview of the presence of the desire to change the workplace.**



The majority of respondents or 57.6% of them had no desire to change their workplace. Of those who wished to do so, 14.4% intended to do it permanently, and 28.1% temporarily, or for a certain period of time.

Table 6 **Overview of absence from work due to a condition caused by increased workload, and duration of sick leave.**

		N	%
Absence from work due to a condition caused by increased workload in the past 6 months	Yes	8	5.8
	No	131	94.2
	Total	139	100.0
Duration of sick leave	Up to 42 days	7	87.5
	More than 42 days	1	12.5
	Total	8	100.0

Out of the total number of respondents, 8 or 5.8% of them stated that they were absent from work due to a condition caused by an increased workload in the past 6 months. Out of that number, the majority or 87.5% of them were on sick leave for up to 42 days, and 12.5% for more than 42 days.

Table 7 **Overview of ways to reduce stress in the work process.**

	N	%
By organizing joint gatherings	41	29.5
By enabling staff to schedule their tasks and responsibilities at the workplace	65	46.8
By enabling staff to complete their private urgent obligations during working hours	18	12.9
By enabling internal replacement among employees in the work process (shift replacement)	29	20.9
The staff is not under stress in the work process	4	2.9

With regard to reducing stress in the work process, respondents most often stated that they enabled staff to distribute their tasks and obligations at the workplace (46.8%), organizing joint gatherings (29.5%), and enabling internal replacements among employees in the work process (change of shifts) (20.9%).

Table 8 **Correlation analysis according to workplace function.**

			Level of stress perceived by the respondents				Total
			No stress	Mild stress	Moderate stress	Pronounced stress	
Workplace function	Head nurse-technician of the institution/clinic	N	11	10	5	1	27
		%	40.7	37.0	18.5	3.7	100.0
	Head nurse-technician of the ward	N	33	44	22	13	112
		%	29.5	39.9	19.6	11.6	100.0
Total		N	44	54	27	14	139
		%	100,0	100.0	100.0	100.0	100.0
rho=0.184; p=0.043							

Correlation analysis of the workplace function influence on the presence of stress showed a statistically significant influence in the sense that there was a higher probability that the head nurses of the department would have a higher level of stress compared to the head nurses clinical-technicians.

DISCUSSION

For the purposes of this article, the study was conducted on a sample of 139 head nurses - technicians of institutions, clinics and departments. From the total number, the most respondents were from Sarajevo according to place of residence, followed by Travnik and Livno. Also, based on health institutions the respondents were employed at, the most respondents were from the Clinical Center University of Sarajevo (56 or 40.3%), followed by Public Hospital Travnik (31 or 22.3%), and from Primary Healthcare Centers of the Canton Sarajevo, 15 or 10.8% of the respondents. The participants of the study were mainly women (120 or 86.3%) whereas men were only present in 13.7% (19). Based on the analysis of professional qualifications of the respondents, the majority of the respondents had university degree (57 or 41.0%), followed by bachelor's degree (55 or 39.6%), and master degrees, medical doctors, professors (20 or 14.4%). Only few respondents had higher medical school diploma. Out of the total number of respondents, 112 or 80.6% were head nurses - technicians of the department, while 27 or 19.4% were head nurses - technicians of

the institution/clinic. Most of the respondents stated that they had been working for 21-30 years, mainly in responsible positions for up to 5 years. In majority of cases, respondents expressed satisfaction with the work of their subordinates as partial, while 7 respondents stated that they were not satisfied with the work of their subordinates. This dissatisfaction mainly resulted from a lack of good communication and non-compliance with the ethical professional code. As the most common reasons for the presence of stress at work, respondents state that they were under stressed due to their work load, poor organization, inadequate interpersonal relationships, while some believed that their superiors caused stress at work. Unfortunately, most respondents thought about work after working hours, but tried not to talk about that (74 or 53.2%). Most respondents did not have any wish to change their workplace.

As for the presence of occupational diseases at work, fortunately most of the respondents answered that they did not have any diseases (94 or 67.6%), while 24 of them answered that they had some of the occupational diseases. As the most common disease, they mentioned discus hernia and problems with the spine in general.

Respondents state that they were heavily burdened with administrative tasks (108 or 77.7%), and that due to their workload they partially made mistakes.

Vučković L (3), in his study under the title "The impact of professional stress on the quality of life of nurses" concluded that in the domain of physical and mental health, male showed significantly better results compared to female respondents. The level of professional education proved to be an important factor for the quality of the living environment, which was increasing in accordance with the level of education. Nurses - technicians were among six professions most exposed to professional stress and work burnout. As a helping profession, nursing is extremely related to relationships with people, and as such is a source of various stressors specific to work environment.

In her study under the title "Burnout syndrome at work in health care workers employed in health and social care institutions", Polegubić - Barešić M (10) proved that health care workers employed in health care institutions showed a greater intensity of burnout syndrome compared to those employed in social care institutions. Years of employment did not have influence on the level of burnout syndrome. Also, she concluded that nurses - technicians showed a higher level of burnout syndrome at work than other health professionals.

Omašić K (11) in her article under the title "The relationship between specific stress factors and the quality of life of nurses employed in palliative care" stated that nurses - technicians employed in palliative care were often exposed to specific stress factors.

Krištofić J (4) examined the topic "Stress and burnout at work in general hospital nursing". The study showed that gender was a significant factor in the overall stress experience, and that length of service was a factor in burnout syndrome. The workload was related to dealing with the patient and family, and uncertainty during the treatment. A high mutual correlation of stressors was shown, and death and suffering were the single strongest stressor.

The significant correlation between the incidence and the level of stress in relation to the employee's occupation showed that stress was present in all occupational structures, but with a higher incidence and high level of stress among managers.

CONCLUSION

Correlation analysis determined the influence of the function at the workplace on the presence of stress in the sense that there was a higher probability that head nurses - technicians of the department would have a higher level of stress compared to head nurses - technicians of the clinic. Respondents who were dissatisfied with the quality of the work environment, the amount of monthly income, the work of subordinates, and communication with subordinates had a great impact on the presence of stress at work. Respondents were most burdened with administrative tasks. In 45 or 34.4% of cases the respondents felt that they were under constant stress due to the work load, and believed that poor organization and inadequate interpersonal relations resulted in stress. As the most common ways to reduce stress, the interviewees stated the following: enabling staff to distribute their tasks and responsibilities at the workplace (65 or 46.8%), organization of social gatherings (41 or 29.5%), enabling internal replacement among employees in the process of work - changing shifts (29 or 20.9%), enabling staff to complete their private urgent obligations during working hours (18 or 12.9%).

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Our contribution to the reduction of cardiovascular diseases in Bosnia and Herzegovina!
Naš prilog redukciji kardiovaskularnih bolesti u Bosni i Hercegovini!

Comparison of the early recovery of patients in the intensive care unit after the coronary artery bypass surgery using the conventional on-pump method compared to the off-pump technique

Uporedba ranog oporavka pacijenata u jedinici intenzivne terapije poslije hiruške ugradnje srčane premosnice konvencionalnom on-pump metodom i off-pump tehnikom

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ABSTRACT

Introduction: although there is the increase in the number of percutaneous procedures, coronary artery bypass grafting (CABG) remains the standard treatment for patients with extensive coronary artery disease. Coronary artery bypass graft surgery should be performed with or without extracorporeal circulation (CPB), therefore there is on-pump and off-pump CABG procedures. There is an ongoing, debate over the superiority of on-pump vs. off-pump CABG methods. Both techniques have their pros and cons, and cardiac surgery units around the world have different approaches and opinio ns on the subject. Aim: to show whether there was a difference in early postoperative recovery in patients in whom cardiac bypass surgery was performed using the on-pump or off-pump CABG method and whether one type of operation was superior to the other. Material and methods: in the period from September 2021 to May 2023 isolated CABG was performed on 230 patients, divided into two groups at the Clinic of Cardiovascular Surgery of the Clinical Center University of Sarajevo. One group with 80 patients had on-pump CABG operation (with CPB), and other was with 150 patients was treated with off-pump CABG technique. Data were collected during preoperative, intraoperative and postoperative period. All patients were elective cases. Results: our study showed that there were more male patients in both group with an average age 63 years which was similar in both groups. There was statistically significant difference in number of grafts implanted in favor of on -pump CABG group. Comparing the comorbidities presented in patients in both groups, there was no significant difference, but a statistically significant difference was in the presence of anemia in favor of patients from the off-pump group, 36.7% versus 11.3%, p 0.0001. There was a statistically significant difference in mean number of blood transfusions units (1.03±1.26:0.53±1.02 units) and fresh frozen plasma (FFP) (1.96±1.35:1.37±1.39 units) in favor of on-pump group during operation. In early postoperative period, in intensive care unit (ICU), data showed significantly higher number of patients on vasopressors in off-pump group, 50.0% compared to 35.0% of cases in the on-pump group. Comparison of blood products transfusions during ICU stay indicate that there was a statistically significant difference in mean number of blood transfusions units (1.5±1.99:0.51±1.06 units) and FFP (1.0±1.41:0.51±1.06 units) in favor of on-pump group. The stay in the ICU was statistically significantly longer for the patients in the on-pump group, 3.56±1.93 days (range 2-18 days) compared to the patients in the off-pump group, 2.74±0.82 days (range 1-7 days). Other observed parameters such as the occurrence of atrial fibrillation, the amount of drainage during 48 hours, the duration of mechanical ventilation, the use of platelets and the recorded fatal outcome did not show a significant difference between the observed groups. Conclusion: the study showed that the intra- and post-operative consumption of blood and fresh frozen plasma is significantly lower if the patient underwent off-pump CABG, avoiding possible complications of transfusion use. Also, patients from the off-pump group had a shorter stay in ICU, which favors faster recovery and lower treatment costs.

Keywords: coronary artery bypass graft surgery, off-pump, on-pump, CABG, early recovery

SAŽETAK

Uvod: iako postoji porast broja perkutanih zahvata, ugradnja srčane premosnice (CABG) ostaje standardni način liječenja bolesnika s opsežnom koronarnom arterijskom bolešću. Operacija ugradnje srčanih premosnica može se izvoditi sa ili bez upotrebe mašine za vantjelesnu cirkulaciju (CPB), tako da postoje CABG

postupci uz upotrebu CPB – on-pump CABG i bez upotrebe CPB - off-pump CABG. Obje tehnike imaju svoje prednosti i mane, a kardiokirurške jedinice širom svijeta imaju različite pristupe i mišljenja o ovoj temi. Cilj: je bio pokazati postoji li razlika u ranom postoperativnom oporavku u bolesnika kod kojih je operacija srčane premosnice učinjena on-pump ili off-pump CABG metodom, te je li jedna vrsta operacije superiornija od druge. Materijali i metode: u periodu od septembra 2021. do maja 2023. godine na Klinici za kardiovaskularnu hirurgiju Kliničkog centra Univerziteta u Sarajevu, urađen je izolirani CABG kod 230 bolesnika, podijeljenih u dvije skupine. Jedna skupina od 80 pacijenata imala je on-pump CABG operaciju (s CPB-om), a druga je bila od 150 pacijenata urađenu off-pump CABG tehnikom. Posmatrani su pre, intra i postoperativni podaci. Svi pacijenti su bili elektivni slučajevi. Rezultati: naše istraživanje je pokazalo da je u obje grupe bilo više muških pacijenata, prosječne starosti 63 godina. Postojala je statistički značajna razlika u broju ugrađenih srčanih premosnica u korist on-pump grupe. Upoređujući komorbiditete prisutne kod pacijenata u obe grupe, nije bilo značajne razlike, ali je statistički značajna razlika bila u prisustvu anemije kod pacijenata iz off-pump CABG grupe, 36,7% : 11,3%, p 0,0001. Postojala je statistički značajna razlika u srednjem broju jedinica transfuzije krvi (1,03±1,26:0,53±1,02 jedinice) i svježe smrznute plazme (SSP) (1,96±1,35:1,37±1,39 jedinica) u on-pump CABG grupi tokom operativnog zahvata. U ranom postoperativnom periodu, u jedinici intenzivne terapije (JIT), podaci su pokazali značajno veći broj pacijenata na vazopresorima u off-pump grupi, 50,0% u odnosu na 35,0% slučajeva u on-pump grupi. Postojala je statistički značajna razlika u upotrebi doza krvi (1,5±1,99:0,51±1,06 jedinica) i SSP (1,0±1,41:0,51±1,06 jedinica) u JIT-u, više se koristila kod pacijenata iz on-pump CABG grupe. Boravak u JIT-u bio je statistički značajno duži za pacijente u on-pump grupi, 3,56±1,93 dana (raspon 2-18 dana) u poređenju sa pacijentima iz off-pump grupe, 2,74±0,82 dana (raspon 1-7 dana). Ostali posmatrani parametri kao što su pojava atrijalne fibrilacije, količina drenaže tokom 48 sati, trajanje mehaničke ventilacije, upotreba trombocita i smrtni ishod, nisu pokazali značajnu razliku između posmatranih grupa. Zaključak: naša studija je pokazala da je intra- i postoperativna potrošnja krvi i SSP značajno manja ako je pacijent podvrgnut CABG bez upotrebe srce-pluća pumpe, čime se izbjegavaju moguće komplikacije upotrebe krvi i krvnih derivate. Također, pacijenti iz off-pump grupe imali su kraći boravak u JIT-u, što pogoduje bržem oporavku i nižim troškovima liječenja.

Ključne riječi: ugradnja srčanih premosnica, off-pump, on-pump, CABG, rani oporavak

INTRODUCTION

Coronary artery bypass grafting (CABG) remains the most frequent surgery in the practice of an adult cardiac surgeon and the most frequently performed cardiac surgical procedure worldwide (1). This surgical procedure reduces mortality and improves quality of life in patients with extensive coronary artery disease.

Conventional coronary artery bypass grafting, on-pump CABG is performed on cardiopulmonary bypass (CPB) and remains the standard intervention for coronary artery disease requiring surgery for coronary revascularization. The techniques of operating with CPB and aortic cross-clamping provide cardiac surgeons with clear vision for coronary bypass, but may also increase adverse neurological sequelae, myocardial ischemia-reperfusion injury and renal impairment (2).

During the use of CPB there are numerous physiologic disturbances affecting the hemostatic mechanisms, immune mediators and inflammatory responses which can culminate in deterioration of function of various organs. Furthermore, handling of an atherosclerotic ascending aorta during cannulation and cross-clamping can enhance embolization and stroke risk (3).

Therefore, off-pump coronary artery bypass grafting was developed to reduce morbidity, and has gained some favor among cardiac surgeons. Currently off-pump CABG is indicated on its own for treatment of single as well as multivessel coronary artery disease and can be combined with coronary angioplasty as a hybrid procedure. Patients with impaired left ventricular function, left main stenosis, advanced age, cerebrovascular accidents, chronic renal failure, chronic obstructive pulmonary disease, sleep apnea syndrome, atheromatous disease of the aorta, acute myocardial infarction (MI), and re-operations are all candidates for off-pump CABG.

In general, the small number of contraindications of off-pump CABG can be divided into absolute (cardiogenic shock, major ischemic arrhythmias) and relative (small, deep intramyocardial target vessels, calcified target vessels, poor ventricular function, reoperation) (4).

During off-pump CABG, avoiding CPB will cause less risk of dissection and embolism due to no aortic cannulation, less atrial injury and arrhythmias due to no atrial cannulation, less risk of plaque embolism, cerebrovascular insult and myocardial infarction due to no cross-clamping, less bleeding and less transfusion due to no activation of coagulation, kallikrein, and inflammation caused by CBP tubing, no potassium load, fluid load, coronary air embolism as there is no cardioplegia use, less equipment is used in off-pump CABG so, the overall cost are less.

Unfortunately, this type of operation needs skilled staff, technically is more difficult (increased risk of anastomotic bleeding, suboptimal revascularization, myocardial ischemia), there is a possibility of myocardial infarction due to non-use of cardioplegia, incomplete revascularization is more frequent (5).

Numerous studies that have been published so far provide data that speak in favor of one method as well as another.

Looking back at the published studies that gave data about the early recovery of patients with on-pump or off-pump CABG, it can be found that after off-pump CABG intensive care unit and hospital length of stay is lower in the off-pump CABG group, as well as lower postoperative blood loss, need for blood transfusion, less arrhythmias, and shorter time of mechanical ventilation. In majority of published studies, the infectious, renal, and neurological complications were found to be similar (6).

AIM

The aim of the study was to show whether there was a difference in early postoperative recovery in patients who underwent cardiac bypass surgery using the on-pump or off-pump CABG method and whether one type of surgery was superior to the other.

MATERIALS AND METHODS

Our study was constructed as a retrospective, comparative cohort study, and it included 230 patients who underwent isolated CABG, and were assigned to either on-pump CABG group with 80 patients or off-pump CABG group with 150 patients. All operations were carried out at the Clinic of Cardiovascular Surgery of the Clinical Center University of Sarajevo in the period from September 2021 to May 2023. Criteria for inclusion in the study were older than 18 years, elective isolated coronary artery bypass grafting. Exclusion criteria were combined cardiac surgery, emergencies surgery or re-do surgery. All patient data, including preoperative, intraoperative and early postoperative data, and complications, were collected.

Anesthesia Management

Diazepam 5 mg orally with 0.1 mg/kg of Morphine subcutaneously was given as premedication one hour before operation. The induction of general anesthesia was achieved using etomidat 0.2-0.6 mg/kg, fentanyl 3-5 mcg/kg and pancuronium 0.1 mg/kg. After endotracheal intubation, a three-lumen central venous catheter and introducer sheath were inserted in the right internal jugular vein, and an arterial line was placed in the left radial artery. The patient was placed on full hemodynamic monitoring according to the protocol for the type of surgery. Transesophageal echocardiography was performed only when indicated (i.e., reduced ejection fraction or known pulmonary hypertension). Anesthesia was maintained by a continuous infusion of fentanyl, propofol and sevoflurane. Depending on the type of surgery, patients received unfractionated heparin as anticoagulant and its effect was monitored using activated clotting time (ACT). For on-pump CABG patients received 400 IU/kg heparin to reach an ACT above 480 s, while off-pump CABG patients received 200 IU/kg heparin to reach an ACT above 300 s.

Surgical Management

The decision to select on-pump or off-pump procedure as well as the type and number of grafts was based on the patient's condition. Off-pump CABG procedures were conducted with the assistance of heart stabilizers to expose the coronary arteries. On-pump CABG was carried out using the standard cardiopulmonary bypass (CPB) technique with ascending aortic cannulation and cannulation of the right atrium with a single two-staged cannula. CPB management protocol were the same for all on-pump CABG, del Nido cardioplegia solution was used, normothermia (>34^{0}C) or mild hypothermia (32-34^{0}C) was maintained during CPB. The left and right internal mammary arteries, as well as saphenous vein grafts were used for grating.

Management in ICU

At the end of the surgery, patients were transferred to ICU, connected to the mechanical ventilation and monitoring. Patients were sedated with propofol, inotropic support was included as needed. After achieving satisfactory hemodynamics and laboratory findings, bleeding control and warming the patient, sedation was stopped, analgesia was started, and the patient was awake and weaned from mechanical ventilation.

Statistical analysis

The data are presented in form of tables and charts by total number of cases, percentage, mean, standard deviation, and range depending on the data type. The testing of possible differences between observed groups was performed using chi-square and Mann-Whytney nonparametric tests. The statistical significance level was set at the confidence level of 95% so the results of the test with $p<0.05$ was considered as statistically significant. Statistical analysis was performed using the statistical software for biomedical sciences, MedCalc v13.0 (Antwerp, Belgium).

RESULTS

The study consisted of 230 patients who underwent CABG, of which 80 or 34.8% underwent on-pump and 150 or 65.2% off-pump CABG.

Table 1 **Comparison of socio-demographic characteristics.**

			Group		Total (N=230)	Sig.
			On-Pump CABG (N=80)	Off-Pump CABG (N=150)		
Gender	Male	N	61	118	179	χ^2=0,177; p=0,739
		%	76.3	78.7	77.8	
	Female	N	19	32	51	
		%	23.8	21.3	22.2	
Age	Mean		64.04	63.48	63.67	Z=-0.455; p=0.649
	Std. Deviation		6.84	8.10	7.68	
	Min.		40	40	40	
	Max		79	80	80	
BMI	Mean		28.75	29.04	28.94	Z=-0.568; p=0.558
	Std. Deviation		2.70	3.85	3.49	
	Min.		21	20	20	
	Max		37	41	41	
No. of grafts	Mean		2.46	2.10	2.23	Z=-3.539; p=0.0001
	Std. Deviation		0.57	0.79	0.79	
	Min.		1	1	1	
	Max		4	4	4	
Lethal outcome		N	6	4	10	χ^2=2.931; p=0.088
		%	7,5	2,7	4,3	

BMI – Body mass index
P-value ≤ 0.05 was considered significant

Comparison of sociodemographic characteristics indicate that there were more male patients in both groups (76.3% and 78.7%) respectively, without statistically significant difference between the groups.

According to their age, the respondent in the on-pump CABG group were slightly older with a mean age of 64.04±6.84 years, compared to patients in the off-pump group and mean age of 63.48±8.10 years without statistically significant difference.

Body mass index (BMI) was slightly higher in the group of patients in the off-pump group - 29.04±3.85 kg/m^2 in comparison with the patients in the on-pump group and mean age of 28.75±2.70 kg/m^2, also without statistically significant difference.

Statistically significant difference was noted according to the number of grafts. Patients in the on-pump group had more grafts implanted during the surgery with mean 2.46±0.57 (range 1-4) compared to patients in the off-pump group and mean od 2.1±0.79 grafts (range 1-4).

Lethal outcome during the first 72 hours was slightly more present in the on-pump group in 7.5% of cases compared to 2.7% of cases in the off-pump group.

Table 2 **Comparison of preoperative data.**

		Group		Total (N=230)	Sig.
		On-Pump CABG (N=80)	Off-Pump CABG (N=150		
HTA	N	57	127	184	χ^2=5.870; p=0.024
	%	71.3	84.7	80.0	
COPD	N	8	8	16	χ^2=1.755; p=0.146
	%	10.0	5.3	7.0	
DM	N	39	60	99	χ^2=1.629; p=0.211
	%	48.8	40.0	43.0	
CVI	N	6	8	14	χ^2=0.428; p=0.567
	%	7.5	5.3	6.1	
MI	N	38	75	113	χ^2=0.130; p=0.782
	%	47.5	50.0	49.1	
Anemia	N	9	55	64	χ^2=16.783; p=0.0001
	%	11.3	36.7	27.8	
Smoking	N	29	54	83	χ^2=0.001; p=0.541
	%	36.3	36.0	36.1	
EF (%)	Mean	46.68	44.29	45.12	Z=-1.844; p=0.065
	Std. Deviation	10.17	9.53	9.80	
	Min.	25	25	25	
	Max	69	65	69	

HTA – Hypertension, COPD – Chronic obstructive pulmonary disease, DM – Diabetes mellitus, CVI – Cerebro-vascular insult, MI – Myocardial infarction, EF – Ejection fraction
P-value ≤ 0.05 was considered significant

Comparison of preoperative data indicate that the statistically significant difference was noted only in case of anemia which was more common 36.7% in the off-pump group, compared to the on-pump group with 11.3%. HTA was slightly more prese nt in the off-pump group (84.7%: 71.3% respectively), as well as myocardial infarction (50.0%: 47.5%, respectively).

Other observed parameters were more present in the on-pump-group: COPD (10.0%:5.3%), diabetes mellitus (48.8%:40.0% respectively), CVI (7.5:5.3% respectively), and smoking (36.3%:36.0% respectively). Ejection fraction was little bit higher in the on-pump group with a mean of 46.68±10.17% (range 25-69%), than in the off-pump group with mean of 44.29±9.53% (range 25-65%).

Table 3 **The intra-operative data.**

		Group		Total (N=230)	Sig.
		On-Pump CABG (N=80)	Off-Pump CABG (N=150)		
Duration of heart lungs machine (minutes)	Mean	98.08	/	/	/
	Std. Deviation	26.35	/	/	
	Min.	27	/	/	
	Max	179	/	/	
Clamp time (minutes)	Mean	54.45	/	/	/
	Std. Deviation	16.11	/	/	
	Min.	19	/	/	
	Max	98	/	/	
Blood transfusions	Mean	1.03	0.53	0.70	Z=-3.209; p=0.001
	Std. Deviation	1.26	1.02	1.13	
	Min.	0	0	0	
	Max	4	6	6	
Fresh frozen plasma	Mean	1.96	1.37	1.57	Z=-3.063; p=0.002
	Std. Deviation	1.35	1.39	1.41	
	Min.	0	0	0	
	Max	4	4	4	
Platelet transfusion	Mean	0.15	0.05	0.09	Z=-0.975; p=0.339
	Std. Deviation	0.66	0.34	0.48	
	Min.	0	0	0	
	Max	3	3	3	

P-value ≤ 0.05 was considered significant

Duration of the CPB in the on-pump group was 98.08 minutes (range 27-179 minutes) and clamp time 54.45±16.11 minutes (range 19-98 minutes).

Comparison of blood products transfusions indicate that there is statistically significant difference in mean number of blood transfusions (1.03±1.26:0.53±1.02 units) and fresh frozen plasma (1.96±1.35:1.37±1.39 units) in favor of on-pump group.

There was no significant difference in the number of platelet transfusions with slightly more used in the on-pump group - 0.15±0.66 (range 0-3 units) than in the off-pump group -0.05±0.34 units (range 0-3 units)

The data from ICU showed that atrial fibrillation was more present in the on-pump group - 13.8%, compared to the off-pump group - 9.3%, but without statistically significant difference.

However, the use of vasopressors was significantly more common in the off-pump group in 50.0% of cases compared to 35.0% of cases in the on-pump group.

The total drainage was similar for both groups of patients and was higher in off-pump group 704.63±345.61 ml, as compared to patients in the on-pump group - 619.31±216.24 ml.

There was no significant difference in the duration of mechanical ventilation during the ICU stay, with longer duration for the patients in the on-pump group - 565.34±533.08 minutes as compared to the off-pump group - 502.30±197.60 minutes.

Comparison of blood products transfusions during ICU stay indicate that there is statistically significant difference in mean number of blood transfusions (1.5±1.99:0.51±1.06 units) and fresh frozen plasma (1.0±1.41:0.51±1.06 units) in favor of on-pump group.

Table 4 **Comparison of postoperative parameters in IC.**

		Group		Total (N=230)	Sig.
		On-Pump CABG (N=80)	Off-Pump CABG (N=150)		
ICU atrial fibrillation	N	11	14	25	χ^2=1.051; p=0.374
	%	13,8	9.3	10,9	
ICU vasopressors	N	28	75	103	χ^2=4.747; p=0.037
	%	35.0	50.0	44.8	
ICU total drainage (ml)	Mean	619.31	704.63	674.96	Z=-1.272; p=0.204
	Std. Deviation	216.24	345.61	309.05	
	Min.	210	0	0	
	Max	1250	2435	2435	
ICU stay (days)	Mean	3.56	2.74	3.03	Z=-5.024; p=0.0001
	Std. Deviation	1.93	0.82	1.37	
	Min.	2	1	1	
	Max	18	7	18	
ICU mechanical ventilation (min)	Mean	565.34	502.30	524.23	Z=-1.626; p=0.104
	Std. Deviation	533.08	197.60	352.63	
	Min.	150	0	0	
	Max	3900	1200	3900	
ICU blood transfusions	Mean	1.50	0.51	0.86	Z=-4.674; P=0.0001
	Std. Deviation	1.99	1.06	1.52	
	Min.	0	0	0	
	Max	8	6	8	
ICU fresh frozen plasma	Mean	1.00	0.50	0.67	Z=-3.232; p=0,001
	Std. Deviation	1.41	1.15	1.26	
	Min.	0	0	0	
	Max	7	6	7	
ICU platelet transfusion	Mean	0.04	0.09	0.07	Z=-1.934; p=0.350
	Std. Deviation	0.34	0.48	0.43	
	Min.	0	0	0	
	Max	3	3	3	

ICU – Intensive care unit
P-value ≤ 0.05 was considered significant

There was no significant difference in the number of platelet transfusions with slightly more used in the off-pump group - 0.09±0.66 (range 0-3 units) than in the on-pump group - 0.04±0.34 units (range 0-3 units).

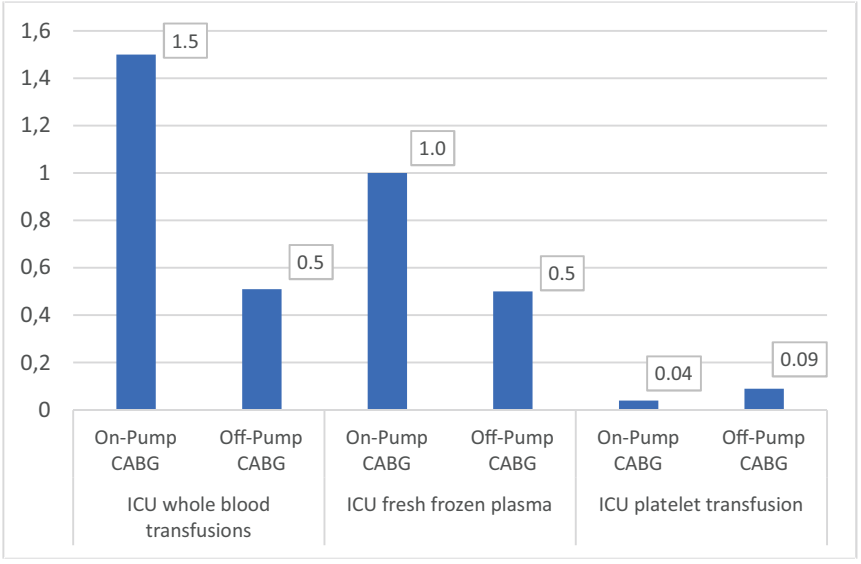

Figure 1 **Blood, Fresh frozen plasma and Platelets units given in ICU.**

The stay in the ICU was statistically significantly longer for the patients in the on-pump group - 3.56±1.93 days (range 2-18 days) compared to the patients in the off-pump group - 2.74±0.82 days (range 1-7 days).

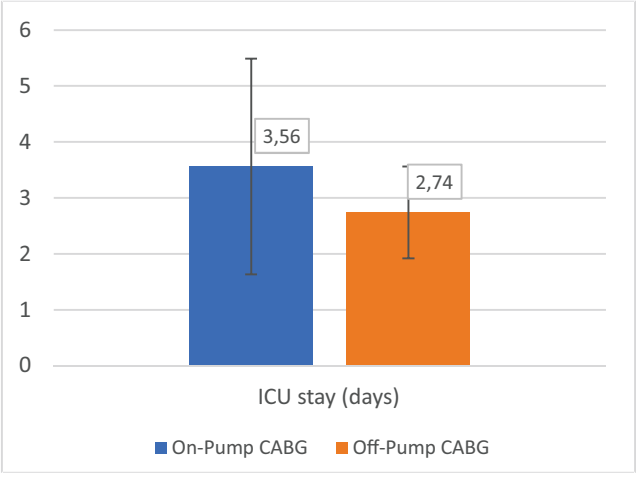

Figure 2 **ICU days of on-pump and off-pump CABG groups.**

In the observed group of 230 patients, regardless of which technique was used during the CABG, we did not noted down appearance of acute renal failure, or neurological incidents such as cerebrovascular insult and transitory ischemic attack.

DISCUSSION

Coronary-artery bypass graft surgery reduces mortality in patients with severe coronary artery disease. During the last 30 years, coronary artery bypass grafting was performed primarily with the use of cardiopulmonary bypass system, on-pump CABG using cardioplegic arrest. Historically, on-pump CABG has shown improvements in ischemic symptoms and prolonged survival in selected patients. Using this approach, peri-operative mortality is about 2%, and 5-7% are additional complications along with mortality like myocardial infarction, stroke, and renal failure.

In the mid-1990s, interest developed in performing off-pump CABG without the use of cardiopulmonary bypass, in order to reduce postoperative complications associated with the use of cardiopulmonary bypass, such as systemic inflammatory response, cerebral dysfunction, myocardial depression, and hemodynamic instability (7).

Trend of off-pump CABG has been increasingly in use in Western countries since the early 1990s, when Benetti and Buffolo published their article in Chest Journal in 1991, study with 700 patients on off-pump CABG, demonstrated excellent benefits possibly associated with the avoidance of cardiopulmonary bypass.

With advances in instruments, myocardial protection and surgical technology, both early and long-term outcomes of surgical revascularization are increasingly improved. Consequently, a growing number of high-risk patients suffering from coronary artery disease are expected to be treated with surgical revascularization (8).

Our study was taken in order to compares the early outcome of postoperative recovery in patients in the intensive care unit who underwent cardiac bypass surgery using the conventional method, the use of CPB (on-pump CABG) and without the use of CPB (off-pump CABG).

All patients included in study were elective cases with isolated CABG. A total of 230 patients divided into two groups were observed. The on-pump CABG group had 80 patients and the off-pump CABG group had 150 patients. The observed data were grouped into preoperative, intraoperative and postoperative data, within 72 hours of the completed operation in the intensive care unit. In our study, bypass revascularization was needed more for male patients than for female patients, which was similar as in other studies. According to the age, on-pump CABG group was slightly older with a mean age of 64.04±6.84 years, compared to patients in the off-pump group and mean age of 63.48±8.10 years.

We noted statistically significant difference according to the number of grafts. Patients in the on-pump group had more grafts implanted during the surgery with mean 2.46±0.57, compared to patients in the off-pump group and mean of 2.1±0.79 grafts. This speaks in favor of the findings of many published studies that indicate more complete myocardial revascularization in on-pump procedures compared to off-pump CABG (7).

Regarding the use of blood and blood derivatives during surgery, a certain difference was observed. Comparison of blood products transfusions indicate that there is statistically significant difference in mean number of blood transfusions units (1.03±1.26:0.53±1.02 units) and FFP (1.96±1.35:1.37±1.39 units) in favor of on-pump group. There was no significant difference in the number of platelet transfusions with slightly more used in the on-pump group - 0.15±0.66, than in the off-pump group - 0.05±0.34 units.

Comparison of blood products transfusions during ICU stay, indicate that there is statistically significant difference in mean number of blood transfusions units (1.5±1.99:0.51±1.06 units) and FFP (1.0±1.41:0.51±1.06 units) in favor of on-pump group. There was no significant difference in the number of platelet transfusions.

In numerous published studies, the finding of the use of transfusion is the same as in our study. Patients with heart bypass surgery using the on-pump method consumed more blood and blood derivatives. Kuss O, et al., in the article showed data from sixteen studies (46%) conducted in Europe, and the remaining was conducted in Northern America. The 35 studies account for a total of 123,137 observations; 49,718 procedures (40.4%) were conducted off-pump. Findings reported highly clinically and statistically significant benefits from off-pump CABG due to usage of red blood cell transfusion (P<0.0001) compared with on-pump CABG (9).

Same findings were reported by Hassain G, et al. They found a reduced need for blood transfusion with off-pump CABG (7). In the Coronary trial, the use of off-pump CABG reduced perioperative transfusions (50.7% *vs.* 63.3%; RR, 0.80; 95% CI: 0.75–0.85; P<0.001) (10).

Atrial fibrillation, in our study, was more present in the on-pump group - 13.8% compared to the off-pump group – 9.3% but without statistically significant difference (10,11,12,13).

Coronary Trial and many more studies had the same data due to atrial fibrillation as our study recorded. But, Kowalewski M, et al. published study in which there was no difference in atrial fibrillation rates between off-pump versus on-pump (14).

In contrast to other studies in which mechanical ventilation lasted shorter if the operation was made as off-pump CABG, our study showed that mechanical ventilation was somewhat shorter with off-pump CABG (502.30±197.60 minutes), compared to on-pump CABG (565.34±533.08 minutes), but this difference was not was significant.

Benefits of off-pump CABG due to shorter mechanical ventilation with off-pump CABG can be seen in the following studies: Dieberg G, et al. (11), Kuss O, et al. (9), Wang C, et al. (15) and Hussain G, et al. (7).

The use of vasopressors was significantly more common in the off-pump group in 50.0% of cases compared to 35.0% of cases in the on-pump group. This data from our study differs from most other studies where vasopressor consumption was significantly lower in off-pump CABG than in on-pump CABG.

In our study the total drainage was similar for both groups of patients, and was higher in off-pump group as compared to on-pump group, but not significant. In the other published studies drainage was statistically significantly less in the off-pump CABG group.

The stay in the ICU was statistically significantly longer for the patients in the on-pump group - 3.56±1.93 days (range 2-18 days) compared to the patients in the off-pump group – 2.74±0.82 days (range 1-7 days). These data are consistent with all published studies, which also proved a statistically significantly shorter stay in the ICU in off-pump CABG patients.

Numerous studies such as, Calafiore AM, et al. (15), Sajja LR, et al. (16), Wang C, et al. (2) and Hussain G, et al. (7), provided data on lower mortality in patients who underwent off-pump CABG compared with on-pump CABG, which corresponds to our data. Our study showed that lethal outcome during the first 72 hours was slightly more present in the on-pump group in 7.5% of cases compared to 2.7% of cases in the off-pump group.

But, the PRAGUE-6 study, ROOBY, and CORONARY, demonstrate no significant differences in early postoperative mortality and morbidity (13,17,18).

CONCLUSION

Our study showed that the intra- and post-operative consumption of blood and FFP was significantly lower if the patient underwent off-pump CABG, avoiding possible complications of transfusion use. Also, patients from the off-pump group had a shorter stay in ICU, which favors faster recovery and lower treatment costs.

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Frequency rate of ectodermal tumors of periorbital and maxillofacial region

Stepen učestalosti ektodermalnih tumora periorbitalne i maksilofacijalne regije

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ABSTRACT

Introduction: basal cell carcinoma (lat. Carcinoma basocellulare, basalioma) is a malignant tumor of the skin, and is one of the most common skin cancers. Its origin is from the undifferentiated cells of the basal layer of the epidermis, hair follicles or sebaceous glands. It can also arise from some genetic syndromes, such as xeroderma pigmentosum, basal cell syndrome or albinism. Approximately 80% the change appears on the scalp, face and eyelids. It is three to four times more common than squamous cell carcinoma. Aim: to confirm the radicality of ectodermal tumor removal in the maxillofacial and periorbital region. Materials and methods: the study included patients who underwent surgery at the Clinic of Head and Neck surgery of the Clinic Centre University of Sarajevo in the period of 6 months from January to June 2023. Patients with eyelid changes were also examined at the Clinic for Eye Diseases of the Clinic Centre University of Sarajevo. The patients were operated under local anesthesia and histopathological analysis were conducted at the Clinic of Pathology, Histology and Cytology of the Clinic Centre University of Sarajevo. The inclusive criteria for this study was a previous dermatoscopic finding that confirmed an ectodermal tumor. The study included 45 patients who had not previously been operated on for malignant diseases.
Results: statistical data support the accuracy of the working hypothesis. Table No. 1 in this article proves that 19% of our patients' cases require another surgical treatment, while the rest had their tumor removed without the necessity for another additional surgical procedure. Conclusion: according to this data, it can be concluded that the degree of radicality confirmed by histopathological analysis does not always require another surgical procedure.

Keywords: ectodermal tumors, histopathological analysis

SAŽETAK

Uvod: bazocelularni karcinom (lat. Carcinoma basocellulare, basalioma) je maligni tumor kože, te je jedan od najčešćih karcinoma kože. Porijeklo mu je iz nediferenciranih stanica bazalnog sloja epidermisa, folikula dlake ili lojnih žlijezda. Također može nastati iz nekih genetskih sindroma, poput xeroderma pigmentosum, bazocelularnog sindroma ili albinizma. Približno 80 % promjena se pojavljuje na koži glave, lica i kapaka. Tri do četiri puta je češći od planocelularnog karcinoma. Cilj: potvrditi radikalnost uklanjanja ektodermalnog tumora u maksilofacijalnoj i periorbitalnoj regiji Materijali i metode: uzeli smo u obzir pacijente koji su operisani na klinici za Hirurgiju glave i vrata Kliničkog Centra Univerziteta Sarajevo u periodu od 6 mjeseci od januara do juna 2023. godine. Pacijenti sa promjenama na očnim kapcima pregledani su i na Očnoj klinici Kliničkog Centra Univerziteta Sarajevo. Pacijenti su operisani u lokalnoj anesteziji i svi su patohistološki obrađeni na Klinici za patologiju, histologiju i citologiju Kliničkog Centra Univerziteta Sarajevo. Inkluzioni kriterij za navedenu studiju je bio prethodni dermatoskopski nalaz koji je potvrđivao ektodermalni tumor. U studiju je uključeno 45 pacijenata koji ranije nisu bili operisani od malignih bolesti. Rezultati: statistički podaci govore u prilog tačnosti radne hipoteze. Tabela br. 1 iz ovog rada dokazuje da 19% slučajeva naših pacijenata iziskuje reoperativni tretman, dok je ostalima tumor odstranjen u cijelosti i bez neophodne reoperacije. Zaključak: iz ovih podataka se zaključuje da stepen radikaliteta potvrdjen patohistološkom analizom ne zahtjeva uvijek reoperativni zahvat.

Ključne riječi: ektodermalni tumori, patohistološka analiza

INTRODUCTION

Basal cell carcinoma (lat. Carcinoma basocellulare, basalioma) is a malignant tumor of skin, and is one of the most common skin cancers. Basal cell carcinoma (BCC) is the most common type of carcinoma worldwide. BCC development is the result of a complex interaction between environmental, phenotypic and genetic factors. Its origin is from the undifferentiated cells of the basal layer of the epidermis, hair follicles or sebaceous glands. It can also arise from

some genetic syndromes, such as Xeroderma Pigmentosum, Basal Cell syndrome or Albinism (1).

Some authors also consider it a semimalignant or locally aggressive tumor. Approximately 80% the change appears on the scalp and face. Most often occurs on the parts of the skin that are most exposed to the sun's radiation. As for the facial skin, basal cell carcinoma is most common on the skin of the nose and eyelids. It is three to four times more frequent than squamous cell carcinoma. More than 26 different subtypes of BCC appear in the literature, but the more common, distinctive, clinicopathologic types include: nodular, micronodular, superficial, morpheaform, infiltrative and fibroepithelial (also known as fibroepithelioma of Pinkus). Combinations of these types can occur as well. The majority of BCCs are amelanotic, but variable amounts of melanin may be present within these tumors (2).

The most at-risk group are Caucasions. The ectodermal tumors occur less often in members of the yellow race, and in members of the black race they are extremely rare. This tumoral change spreading in depth and width leads to damage to the surrounding tissues.

Basal cell carcinoma is also characterized by an extremely rare occurrence of recurrence, which is the frequency of recurrence less than 1%. Metastases of this disease are also a rare phenomenon. Literature so far describes less than 150 patients with lymphogenous and hematogenous metastases. Basal cell carcinomas are common skin cancers that tend to appear on sun-exposed skin. Pathobiologically, activation of the Hedgehog signaling pathway characterizes the majority of cases. In general, BCCs are slow-growing and rarely metastasize. Nevertheless, they are locally invasive and can be destructive (3).

Basocellular is characterized by de novo formation after exposure to UV rays, more precisely, UVB rays. Exposure to sunlight is the main etiological factor of this disease. Thereafter, risk factors for the development of basal cell carcinoma are also UV lights such as photochemotherapy with psoralen (PUVA), solarium, gamma radiation, contact with tar derivatives, arsenic and immunocompromised conditions (4).

Basal cell carcinoma is most often manifested as whitish or brown raised areas papules or nodules. There may also be erosions that do not heal. Tumorous changes often cover thin skin that can be with or without ulceration, and with dilated blood vessels on periphery, telangiectasias. In the treatment of primary lesions, the initial goal is to complete tumor removal, whether by conventional surgical excision, Mohs micrographic surgery, cryosurgery, electrodesiccation and curettage, topical application of imiquimod or fluorouracil, photodynamic therapy, or radiation therapy. Of these treatments, surgical excision and Mohs surgery are the most commonly used because of their association with a low recurrence rate and the ability to confirm residual tumor pathologically (3,4,5).

There are several clinical types of basal cell carcinoma:

- Nodular type
- Ulcerative type
- Multiform type
- Superficial type
- Pigmented type
- Cystic type
- Sclerosing type
- Basosquamous type.

Although these changes are destructive, they rarely metastasize, and theirs most common complications are occurrences of secondary infections. Risk factors for BCC include: advanced age, male sex, fair skin, low ability to tan, intense intermittent UVR exposure during childhood, signs of actinic damage (skin changes due to excessive sun exposure), personal/family history of skin cancer, excessive sun bed use, phototherapy, radiotherapy, systemic immunosuppression and a genetic predisposition (5,6).

The multiform type of basal cell carcinoma occurs on the nose and cheek, and manifests itself in the form of an atrophic scar or whitish plaque with visible blood vessels. Locally is very aggressive, and quickly spreads into deeper structures. The diagnosis of tumors of the facial region is based on a properly taken history and clinical examination.

On the basis of family diseases data, we can make presumption about the existing predisposition to malignant neoplasms. Total excision is a diagnostic-therapeutic method during which the tumor change is completely removed followed by thorough histopathologic analysis in order to achieve the correct diagnose. The next step is to determine the therapeutic course based on the histopahtological findings (7,8).

AIM

The aim of this study was to confirm the radicality of ectodermal tumor removal in the maxillofacial and periorbital region. The hystopathological analysis should confirm that the surgery was successful.

MATERIALS AND METHODS

In our study we performed the surgery patients who were examined at the Clinic of Head and Neck and Clinic for Eye Diseases of the Clinic Center University of Sarajevo. All patients underwent surgery at the Clinic of Head and Neck in the period of 6 months, specifically from January to June 2023. The patients were operated in local anesthesia and all removed changes were histopathologically analysed at the Clinic of Pathology, Histology and Cytology of Clinic Center University of Sarajevo. The inclusive criteria for this study was a previous dermatoscopic findings that confirmed an ectodermal tumor. The study included 45 patients who had not previously been operated on for any malignant diseases.

Formulation of the problem: the question arises of the frequency of ectodermal tumors of the head, neck and eyelidy in patients who were operated at the Clinic of Head and Neck Surgery, as well as the success of radicalization confirmed by histopathological analysis.

Null hypothesis: the degree of radicality of the removed ectodermal tumors requires a reoperative procedure.

Working hypothesis: the degree of radicality of the removed ectodermal tumors does not require reoperative procedure.

Standard surgical excision, which is the most common therapy for this type of tumor, is indicated for small changes, favorable localization.

In our study, we used this method to remove tumor changes completely with primary wound closure. In this way, the treatment itself is achieved, moreover if the hystopathological findings confirm that the edges of the exiced tissue are "clean", that is that there are no tumor cells and remains in them.

We consider as an adequate lateral tumor-free margin in situations where there is 3 milimeters or more away from the lesion, zone-free -tumor cells from the edge as well as in the depth of the resection margin. If the tumor change is not completely removed, there is a high risk of recurrence.

There are almost no absolute contraindications for this type of treatment, except for patients with bone aplasia and heart disease, with an increased risk for this type of treatment.

RESULTS

In order to prepare this study, a total number of 45 patients were taken into consideration in period of 6 months time. All patients underwent the surgery in local anesthesia, and each and every single change was hystopathologically analized at the Clinic of Pathology, Histology and Cytology of the Clinic Center University of Sarajevo.

The inclusive criteria for the conducted study was a previous dermatoscopic finding that confirmfferentioationed existance of the ectodermal tumor.

The obtained results were in favor of the fact that ectodermal tumors of maxillofacial and periorbital region most often occured in people between the 40 and 80 years old.

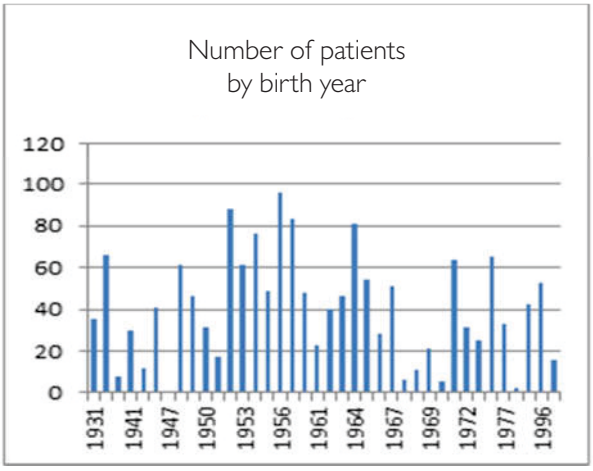

Figure 1 **Number of patients by date of birth**.

Analizing data, we have found that all the patients who were treated were in range from 40 to 80 years old, with the prevalence of patiens between 60 - 70 years old.

Table 1 **Percentage of patients by gender**.

Valid Gender		Frequency	Percent	Valid Percent	Cumulative Percent
	male	20	44.4	44.4	44.4
	female	25	55.6	55.6	100.0
	Total	45	100.0	100.0	

Analizing the data from the table 1., we can see that gender is not a deciding factor for reoperation and that the differentiation by gender is not influential. Meaning that the number of women and men affected by these type of tumors is almost equal.

Our null hypothesis claimed that the degree of radicality required reoperation. The results of this study disprove it. The statistical data are in favor of the accuracy of the working hypothesis.

Table 2 **Relation between histopathological diagnosis and operation.**

		Reoperative procedure	Histopathologic diagnose
Pearson Correlation	Reoperative procedure	1.000	.194
	Histopath. diagnose	.194	1.000
Sig. (1-tailed)	Reoperative procedure	.	.003
	Histopath. diagnose	.003	.
N	Reoperative procedure	45	45
	Histopath. diagnose	45	45

Data from the Table 2 in our study prove that 19% of the cases of our patients require reoperative treatment, while the others 81% the tumor was completely removed by the first surgical treatment.

Table 3 **Variety of PHD diagnosis**.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	BasalcellCaunceronod.Tip,PT1RO	5	11.1	11.1	11.1
	BasalcellCapt1Ro	13	28.9	28.9	0.0
	BasalcellCmetatipPt1,RO	1	2.2	2.2	42.2
	BasalcellCmikronodulPt1R1	5	11.1	11.1	53.3
	BasalcellCapseudoadenoidni	2	4.4	4.4	57.8
	BasalcellCamixedPt1Ro	3	6.7	6.7	64.4
	BasalcellCanodul,ptx,Rx	3	6.7	6.7	71.1
	BasalcellCanodullpigmenttipPt1Ro	1	2.2	2.2	73.3
	BasalcellCaPt3,Ro	1	2.2	2.2	75.6
	BasalcellCanoduli mikromodulpt1Ro	2	4.4	4.4	80.0
	Other	9	20.0	20.0	100.0
	Total	45	100.0	100.0	

Obtained data from our patients in table 3, prove that the histopathological analysis shows succesfull findings by confirming the desired degree of radicality (R0). In these patients the reccurence of tumor is not expected.

DISCUSSION

Basal cell carcinomas are common skin cancers that tend to appear on sun-exposed skin. Pathobiologically, activation of the Hedgehog signaling pathway characterizes the majority of cases. In

general, BCCs are slow-growing and rarely metastasize. Nevertheless, they are locally invasive and can be destructive. While typical cases are diagnosed based on clinical findings, the clinicopathological manifestations are varied. Consequently, skin biopsy is essential to confirm the diagnosis and evaluate the risk of recurrence. In the treatment of primary lesions, the initial goal is to complete tumor removal, whether by conventional surgical excision, Mohs micrographic surgery, cryosurgery, electrodesiccation and curettage, topical application of imiquimod or fluorouracil, photodynamic therapy, or radiation therapy. (9,10)

The totall of 45 patients were included in our retrospective study which was conducted at the Clinic for Head and Neck surgery and Eye Clinic in period from january till june 2023. In every case of all patients the histopathological analysis of the removed tumor has been processed at the Clinic for Pathology Clinic Center University Sarajevo. And in all of the patients was confirmed diagnosis of basal cell carcinoma.

In the case of 29 patients, the histopathological analysis approved the succesfull findings by confirming the desired degree of radicality (R0), and it has not occurred in these patients and is not expected to occur recurrence of the disease. Consequently therefore, reoperative procedure is not indicated.

In 9 of them, by histopathological analysis, the existence of altered cells was verified in the edges, and therefore it is concluded that a sufficient degree of radicality was not achieved during surgery. Given the fact of altered cells in the edges, reoperative procedure is indicated for these patients, in order to prevent recurrence of the disease.

In the case of the remaining 7 patients from our study, our colleagues pathologists were not specific abot their own findings, they could not clearly and decisively express that are there any changed cells left in the edges cut. We have been checking these patients and do the follow up procedure every month to two. The recurrence is expected, if so that the most likely reoperative procedure will be necessary.

Most of our patients had none subjective complaints and symptoms of the disease, and were most often reported to our dermatological department examination due to aesthetic disturbances. Given the fact that the tumors were localized in areas that affect the expressed and conspicuous areas such as the head, neck and eyelids.

According to the most recent European guidelines, topical and local destructive treatments should be reserved for low risk or superficial BCCs (10). Surgery is the treatment of choice in most cases. Mohs surgery or margin control techniques are the gold standard surgical approaches in high-risk recurrent BCCs, especially in critical anatomic areas, because they offer the highest cure rates (11,12). Basal cell carcinoma is the most common tumor in humans and its incidence is expected to increase in the future. When managing the disease, a one-dimensional orientation towards the clinical or histological subtype is not sufficient because of the heterogeneity of the tumor. The primary implementation of risk stratification, which is decisive for the further diagnostic and therapeutic steps, is becoming increasingly important. The gold standard in treatment continues to be the surgical procedure, which should be carried out using micrographically controlled surgery if possible (13).

According to the German study group, due to BCCs high tendency of recurrence, an important parameter in the planning of therapy is the risk of recurrence. After clinical and histological diagnosis, the majority of tumors are treated surgically, although radiation and topical procedures are also possible therapeutic alternatives in certain constellations. Hedgehog inhibitors, a completely new class of substances, have recently been approved for rare metastatic and locally advanced diseases, thus significantly expanding the range of treatments. This article provides an overview of the current guideline-based diagnosis and therapy of basal cell carcinomas in Germany (14). Recent advances in our understanding of the molecular pathways that are involved in the proliferation of BCC tumor cells have led to the development of new targeted therapies. The Hedgehog (Hh) pathway is abnormally activated in patients with both sporadic and inherited BBCs (Gorlin syndrome), and inhibition of this pathway appears to result in significant clinical responses.

The goal of BCC treatment according to the National Comprehensive Cancer Network (NCCN) is cure and maximal preservation of function and cosmetics. Early treatment of BCC is curative in the vast majority of cases, thus preventing progression with local approaches such as surgical excision, radiotherapy, topical imiquimod, or photodynamic therapy. The likelihood of recurrence following treatment is used to categorize lesions as low or high risk. Thus, high-risk BCC denotes primary or already relapsed tumors with a significant risk of further relapse after local treatment. The overall 5-year recurrence rate has been estimated to be around 4–5 % . Surgery and radiotherapy are the treatment of choice for most patients with high-risk lesions (15,16).

According to the data we received from our studies, basal cell carcinoma is presented both in men and women, almost equally. 45% of cases of basal cell carcinoma were noticed in the group of male, while 55% appeared in the group of female.

CONCLUSION

From these data, it can be concluded that the degree of radicality confirmed by histopathologic analysis does not always require a reoperative procedure. The available data suggest that surgical methods remain the gold standard in BCC treatment, with Mohs micrographic surgery typically utilized for high-risk lesions.

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Bosnia and Herzegovina versions of Guidelines for Patients!
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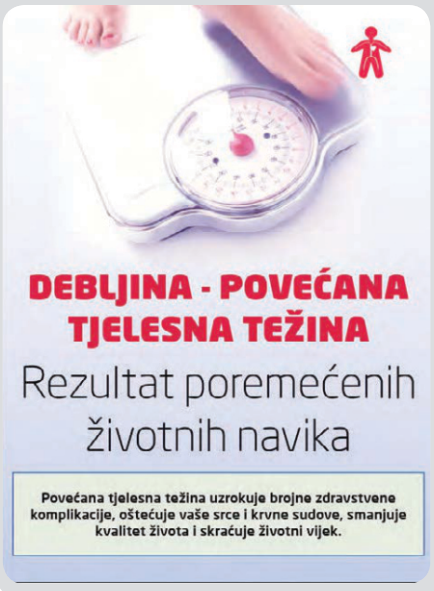

Drug interactions and adverse effects in the elderly population

Interakcije i neželjeni efekti lijekova u starijoj populaciji

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ABSTRACT

Introduction: the world population is aging. Almost every country in the world records an increase in the number and share of elderly people in its population. Globally, the population of people aged 65 and over is growing faster than all other age groups. According to the United Nations document (World Population Prospects: the 2019 Revision), by 2050 one of six people in the world will be older than 65 (16%), compared to one of 11 in 2019 (9%). In 2018, for the first time in history, the number of people aged 65 and over exceeded the number of children under the age of five globally. The number of people aged 80 or over is projected to triple, from 143 million in 2019 to 426 million in 2050. The world continues to experience an unprecedented and sustained change in the age structure of the world's population induced by increasing life expectancy and declining fertility. People are living longer, and both the share and the number of elderly people in the total population are growing rapidly. In 2020, there were 727 million people aged 65 or over in the world. Considering that women live longer than men, on average they make the majority of elderly people, especially in old age. In the next three decades, it is predicted that the number of elderly people worldwide will more than double and reach over 1.5 billion in 2050. In all parts of the world, there will be an increase in the elderly population in the period from 2020 to 2050. The share of the population over 65 is expected to increase from 9.3 percent in 2020 to around 16.0 percent in 2050. Aim: to point out the importance of clinical pharmacology in prescribing drugs to elderly people, monitoring possible drug interactions and detecting, monitoring and reporting their side effects. Conclusion: clinical pharmacology in the elderly population is gaining more and more importance, taking into account that society is getting older and the most common medical intervention in this population is prescribing of drugs, both due to changes in physiological functions and due to the presence of comorbidities. In accordance with the aforementioned changes, the pharmacokinetic and pharmacodynamic characteristics of drugs change with aging, but not equally for each drug or group of drugs. These changes result in an increased incidence of side effects in the elderly population, while at the same time the possibility of interactions is also increased. One of the problems related to the detection, monitoring and reporting of side effects is the education of both health professionals and patients. Namely, there are not isolate d cases where the appearance of an side effect due to the use of a certain drug or as a result of an interaction is interpreted as a newly developed disease that begins to be treated with the initiation of a new drug. From the aspect of clinical pharmacology, when it comes to the use of drugs in elderly people, special attention should be paid to changes in organ systems, pharmacokinetics and pharmacodynamics of drugs, possible interactions and occurrence of side effects of drugs.

Keywords: old age, drugs, drug interactions, adverse effects, clinical pharmacology

SAŽETAK

Uvod: svjetsko stanovništvo stari. Gotovo svaka zemlja na svijetu bilježi porast broja i udjela starijih osoba u svojoj populaciji. Globalno, populacija stanovništva 65 godina i više raste brže od svih ostalih dobnih skupina. Prema dokumentu Ujedinjenih nacija (World Population Prospects: the 2019 Revision), do 2050. godine jedan od šest ljudi u svijetu bit će stariji od 65 godina (16%) u odnosu na jedan od 11 u 2019. godini (9%). U 2018. godini, prvi put u historiji, broj osoba dobi 65 ili više godina premašio je broj djece mlađe od pet godina na globalnoj razini. Predviđa se da će se broj osoba dobi 80 ili više godina utrostručiti, sa 143 miliona u 2019. na 426 miliona u 2050. godini. Svijet nastavlja da doživljava neviđenu i održivu promjenu starosne strukture svjetske populacije potaknutu povećanjem očekivanog životnog vijeka i smanjenjem fertiliteta. Ljudi žive duži život, a i udio i broj starijih osoba u ukupnoj populaciji brzo rastu. U svijetu je 2020. godine bilo 727 miliona osoba dobi 65 godina ili više. Obzirom da žene žive duže od muškaraca, u prosjeku čine većinu starijih osoba, posebno u starijoj dobi. U naredne tri decenije, predviđa se da će se broj starijih osoba širom svijeta više nego udvostručiti i dostići preko 1,5 milijardi u 2050. godini. U svim dijelovima svijeta će doći do porasta starije populacije u periodu od 2020. do 2050. godine. Očekuje se da će se udio stanovništva starijeg od 65 godina povećati sa 9,3 posto u 2020. na oko 16,0 posto u 2050. godini. Cilj: ukazati na značaj kliničke farmakologije u propisivanju lijekova osobama starije životne dobi, praćenja mogućih interakcija primijenjenih lijekova te otkrivanja, praćenja i prijavljivanja neželjenih efekata istih. Zaključak: klinička farmakologija u starijoj populaciji dobiva na sve većoj važnosti uzimajući u obzir da društvo sve više stari a najčešća medicinska intervencija u ovoj populaciji je propisivanje lijekova, kako zbog promjene fizioloških funkcija tako i zbog prisutnog komorbiditeta. U skladu s navedenim promjenama,

starenjem se mijenjaju farmakokinetičke i farmakodinamske karakteristike lijekova, ali ne jednako za svaki lijek ili skupinu lijekova. Ove promjene rezultiraju povećanom incidencom pojave neželjenih efekata u starijoj populaciji dok je istovremeno povećana i mogućnost nastanka interakcija. Jedan od problema vezanih za otkrivanje, praćenje i prijavljivanje neželjenih efekata je i educiranost kako zdravstvenih profesionalaca tako i pacijenata. Naime, nisu izolirani slučajevi da se pojava neželjenog efekta usljed primjene određenog lijeka ili kao posljedica interakcije interpretira kao novonastalo oboljenje koje se počinje liječiti uvođenjem novog lijeka. S aspekta kliničke farmakologije, kada je u pitanju primjena lijekova u osoba starije životne dobi, posebnu pažnju treba posvetiti promjenama u organskim sistemima, farmakokinetici i farmakodinamici lijekova, mogućim interakcijama i pojavi neželjenih efekata lijekova.

Ključne riječi: starija dob, lijekovi, interakcije lijekova, neželjeni efekti, klinička farmakologija

INTRODUCTION

Physiologically, the aging process begins at birth, with the fact that in childhood and youth, processes in the body take place in terms of the development and maturation of certain functions, while the third age is characterized by the slowing down and "shutdown" of certain functions - both physiologically and as a result of various diseases. The age limit for determining the population of older persons differs between individual countries and mainly depends on the level of development of a particular country (developed countries, developing countries, etc.). Most of the developed countries of the world have accepted the chronological age of 65 years as the definition of an elderly person. The United Nations document (2019) states that the elderly are considered to be persons aged 60 or 65 years and over. (1) In the same document, it is stated that aging is the result of the demographic transition, a process in which the reduction in mortality is accompanied by a reduction in fertility. Together, the mentioned reductions eventually lead to a smaller share of the population group of children and a larger share of the group of elderly people in the total population of a country (1,2,3).

Changes in organ systems in old age

Elderly people often experience symptoms (e.g. fainting, loss of appetite, dizziness, etc.) that require special attention as they might be the result of disorders of multiple organ systems.

Hypertension and heart failure are the most common diseases of the cardiovascular system in the elderly. As a result of changes in the arterial blood vessels, the cardiac output decreases as well as the heart rate. The total peripheral resistance increases by more than 1% per year, which results in a decrease in organ perfusion while simultaneously decreasing all respiratory functions. The vital capacity of the lungs decreases by about 1 liter in old age.

The capillaries of the renal glomeruli are also subject to degenerative changes. The total mass of the kidneys and perfusion decrease, and creatinine clearance decreases annually by 0.8 ml/min/1.73m^2 of body surface. As a consequence of these changes, plasma flow through the kidneys decreases with a consequent decrease in glomerular filtration.

Changes also occur in the gastrointestinal tract and are manifested by a decrease in the motility of the esophagus as well as the amount of the produced gastric acid, decrease in blood flow through the liver, its mass and detoxification capacity, along with a decreased activity of microsomal enzymes.

As changes occur in all organ systems, a high prevalence of anemia of various causes occurs, as one of the most common hematological disorders.

In old age, there is an increased frequency of infectious, malignant and autoimmune diseases, and there is a general decline in the ability to produce antibodies. Malignancies show an increasing prevalence. Autoimmune diseases arise as a result of the reduced ability of the body to distinguish its own from foreign, and the level of autoantibodies increases in old age.

Due to the loss of the organic and mineral composition of the bone tissue in the elderly, the bones are more susceptible to fractures. The total muscle mass is reduced by 1/3. Degenerative changes also affect the nervous system so that the loss of myelin in the axons is recorded, which results in a decrease in their conductivity. The total brain mass decreases by 7-10% and the changes are most obvious in the cerebral cortex (4).

Pharmacokinetics of drugs in the elderly

Pharmacokinetics is the study of how an organism affects the drug, in terms of its absorption, distribution, metabolism (biotransformation) and elimination (ADME). The pharmacokinetic characteristics of each drug can potentially be altered as a consequence of physiological processes in the context of aging (5). The pharmacokinetics of drugs can be affected by various factors such as age, gender, genetic variability, some diseases, drug interactions, drug interactions with food, disease, and more (6). The metabolism and excretion of many drugs decline with age, and physiological changes require dose adjustments of some drugs. (7) In the elderly, changes in the pharmacokinetics of drugs affect all phases.

Absorption

Although the absorptive surface of the small intestine decreases and there is an increase in the gastric pH value, changes in drug absorption are usually not of great clinical significance. Stomach emptying slows down, which for drugs that are absorbed in the small intestine can affect the time to reach the maximum concentration of the drug in the serum, result in a delayed effect of the drug while the relative bioavailability of the drug does not change.

Distribution

In old age the volume of drug distribution changes. The volume of distribution indicates the relationship between the amount of the drug in the body and the concentration of the drug in the blood or plasma. The volume of distribution does not represent a real volume, but must be understood as the amount of body fluids that would be needed if the drug were to be evenly distributed throughout the body, which is usually not the case (8,9).

Aging increases the proportion of adipose tissue in the body, which results in an increase in the volume of distribution of lipophilic drugs and an extension of the half-life ($t_{1/2}$) of drugs such as benzodiazepines and phenobarbitone. Lipophilic drugs have a

higher volume of distribution compared to younger age. Hydrophilic drugs have a small volume of distribution and are mainly found in the blood, slightly in the tissues, because they are distributed in the total amount of water in the body, which in old age is reduced by 10-15% compared to younger age. In old age, there is a slight decrease in serum albumin and a slight increase in α-1-globulin. A decrease in the concentration of serum albumin can result in an increase in the fraction of free (unbound) drug in the plasma, which, for drugs with a narrow therapeutic range, is of significant clinical importance because the possibility of the appearance of not only unwanted but also toxic effects of the drug increases. Phenytoin and warfarin are examples of highly protein-bound drugs with a greater risk of toxic effects when serum albumin levels decrease. (10)

Metabolism (biotransformation)

Drug metabolism or biotransformation of drugs in most cases occurs in the liver, especially through the cytochrome P450 (CYP) system of isoenzymes. Although drugs are usually inactivated by biotransformation, some metabolites are pharmacologically active, sometimes even more effective than the active substance, and in some cases the drug becomes pharmacologically active only after being metabolized.

With aging, the mass and blood flow through the liver decrease. These changes have a clinically significant implication only when the drug has a pronounced so-called "the first passage" through the liver and the concentration of the drug in the plasma increases as a result. Cytochrome P-450 isoenzyme expression does not decrease with aging, although enzyme activity decreases. In order for clinically significant changes to occur, the hepatic metabolism of drugs should be reduced by at least 30-40% (Table 1) (5,7).

Elimination

The kidneys are the main organ of excretion of water-soluble drugs. The biliary system contributes to excretion if the drug is not reabsorbed from the digestive tract. Excretion through the intestines, saliva, sweat, milk and lungs is less prevalent, except for the elimination of anesthetics through the lungs. Excretion in milk is clinically significant because of the possible effect of drugs on the infant.

In old age, the ability to excrete drugs through the kidneys decreases. After the age of 30, creatinine clearance decreases by 8 ml/min/1.73 m^2 every 10 years, and thus the clearance of drugs that are eliminated through the kidneys also decreases, as shown in Table 1 (5).

Although there is a decrease in glomerular filtration, elderly people create less creatinine due to less muscle mass, so serum creatinine concentrations usually do not change. Due to the weakening of glomerular and tubular function, the excretion of some drugs via the kidneys is also reduced.

Clinical implications depend on the share of renal excretion in the total elimination of the drug and on the therapeutic index (ratio of the most tolerated to the lowest effective dose) of the specific drug. As renal functions are dynamic, maintenance doses should be adjusted when the patient becomes ill, dehydrated or has just recovered from dehydration (7).

Table 1 **Medicines with reduced hepatic metabolism or renal excretion in old age.**

Drug group	Decreased hepatic metabolism	Decreased renal excretion
Analgesics	ibuprofen morphine naproxen	-
Antibiotics	-	amikacin ciprofloxacin gentamicin netilmicin nitrofurantoin
Diuretics	-	amiloride furosemide hydrochlorothiazide triamterene
Cardiovascular drugs	amlodipine diltiazem nifedipine propranolol verapamil	enalapril captopril lisinopril procainamide
Psychoactive drugs	alprazolam chlordiazepoxide diazepam imipramine nortriptyline triazolam	-
Other	levodopa teophylline	chlorpropamide lithium methotrexate ranitidine

Pharmacodynamics of drugs in the elderly

Pharmacodynamics studies the effect of drugs on the body and its functional systems (8,9). The effectiveness of certain drugs changes with age and can be higher or lower than in younger people (6). Pharmacodynamic changes in old age are manifested as: a change in the sensitivity of specific receptors and a change in the mechanism of maintaining homeostasis.

Changes in receptor sensitivity

Receptor sensitivity is changed in the elderly population. Due to the increased concentration of catecholamines in the blood in the elderly, the number and affinity of beta-adrenergic receptors for agonists is reduced. Liver cells are more sensitive to the action of oral anticoagulants. It is more difficult for the central nervous system to adapt to the changed function that is a consequence of the drug's action, as well as a consequence of the increased sensitivity of CNS receptors, and this often results in confusion, disorientation, restlessness, excessive sedation and depression (5).

Changes in the homeostasis maintenance mechanism

In the elderly population, cardiac reserve and kidney function are reduced, while hypersecretion of antidiuretic hormone (ADH) is noted, so the use of rapid infusions of saline can result in cardiac decompensation. The response to the decrease in the volume of

extracellular fluid is slowed down, which, together with the reduction of aldosterone secretion, increases the risk during the use of diuretics and restriction of salt intake in the body. Postural hypotension is a frequent consequence of reduced sensitivity of baroreceptor mechanisms, activity and sensitivity of the sympathetic system, vasomotor ability of arterioles and veins, and volume regulation mechanisms. Antihypertensives, diuretics, phenothiazines and tricyclic antidepressants are the drugs that most often cause postural hypotension in the elderly. The weakening of thermoregulatory mechanisms is the cause of the higher frequency of hypothermia during the use of phenothiazines, barbiturates, tricyclic antidepressants and narcotic analgesics. (5)

Drug interactions in the elderly population

We refer to interaction when one drug can change the intensity of the pharmacological effects of another drug. The possibility of interaction exists when two or more drugs are used at the same time, but in addition to drug interactions, we distinguish between drug interactions with food, disease, and the patient's genotype (6). Drug interactions mainly involve reactions resulting in negative outcomes for the patient's health, but there are also drug interactions that we use in pharmacotherapy in order to achieve the desired therapeutic effect. In that case we are talking about the combined use of drugs, specifically about polytherapy. Hypertension therapy is often carried out with a combination of two or three drugs. The same applies to heart failure therapy (diuretic, vasodilator, cardiotonic). Oncological therapy is usually carried out by the combined use of several drugs according to special protocols. In all cases of combined use of drugs, the doctor must be reliably informed about the possibility of positive or negative drug interactions (8,9). One of the leading problems in the prescription of medicines, both in the whole world and in our country, is *polypharmacy* - the purposeless and irrational use of several medicines, which is most common in the elderly.

Pharmacokinetic interactions

Pharmacokinetic interactions imply the effect of one drug on the absorption, distribution, metabolism or excretion of another drug, which can result in a change in the serum concentration of the drug and thus in a change in the clinical response (11,12).

Interactions in the absorption phase

Mechanisms of interactions in the absorption phase in the elderly include pH changes in the sense of an increase in gastric pH value, complex formation, reduction of motility and blood flow in the gastrointestinal tract. Changes in gastric pH values due to the use of H2 blockers or proton pump inhibitors can affect the absorption of ketoconazole, itraconazole and salicylate, for optimal absorption the acidity of this environment is necessary. Anticholinergic drugs, which are used relatively often in the elderly, slow down gastric emptying. The result of the use of these drugs is, for example, reduced bioavailability of levodopa by 50%. (12) There is also a great possibility for the formation of complexes in the gastrointestinal tract in the elderly due to the frequent use of preparations containing aluminum, magnesium, calcium and iron, such as the prescription of bisphosphonates with calcium supplements in the treatment of osteoporosis. This type of interaction can be prevented by a dosage regimen that includes sufficiently long inter-dose intervals of individual drugs.

Interactions in the distribution phase

The distribution of drugs in the elderly has changed due to a decrease in body weight, total water content in the body, an increase in the percentage of adipose tissue and a decrease in the concentration of serum albumins. Due to an increase in the amount of fat tissue and a decrease in water content, the volume of distribution of liposoluble drugs (e.g. diazepam) increases in the elderly, which can result in the accumulation of the drug. On the other hand, the volume of distribution of water-soluble drugs (e.g. lithium and digoxin) decreases, so the doses of these drugs must be reduced.

Due to the decrease in serum albumin concentration, there may be an increase in the free fraction of acidic drugs and an increase in the possibility of unwanted effects.

Drugs that bind competitively to albumin such as warfarin, phenytoin and tolbutamide can displace other drugs from the albumin binding site which can result in toxic effects, e.g. warfarin causes bleeding and glipizide causes hypoglycaemia. On the other hand, the concentration of α1 acid glycoprotein can increase, which can result in a decrease in the free fraction of basic drugs such as antidepressants, antipsychotics and beta blockers. (12)

Interactions in the phase of metabolism

In old age, liver mass and blood flow through the liver decrease by about 30%, and changes in enzyme activity also occur. Interactions in the phase of drug metabolism are the most common and best-studied drug interactions. The most common interactions involve microsomal isoenzymes of the liver (cytochrome P450), while rarely interactions occur in drug conjugation processes. Cytochrome P450 isoenzymes are important in oxidation reactions, and CYP3A4, CYP2D6 and CYP1A2 are most often involved in drug metabolism.

A good understanding of substrates, inhibitors and inducers can help predicting the risk of drug interactions occurring in certain combinations.

Enzyme induction

Enzyme induction results in a decrease in the concentration of the drug in the plasma due to the acceleration of its metabolism. Phenytoin, which is a known enzyme inducer, in combination with simvastatin reduces its therapeutic effect. An increase in cholesterol levels from 9.4 mmol/L to 15.9 mmol/L can be observed. Similarly, omeprazole in combination with warfarin/imipramine reduces their therapeutic effect.

Enzyme inhibition

It is most often the result of competitive binding at the enzyme binding site. Cisapride is a drug for the treatment of gastroparesis, ileus, gastroesophageal reflux. If it is used in combination with erythromycin, its action is blocked and the plasma concentration of cisapride increases. This results in prolongation of the QT interval with the possibility of torsade de pointes.

Interactions in the phase of elimination

After the age of 55, blood flow through the kidneys, glomerular filtration and tubular secretion decrease. Weakening of renal function reduces the excretion of many drugs, which can result in

the appearance of unwanted drug effects. Toxicity is most often caused by drugs that are mainly eliminated through the kidneys and have a narrow therapeutic index, such as lithium, digoxin and aminophylline.

Pharmacodynamic interactions

Physiological changes and disturbances of homeostasis in old age result in changes in the pharmacodynamics of drugs. Pharmacodynamics is defined as a science that studies the way a drug acts on an organism or as an organism's response to a drug. For example acetylsalicylic acid (ASA) blocks platelet function resulting in prolonged bleeding time. Therefore, bleeding is a pharmacodynamic effect of acetylsalicylic acid. As an example of a pharmacodynamic interaction, we can cite the example of an elderly person who is taking ASA and Ginko preparation for memory improvement. In the meantime, due to the development of atrial fibrillation, the cardiologist prescribes warfarin to prevent myocardial infarction. ASA blocks platelets and warfarin affects coagulation factors. Both increase the risk of bleeding, so the pharmacodynamic interaction is bleeding (13).

Also, the use of angiotensin-converting enzyme inhibitors (ACE inhibitors) in combination with potassium-sparing diuretics increases the risk of hyperkalemia (12).

In older people, the effect of the medicine at the site of action may be greater or less than in younger people. Differences can arise as a result of drug-receptor interactions, post-receptor changes or non-adaptation of the organism to homeostatic changes, but most often as a result of pathological changes in the organs (14).

Elderly people are especially sensitive to the anticholinergic effects of drugs. Many drugs (tricyclic antidepressants, antihistamines with sedative effects, antimuscarinic drugs for the urinary tract, some antipsychotics, Anti-Parkinson's drugs with atropine-like action, many OTC hypnotics) cause anticholinergic effects in the elderly. The use of such drugs in elderly people, especially in those with impaired cognitive functions, can result in the appearance of unwanted effects from the CNS, so such people become confused and sleepy.

Anticholinergic drugs (eg atropine, biperiden) also usually cause constipation, urinary retention (especially in elderly people with benign prostatic hyperplasia), blurred vision, orthostatic hypotension and dry mouth. In general, the elderly should avoid drugs with pronounced anticholinergic effects whenever possible (14).

Some drugs, such as amoxicillin, can be administered in a dose of 2 g without having any toxic effects. On the other hand, in some drugs (warfarin), a change in dosage of just 1 mg can have disastrous consequences for the patient, because each drug has its own framework of beneficial and toxic effects, or therapeutic index - TI (13)

The therapeutic index is the quotient between the mean lethal dose and the mean effective dose, i.e. TI = LD50 : ED50. It is very important for the practical application of the drug. If the value of TI is higher, it is more likely that the drug will cause fewer unwanted and toxic effects. Potentially useful drugs should have a TI of at least 10 and above. No drug, no matter how effective, cannot be used in therapy if it has a low therapeutic index, i.e. if its therapeutic dose is very close to the toxic dose (8,9).

Elderly people often use herbal preparations and other nutritional supplements without informing the doctor or the people who take care of them. Herbal preparations can interact with drugs, which can result in unwanted drug effects (12).

The simultaneous use of a large number of drugs in the treatment of the elderly is often necessary in order to achieve the desired therapeutic effect. Therefore, treatment in the elderly represents a serious challenge because there is an increased possibility of drug interactions resulting in unwanted effects, treatment failure or loss of drug effect. As the number of medications increases, the possibility of interactions with medications increases. The risk of adverse drug effects is estimated at 13% for two drugs, 58% for five drugs, and 82% for seven or more drugs. It is estimated that the total frequency of drug reactions in elderly patients is at least twice as high as in the younger population due to mistakes of the prescribing physician and the patient (12). Practical mistakes of doctors occur due to lack of knowledge about clinical pharmacology in the elderly population and failure to reevaluate the patient's therapy. Mistakes on the part of the patient may be the result of non-cooperation and the simultaneous administration of a large number of drugs.

The drugs that most often cause clinically significant interactions are shown in Table 2.

Table 2 **Group of drugs that most often causes clinically significant interactions.**

drugs with a narrow therapeutic range:	warfarin, digoxin, teophylline, cyclosporine, antiepileptics
drugs for which dose control is important	antidiabetics, antihypertensives
enzyme inhibitors	cimetidine, ketoconazole, ciprofloxacin, erythromycin
enzyme inducers	phenytoin, barbiturates, rifampicin, carbamazepine

Side effects of drugs in the elderly population

A large part of the elderly population in the world and in our environment takes medicines both by prescription and over the counter (so-called OTC medicines). According to some data, an elderly person takes an average of 4-5 prescription drugs, and buys 1-2 drugs over the counter, and receives about 15-17 prescriptions on average per year. (6) According to some data, about two-thirds of elderly patients make mistakes when taking medication, and this is especially true for people of biological age over 75 years. Mistakes are more pronounced in patients who live alone and in those who suffer from multiple diseases. Adverse drug effects in people aged 70 to 79 are seven times more common than in those aged 20 to 29. Adverse drug effects are twice as common in patients over 80 years old compared to 41 to 50 years old. Data indicate that the prevalence of adverse drug effects in people over the age of 65 is in the range of 5-35%. (6)

Poudel DR, et al. (2017) published the results of a study conducted in the United States of America (USA) with the aim of determining the rate, specific causes and outcomes of hospitalizations that followed as a result of adverse drug events (ADEs) (19). Statewide patient ADE data from 2008 to 2011 were used. Outcomes monitored included the annual prevalence, costs, length of stay, and mortality of ADE-related hospitalizations. It was estimated that a total of 9,440,757 patients (6.28% of the total number of hospitalized) were hospitalized due to ADE in the mentioned period. The increase in hospitalizations recorded in this

period ranged from 5.97% in 2008 to 6.28% in 2011, with an annual rate of change of 4.37%. It was found that patients with ADE were significantly older (2011: mean age was 61.42) and had more comorbidities. Steroid drugs (14.49%), antineoplastic drugs (13.06%), anticoagulants (11.33%), non-steroidal anti-inflammatory drugs (8.78%) and opiates/narcotics (6, 48%). It was found that the hospitalization of patients with ADE lasted longer (by 1.89 days) compared to other patients, and that the costs of their treatment were higher with a higher probability of death (19). It often happens that the patient suffers from a mild intensity of unrecognized side effects for months, which gradually leads to a reduction in functional abilities, but also that they manifest in a severe and unusual form. Therefore, it is necessary to study in detail the relationship between risk and benefit (risk/benefit) of the administered drugs. Side effects of drugs often occur as acute conditions (cardiovascular, gastrointestinal, skin, neurological and renal side effects, as well as anaphylactic reactions).

Alhawasi TM, et al. (2014) performed a systematic review of published literature data with the aim of assessing the prevalence of adverse effects in elderly people treated for acute conditions, as well as in order to identify factors that accompany the increase in the risk of adverse effects in the elderly (20). The systematic literature review included studies published between 2003 and 2013 based on the Cochrane Database of Systematic Reviews, EMBASE, Google Scholar and MEDLINE. Only studies focused on the occurrence of adverse effects in the elderly and containing an explicit definition of what was considered an adverse effect and/or an explicit assessment of causality as well as a clear description of the methods used in the identification of adverse effects were included. In addition to the above, studies had to include a description of factors associated with an increased risk of side effects.

Based on the set requirements, data from 14 observational studies conducted in hospitals were processed. The aim of these studies was to investigate the occurrence of side effects in elderly people treated for acute conditions. The mean prevalence of side effects in these studies was 11.0%. The median prevalence of adverse effects requiring hospitalization was 10.0%, while the prevalence of adverse effects during hospitalization was 11.5%. A large variation in the overall prevalence was recorded, ranging from 5.8% to 46.3%.

For female sex, more complex comorbidity and a greater number of medications, a significant association with an increased risk of side effects was established. Lower prevalence have been reported in retrospective studies and studies based on data on identification of adverse effects by usual treatment teams.

Based on the review, the authors conclude that side effects represent a significant health problem in the population of elderly patients who are treated for acute conditions. Although there is a large variation in the prevalence of adverse effects in this population, based on research results, at least one in ten elderly patients will experience an adverse effect that will lead to hospitalization or will occur during hospitalization (20).

The types of drugs that the elderly use the most depend on the circumstances, and in home treatment, analgesics, drugs for cardiovascular diseases, diuretics and sedatives are mostly used, while in inpatient treatment (hospitals and homes for the elderly), drugs for cardiovascular diseases, antimicrobial drugs, diuretics and psychoactive drugs.

Side effects, especially those that can be prevented, represent one of the most serious problems when it comes to prescribing medications to older people in primary health care, that is, in outpatient settings (22). In order to obtain the appropriate therapeutic effect, and at the same time avoid the possibility of side effects of drugs, cooperation and adherence to the therapy (compliance, adherence) on the part of the patient is necessary.

Cooperation (compliance)

Cooperation or perseverance can be defined as the degree to which the patient adheres to the recommendations and carries out the instructions on taking medications as prescribed by the doctor. In contrast to the above, non-cooperation or non-persistence is the failure to take medicines on time in the prescribed doses and is dangerous and expensive like many diseases. The well-known Anglo-Saxon name that is often used in many countries is compliance (in the professional literature also "adherence to medication"). Overcompliance can be defined as taking a higher dose of the drug than prescribed by the doctor. Cooperation can therefore vary from 0% to 100% and, in the case of over-cooperation, even more than 100%.

According to some estimates, about 50% of prescribed drugs in the US are not taken correctly (about one-third of patients do not use prescribed drugs at all). The negative effects of non-cooperation are manifested by fatal outcomes, worsening of the disease with more than 30% of admissions to hospitals and other health institutions (according to some authors up to 69%), which represents significant financial costs that are measured at around 100 billion US$. In Great Britain, about 5% of prescriptions are never fulfilled, and in elderly people this amounts to about 20%. The reason is not of a financial nature, but a lack of motivation for treatment. (6)

Significant non-compliance (taking 50-90% of the prescribed dose) or not taking the drug at all is reported in 25-50% or more of patients in the UK. (20) Patient cooperation is therefore one of the fundamental prerequisites for successful treatment. A positive attitude towards treatment is one of the necessary elements of good patient cooperation. The simpler the method of administration of the drug, the greater the probability that the patient will carry out the treatment in accordance with the doctor's advice. Cooperation is good if the medicine is taken once (ideal intake) or twice a day, and cooperation decreases if it is taken three or more times a day. Polypharmacy in the sense of polytherapy, i.e. justified simultaneous taking of three or more drugs, also reduces the patient's cooperation. Cooperation also decreases with regard to the duration of treatment, and the rate is higher in the treatment of acute compared to chronic conditions. According to the results of a study conducted at Harvard, the cooperation rate is lower than 50% in chronic patients (6). An example of such treatment is the use of statins, where after six months of treatment only half of the patients remain persistent in the use of the drugs.

The prevalence of polytherapy increases with age. It was found that more than 40% of people over the age of 65 used 5 or more drugs, and 12% use even 10 or more different drugs. (22) In this case, we are talking about polypharmacy, that is, irrational and inappropriate use of drugs.

Pharmacovigilance

Recognizing, reporting and monitoring the occurrence of unwanted drug effects is an integral part of the national drug policy of all countries. In 1971, the World Health Organization (WHO) established an international system for monitoring adverse drug effects, the Uppsala Monitoring Center (UMC), based in Sweden.

The Center uses information received from member states. The headquarters of the World Health Organization (WHO) is responsible for the organization's policy, while the responsibility for monitoring side effects belongs to UMC in Uppsala. The center started working with 10 countries that already had a national system of spontaneous reporting of the drug side effects and agreed to transfer their data to the center in Uppsala. (15) For more than 40 years, UMC has provided scientific progress and operational support to the World Health Organization's Program for International Drug Monitoring (WHO PIDM) (15,16).

The WHO PIDM was established in 1968 to ensure that evidence of harm to patients is gathered from as many sources as possible. This allows individual countries to be alerted to harmful patterns that are emerging around the world, but which may not be apparent from their local data alone. Program members work nationally and collaborate internationally to monitor and identify drug-related harm, reduce patient risks, and establish world-class pharmacovigilance standards and systems. The UMC has been responsible for the technical and operational aspects of the WHO PIDM since 1978. WHO PIDM with more than 170 full members and associate members in the 2022 program, covers about 99% of the world's population.

The Monitoring Center in Uppsala, as the World Health Organization's Collaborating Center for International Drug Monitoring, supports program members in establishing and developing national drug safety monitoring systems. Supported by a global network, program members submit reports of suspected adverse drug reactions to WHO's VigiBase database, maintained by the UMC. The repository of program reports in VigiBase grows by several million reports per year, and 30 million reports passed in 2022 (17).

VigiBase is used to analyze reports of suspected drug harm, to find what are known as "signals" of potential drug side effects. The advantage of consolidating reports in a large, global database is that damaging patterns can emerge from large amounts of global data that may not be visible in smaller national databases.

Bosnia and Herzegovina (BiH) has been an associate member of the UMC since 2010, and the system for monitoring and reporting side effects of drugs is carried out within the framework of the Agency for Medicines and Medical Devices of Bosnia and Herzegovina (ALMBIH). Based on the brochure of the World Health Organization ("Safety of Medicines - A guide to detecting and reporting adverse drug reaction" from 2002), ALMBIH developed the following documents: Rulebook on the method of reporting, collecting and monitoring adverse drug reactions ("Official Gazette of Bosnia and Herzegovina", number 58/12); Guide for detecting and reporting adverse drug reactions as well as various Forms (Adverse drug reaction reporting form for healthcare workers, Adverse drug reaction reporting form for license holders, Vaccine adverse reaction reporting form for healthcare workers). According to the Rulebook, the definitions of certain terms used in this area are also listed.

CONCLUSION

The most common medical intervention in the population of older people is the prescription of drugs, which often, due to physiological applications in old age, and due to the morbidity that accompanies this age, implies the administration of three, five, ten, and sometimes even more drugs in one patient. Polytherapy as the justified use of several drugs in order to achieve the desired therapeutic response (e.g. hypertension treatment, oncology patients) differs from polypragmasy, the irrational and purposel ess use of drugs. While polytherapy increases the possibility of noncompliance, polypharmacy increases the risk of drug interactions and side effects, which, in addition to a negative impact on the outcome of treatment, further impairs the patient's health, resulting in death, and is an unnecessary waste of health care resources. Interactions and side effects of drugs are a common occurrence and most can be prevented in the elderly population in outpatient settings, with prior adequate consultation of clinical pharmacology specialists. The strategy for the prevention of the occurrence of unwanted effects of drugs should be focused on educating patients, recognizing and reporting unwanted effects with the previously developed awareness of doctors about the reasonable prescription of drugs, where one of the important roles can be played by clinical pharmacology. Activities aimed at better patient compliance with prescribed medication regimens and re-evaluation of prescribed therapy may also be beneficial.

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A rare case of primary mediastinal tumor in a twenty eight-year-old man

Rijetki primarni medijastinalni tumor kod dvadesetosmogodišnjeg muškarca

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ABSTRACT

Introduction: germ cell tumors account for only 1% to 4% of all tumors found in the mediastinum and can be benign or malignant, with seminoma being a malignant tumor of the mediastinum Aim: we presented a case of primary mediastinal seminoma in a 28-year-old man admitted to the Clinic of Lung Diseases and Tuberculosis of the Clinical Centre University of Sarajevo due to a CT-verified mass in the anterior mediastinum. Case report: apart from a dry cough that lasted for a month, the patient did not report any other symptoms. Chest CT scan revealed an expansive mass in the upper, middle, anterior, mediastinum, located retrosternal and left parasternal, which compressed the large blood vessels to the right. No significant lymphadenopathy was seen. CT-guided needle biopsy of the mediastinal mass was performed. Pathohistological finding confirmed that it was a tumor of germ cells-seminoma. An ultrasound of the abdomen, pelvis and scrotum was also performed. Both testicles with homogeneous parenchymal structure without clearly isolated focal lesions. The left ductus epididymis in the area of the head had cysts up to 6 mm, the same was of borderline size. Chemotherapy based on platinum, etoposide and bleomycin was started. Results: after four cycles of chemotherapy chest CT scan was performed and compared with the previous one showing a significant regression in size and the remaining part of the tumor mass was mostly calcified. Then a resection of the right upper lobe and the anonymous vein was performed. Pathohistological findings without signs of tumor with extensive necrosis and three interlobar lymph nodes without tumor. Given the complete response, only further follow-up was determined. Conclusion: each tumor mass verified in the mediastinum requires a detailed evaluation, especially because tumors of the mediastinum are most often of metastatic origin. Diagnosis of primary mediastinal seminoma established in time ensures long-term survival of the patient.

Keywords: primary mediastinal seminoma, diagnosis, treatment

SAŽETAK

Uvod: tumori zametnih ćelija čine samo 1% do 4% svih tumora pronađenih u medijastinumu i mogu biti benigni ili maligni, pri čemu je seminom maligni tumor medijastinuma. Cilj: Predstavljamo slučaj primarnog medijastinalnog seminoma kod 28.-godišnjeg mladića primljenog na Kliniku za plućne bolesti i TBC-Klinički centar Univerziteta u Sarajevu, a zbog CT verifikovane mase u prednjem medijastinumu. Prikaz slučaja: osim suhog kašlja koji je trajao mjesec dana, pacijent nije prijavio nikakve druge simptome. CT grudnog koša otkrio je ekspanzivnu masu u gornjem, srednjem, prednjem, medijastinumu, smještenu retrosternalno i lijevo parasternalno, koja je komprimirala velike krvne žile na desnoj strani. Nije uočena značajna limfadenopatija. Urađena je biopsija medijastinalne mase vođena CT iglom. Patohistološki nalaz je potvrdio da se radi o tumoru zametnih ćelija-seminom. Urađen je i ultrazvuk abdomena, karlice i skrotuma. Oba testisa sa homogenom parenhimskom strukturom bez jasno izolovanih fokalnih lezija. Lijevi duktus epididimis u predjelu glave imao je ciste do 6 mm, iste su bile granične veličine. Započeta je kemoterapija na bazi platine, etopozida i bleomicina. Rezultati: nakon četiri ciklusa kemoterapije urađen je CT grudnog koša koji je u poređenju sa prethodnim pokazao značajnu regresiju veličine i preostali dio tumorske mase je uglavnom kalcificiran. Zatim je urađena resekcija desnog gornjeg režnja i anonimne vene. Patohistološki nalaz bez znakova tumora sa opsežnom nekrozom i tri interlobarna limfna čvora bez tumora. S obzirom na potpuni odgovor, određeno je sam o daljnje praćenje. Zaključak: svaka tumorska masa verifikovana u medijastinumu zahteva detaljnu procenu, posebno zato što su tumori medijastinuma najčešće metastatskog porekla. Pravovremeno postavljena dijagnoza primarnog medijastinalnog seminoma osigurava dugotrajno preživljavanje bolesnika.

Ključne riječi: primarni medijastinalni seminom, dijagnoza, terapija

INTRODUCTION

Germ cell tumors account for only 1% to 4% of all tumors found in the mediastinum and can be benign or malignant, with seminoma being a malignant tumor of the mediastinum. It usually occurs in the anterior-superior mediastinum in men aged 20-40 years, and as many as 30% of patients have no symptoms. Seminomas can also occur in the sacrococcygeal region and the central nervous system in the pineal gland. This is more common in children (1,2).

Primary mediastinal seminoma has a good prognosis. Approximately 80% of patients with seminoma have stage I disease, with a survival rate of approximately 90%, regardless of the treatment strategy chosen (3).

CASE REPORT

In this paper, we presented a case of primary mediastinal seminoma in a 28-year-old male patient, with non-specific symptoms. He was admitted to the Clinic of Lung Diseases and Tuberculosis of the Clinical Centre University of Sarajevo, for clinical evaluation due to a verified mass in the mediastinum.

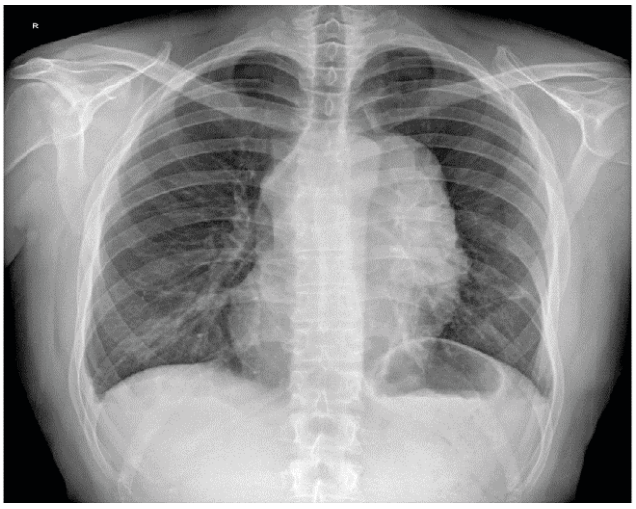
Medical history

The patient started coughing with no expectoration one month before admission to the hospital. No fever, chest pain, fatigue and difficulty breathing were notified. He did not notice a significant loss in body weight. So far he was healthy. He denied previous illnesses and hospitalisations. He got over the Covid-19 infection and received two doses of Pfeizer vaccines against the COVID-19 infection. No drug and food allergy; non smoker.

Basic laboratory findings were also performed

Leukocytes 4.76 x10^9/L, Erythrocytes 5.75 x10^12/L, Hemoglobin 150 g/L, Hematocrit 55 %, MCV 96 fL, MCH 26 pg, MCHC 270 g/L, MPV 7.2 fL, Platelets 296 x10^9/L, DKS - Neutrophil granulocytes 3.28 x10^9/L, Lymphocytes 0.9 x10^9/L, Monocytes 0.4 x10^9/L, Eosinophilic granulocytes 0.11 x10^9/L, Basophilic granulocytes 0.04 x10^ 9/L. Coagulation: INR 0.9, APTT 30.1 sec. Clinical biochemistry: Sodium 137 mmol/L, Potassium 4.1 mmol/L, Calcium 2.45 mmol/L, Chlorides 100 mmol/L, Magnesium 0.81 mmol/L, Glucose 4.5 mmol/L, Urea 4.7 mmol/L, Creatinine 76 umol/L , Total bilirubin 45.0 umol/L, AST 13 U/L, ALT 9 U/L, CK 76 U/L, LDH 335 U/L, CRP 6.6 mg/L, Alkaline phosphatase 91 U/L. All the mentioned laboratory analyses were within the reference values.

Upon admission, chest X-ray (Figure 1) was performed and verified the enlarged shadow of the middle and lower part of mediastinum. Both sides of the pulmonary pattern were accentuated and small platine atelectasis in the left parahilar area was present. The right hemidiaphragm was regular, but the left one was elevated. Phrenicocostal sinuses were free.



Figures 1 **Chest X-ray showed a tumor mass in the mediastinum.**

Figure 2 **Chest CT scan showed a tumor mass in the anterior mediastinum.**

Chest CT scan (Figure 2) showed an extensive tumor formation in the anterior mediastinum**.** The described tumor mass was partly riddled with massive calcifications, especially in the basal parts. The mediastinal structures were strongly compressed towards the back, especially the truncus pulmonalis (pulmonary trunc), the ascending aorta and the aortic arch, and in the more caudal layers, the trachea and the main bronchi, especially the initial part of the left main bronchus. Ventrally, the mass was not clearly separated from the retrosternal space and parasternal space on the left, caudally it followed the upper contour of the left ventricle. Also compressed outflow blood vessels of the aortic arch. Both hilus without significantly enlarged lymph nodes. In the left lower lobe there was a few zone of ground glass opacifications, and postinflammatory spikes of the pleura on both sides posterobasally.

Following the admission, CT-guided needle biopsy of the mediastinal mass in the anterior mediastinum was performed with an 18G biopsy needle (Figure 3). Four tissue cylinders were obtained for analysis. The procedure was completed without

complications. The procedure was performed without complications.

Subsequently, the patient underwent bronchoscopy, which was without pathomorphological changes.

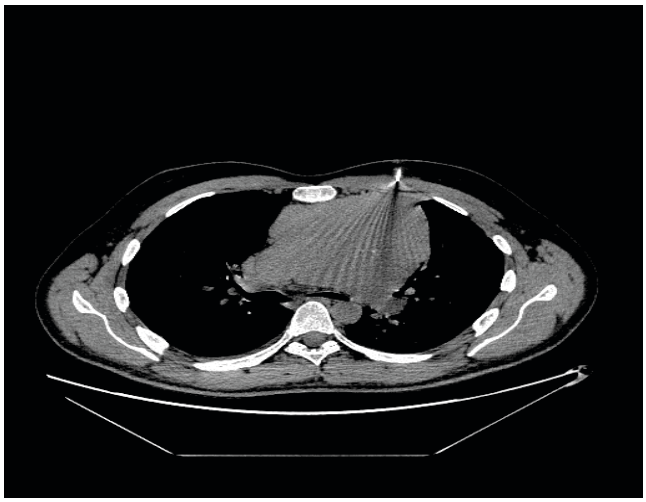


Figure 3 **Chest CT scan shows the performanceof a biopsy of a mass in the anterior mediastinum.**

Pathohistological finding of mediastinal tumor mass

Morphological and immunohistochemical findings confirmed a tumor of germ cells-seminoma (Figure 4).

Microscopic description: In the samples the tumor was made up of round to polygonal, fairly uniform tumor cells, with round to oval nuclei with vesicular chromatin and large nucleoli. Tumor cells were rich in glycogen, amphophilic to slightly eosinophilic cytoplasm and various cell membranes that grew in confluent and irregular lobules surrounded by stroma in which there were small lymphocytes.

mmunohistochemically the cells were negative for CK (AE1/AE3), positive for Oct3/4, with lower intensity for SALL4 and negative for NUT4.

Comment of the pathologist: out of the total number of patients with mediastinal seminomas, 94% were classified as having a good prognosis and 6% as having an intermediate prognosis (defined by the absence or presence of non-pulmonary visceral metastases, respectively, and normal AFP and whatever level of β-HCG and LDH).

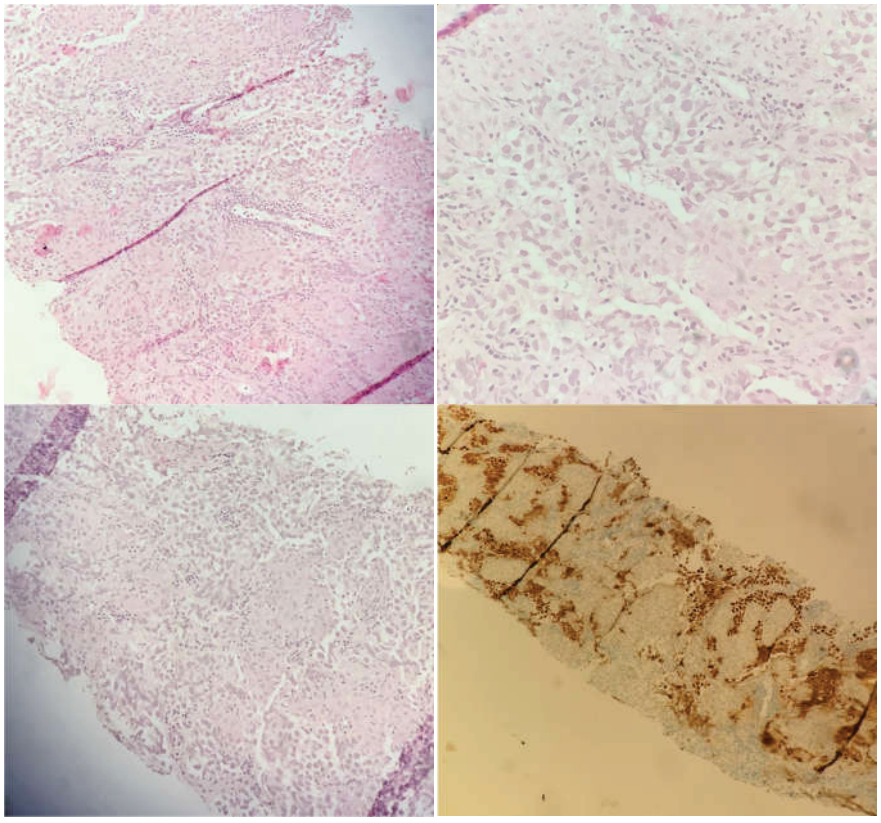


Figure 4 **Pathohistological presentation of seminoma: CK negative, NUT negative, SALL midlly positive and OCT 3/4 positive.**

Upon receipt of the pathohistological findings, a detailed evaluation of the disease was continued.

Additional laboratory findings were performed: LDH 546 (increased level), ß HCG 19.5 (increased level), AFP 4.6 (normal range).

Belly, pelvis and scrotum ultrasound was performed: liver of adequate size and echogenicity, homogeneous structure of parenchyma. Gall bladder, bile duct without pathological changes. The visible part of the pancreas was slightly more echogenic, regular in size, homogeneous. Spleen was of decent size, homogeneous. Both kidneys had adequate size and width of

parenchyma and without echo signs of ectasia and calculosis. Retroperitoneally there was no significant lymphadenopathy. Urinary bladder wall was postinflammatory altered, echo free. Prostate was of appropriate size and echo structure. Bilateral inguinal regions were without significant lymphadenopathy. Both testicles were properly located, of appropriate size, with homogeneous parenchymal structure and without clearly isolated focal lesions. The left ductus epididymis in the area of the head had cysts up to 6 mm and is of borderline size. Also left incipient signs of varicocele were recorded.

CT scan of the abdomen and pelvis was performed. Hepatomegaly without isolated focal lesions was notified. There was no significant lymphadenopathy.

Then the case was presented at the Multidisciplinary Oncology Council, where chemotherapy based on platinum, etoposide and bleomycin was indicated.

Chest CT scan was performed after four cycles of chemotherapy and compared with the previous one showing a significant regression in size and the remaining part of the tumor mass was mostly calcified (Figure 5).

Control laboratory findings: LDH 351, ß HCG 2.40 (in normal ranges), AFP 4.33 (normal range).

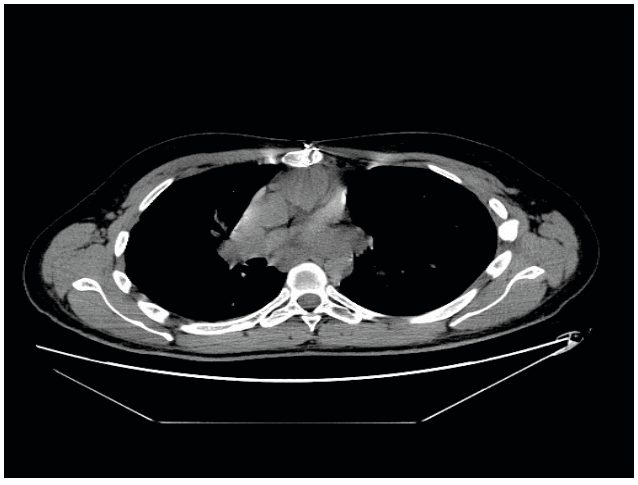


Figure 5 **Chest CT scan showed excellent regression of the tumor mass in the anterior mediastinum (after chemotherapy)**

Subsequently a resection of the right upper lobe and the anonymous vein was performed in one of the Clinics in Western Europe.

Pathohistological finding after surgery: without evidence of tumor with extensive necrosis and three interlobar lymph nodes without tumour.

Given the complete response, only further monitoring of the patient was indicated.

DISCUSSION

Testicular cancer is a rare malignancy, accounting for only 1% of all malignant tumors in men. However, it is the most common cancer in men aged 15-40, and its global incidence is constantly increasing. Germ cell tumors (GCTs) account for 95% of testicular cancers, which are broadly divided into seminomatous and nonseminomatous GCTs (NSGCTs). Germ cell tumors *rarely occur outside the gonads*, with an incidence of only 5% to 7%. If there is no primary testicular or ovarian mass, the tumor is considered extragonadal. The mediastinum and retroperitoneum are the most common sites for extragonadal occurrence, with the mediastinum being the most common extragonadal location. Mediastinal germ cell tumors represent a rare 3-10% of all mediastinal tumors and account for less than 5% of all germ cell neoplasms. Only 3% of mediastinal germ cell tumors arise in the posterior mediastinum, while the majority arise in the anterior mediastinum (1). Metastatic disease occurs in less than half of cases, and when it does, it usually spreads to neighboring groups of lymph nodes in the neck, mediastinum or abdomen. Hematogenous metastases are rare, but can occur in the lungs, bones, liver, spleen, thyroid gland, and brain (4). Clinical signs and symptoms are mainly associated with chest complaints, such as dyspnea, chest pain or cough. Systemic symptoms and signs include weight loss, nausea, fever, and gynecomastia. They may also present with complications such as superior vena cava syndrome or may be discovered incidentally with imaging techniques (5).

Staging of mediastinal germ cell tumor (1):

Stage 1: Well-circumscribed tumor with or without adhesions to the pericardium or pleura, but no evidence of any microscopic invasion of adjacent structures

Stage 2: Tumor is confined to the mediastinum with evidence of macroscopic and/or microscopic infiltration into adjacent structures, including the pleura, pericardium, or great vessel.

Stage 3: Tumor present with metastases

Stage 3A: Metastatic disease present in intrathoracic organs

Stage 3B: Extrathoracic metastases

Treatment of seminoma consists of chemotherapy and radiotherapy. Mediastinal seminoma is a radiosensitive tumor with a radiation dose of 4500-5000 cGy.

Approximately 65% of patients recover after radiotherapy. In recent years, chemotherapy in the treatment of mediastinal seminoma has been further developed. A platinum-based chemotherapy regimen for seminoma consists of bleomycin, etoposide, and cisplatin. Some investigators have concluded that 85% of patients recover after cisplatin-based chemotherapy. Combining chemotherapy with radiotherapy can improve the prognosis by 100% (2).

In the presented patient, seminoma was diagnosed by CT-guided needle biopsy. Chemotherapy was carried out according to the PEB protocol, which included prescribing: platinum, bleomycin and etoposide. A total of four chemotherapy cycles were performed, to which the patient responded extremely well, with an excellent chest CT-verified regression of the tumor mass and a decrease in LDH and ß HCG values. Germ cell tumor prognosis is related to several tumor characteristics, not only histology (seminoma vs nonseminoma) and disease extension, but also involvement of primary and metastatic visceral sites and production of tumor markers such as human chorionic gonadotropin (HCG), α-fetoprotein, and lactate dehydrogenase (LDH). Primary mediastinal nonseminoma is characterized by a poor outcome and is independent of other factors as well as is resistant to standard doses and high doses of chemotherapy, while primary mediastinal seminoma has a good prognosis (6). Approximately 80% of patients with seminoma have stage I disease with a survival rate of approximately 99%, regardless of the treatment strategy chosen (7).

CONCLUSION

Any tumor mass verified in the mediastinum requires a detailed treatment and evaluation, especially because tumors of the mediastinum are most often of metastatic origin. In addition, we concluded that a multimodal approach to patient management is the best treatment choice to ensure long-term survival in patients with primary mediastinal seminoma.

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Authors' Contributions: BP and NA-S gave substantial contribution to the conception or design of the article and in the acquisition, analysis and interpretation of data for the work. Each author had role in article draftingand in process of revision. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Delayed presentation of diaphragmatic trauma complicated by gastric herniation

Kasna prezentacija traume dijafragme kompliciranе hernijacijom želuca

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ABSTRACT

Introduction: diaphragmatic rupture is a rare pathology occurring in less than 0.5% of all trauma cases, with signs and symptoms that can easily be misdiagnosed. In most cases, the mechanism of traumatic injury to the diaphragm includes blunt abdominal trauma, which in more than 90% of cases is the result of traffic accidents. We present a rare case of a large diaphragmatic rupture with a transthoracic gastric hernia that was successfully repaired, with a review of the literature. Case report: a 64-year-old female patient who had a serious traffic accident 9 months ago. He comes to the emergency center because of abdominal pain, nausea and vomiting. CT verifies a diaphragm defect with herniation of part of the stomach and omentum into the chest cavity. After diagnostic treatment, the patient underwent surgery. Through a thoracotomy, access is made to the chest cavity, the stomach and omentum are freed from the surrounding structures, and they are repositioned in the abdominal cavity. This is followed by suturing the diaphragm defect with slow resorbable sutures in two layers. The postoperative course went well, the patient was well at the last examination at the Clinic. Conclusion: awareness of post-traumatic diaphragmatic hernia and its initial treatment is necessary in order to avoid a wrong diagnosis and to set an indication for operative treatment in time in order to avoid late complications that can be life-threatening.

Keywords: diaphragmatic hernia, trauma, abdominal injuries, traffic accidents, thoracotomy

SAŽETAK

Uvod: ruptura dijafragme je rijetka patologija koja se javlja u manje od 0,5% svih slučajeva traume, sa znakovima i simptomima koji se lako mogu pogrešno dijagnosticirati. U najvećem broju slučajeva mehanizam traumatske povrede dijafragme uključuje tupu abdominalnu traumu, koja je u više od 90% slučajeva posljedica saobraćajnih nesreća. Prikazujemo rijedak slučaj velike rupture dijafragme s transtorakalnom hernijom želuca koja je uspješno sanirana, uz pregled literature. Prikaz slučaja: 64-godišnja pacijentica koja je prije 9 mjeseci imala težak saobraćajni udes. Javlja se u urgentnom centru zbog bolova u abdomenu, mučnine i povraćanja. CT verificira defekt dijafragme sa hernijacijom dijela želuca i omentuma u grudnu šupljinu. Pacijentica nakon dijagnostičke obrade podvrgnuta operativnom zahvatu. Torakotomijom se pristupa u grudnu šupljinu, želudac i omentum se oslobađaju od okolnih struktura, isti se reponiraju u trbušnu šupljinu. Slijedi šivanje defekta dijafragme spororesorptivnim šavovima u dva sloja. Postoperativni tok protekao uredno, pacijentica je bila dobra na posljednjem pregledu u Klinici. Zaključak: svijest o posttraumatskoj dijafragmalnoj herniji i njenom početnom liječenju potrebna je kako bi izbjegla pogrešna dijagnoza i na vrijeme postavila indikaciju za operativni tretman u cilju izbjegavanja pojave kasnih komplikacija koje mogu biti opasne po život.

Ključne riječi: dijafragmalna hernija, trauma, abdominalne povrede, saobraćajne nesreće, torakotomija

INTRODUCTION

Diaphragmatic hernia is a recognized consequence of traumatic injuries to the upper abdomen, often eluding timely diagnosis during clinical and diagnostic assessments (1). Trauma to the abdominal region, especially the thoracoabdominal region, carries the risk of diaphragmatic hernias, which can have severe consequences, particularly when undetected (2). It has been reported that 1-7% of patients with major blunt thoracoabdominal trauma and 10-15% of patients with penetrating trauma will suffer a diaphragmatic rupture (3). Larger defects will herniate intra-abdominal contents, causing mediastinal displacement, respiratory failure, and shock. CT is the gold standard for confirming the diagnosis (4). Approximately 40–62% of trauma patients subsequently present to the emergency department for chronic diaphragmatic hernia with symptoms of obstruction, pain, nausea, or pulmonary dysfunction (5).

What remains unclear is the exact prevalence of diaphragmatic hernias following trauma and the factors that influence their development. Additionally, the specific reasons behind the frequent failure to diagnose these hernias in a timely manner are yet to be fully elucidated. The diagnostic challenges, especially during the acute phase of trauma, warrant further investigation to understand the barriers to early identification.

In this context, there is a need for a more comprehensive understanding of the incidence and risk factors associated with diaphragmatic hernias in patients with a history of upper abdominal trauma. Furthermore, strategies for improving the timely recognition of these hernias should be explored to prevent life-threatening complications. This case report aims to contribute to the existing knowledge on post-traumatic diaphragmatic hernias and underscores the importance of early diagnosis and treatment.

CASE REPORT

We encountered the case of a 64-year-old patient who had a serious traffic accident 9 months ago. During the examination, the patient complained that for the past 10 days she had had 3-4 diarrheal smelly, liquid-mushy stools, without admixture of blood and mucus. She vomited several times. She denied feverishness, respiratory and dysuric complaints. Formerly hypertensive and diabetic on oral therapy. In 2004, the gallbladder was surgically removed. 1984 ligament surgery on the left lower leg. In January 2023, she had a serious traffic accident, loosing about 20 kg, as she spent 3 months in bed.

In laboratory findings: Le 13.2, SE 26, GUK 10.31, GGT 56, Na 134, CL 93, URINE: cloudy, proteins opal, bacteria few. Ultrasound of the abdomen indicated hepatomegaly, and steatosis of the parenchyma of the liver and pancreas. No other pathomorphological changes were observed in the other organs of the abdomen. During the examination, the patient was conscious, oriented, communicative, afebrile 36.1°C, eupnoic, euhydric. Throat calm, tongue moist, uncoated. The action of the heart was rhythmic, no murmur was heard. Auscultatory examination of the lungs on the left showed a somewhat weakened basal breath murmur, without pathological sound phenomena. The abdomen was soft, painless on palpation, the liver and spleen were not palpated enlarged. LL painfully insensitive to succussia. Meningeal signs negative. TA 125/85 SpO2 94%. A chest X-ray revealed a twisted nasogastric tube in the left hemithorax. As the patient was hemodynamically stable, a CT scan of the chest and abdomen was performed, which confirmed the existence of a large diaphragmatic hernia of the stomach in the left chest cavity with left lung collapse and mediastinal displacement. No other intrathoracic and abdominal injuries were found. After a short preoperative preparation, the patient underwent an operation to treat a diaphragmatic hernia.

The imaging findings were confirmed intraoperatively, the stomach was shown, with the fundus and the greater part of the body in the chest with part of the omentum (Figure 1), and the protrusion of the organ was through a diaphragm defect in its tendinous part, which extendsed obliquely behind and laterally and forward and medially ending directly next to the sternal junction. After release, the omentum and stomach were repositioned in the abdominal cavity (Figure 2), and the diaphragm defect was sutured with individual slow resorbable sutures, and the suture line was reinforced with an extension suture, with satisfactory result (Figure 3). The tissue was in good condition, the suture line was sufficient, the excursions of the diaphragm awere in order, therefore we decided not to place the mesh.

Figure 1 **Intraoperative findings showing the fundus and the greater part of the body of the stomach with the omentum in the chest.**

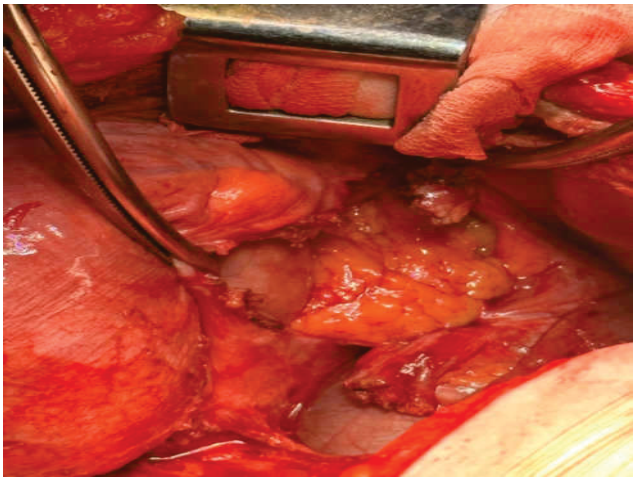

Figure 2 **Illustration of a defect on the diaphragm after repositioning the stomach and omentum in the abdominal cavity.**

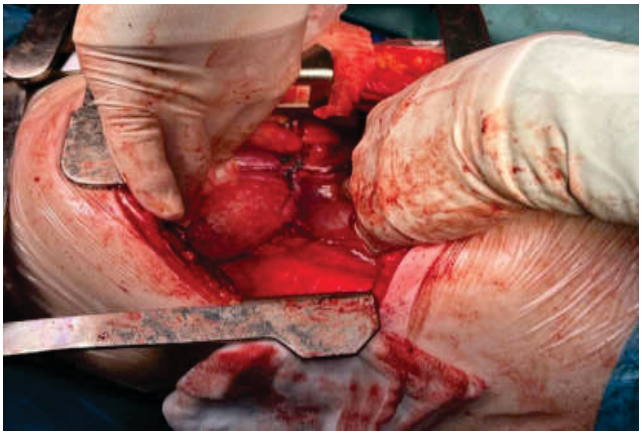

Figure 3 **Diaphragm suturing in two layers with single and extended slow resorbable sutures (final appearance).**

On the first postoperative day, the patient felt well and tolerated clear liquids. Control laboratory findings in reference values. The radiological finding was satisfactory. The drains were afunctional, and they were removed on the third postoperative day. The postoperative period passed smoothly and the patient was discharged home on the fifth postoperative day.

DISCUSSION

Trauma is a well-established leading cause of acquired diaphragmatic hernias, with left-sided rupture being the most common (80%), followed by right-sided (15%) and bilateral (5%) (6). However, the main challenge in the successful treatment of diaphragmatic hernia is early diagnosis, often missed during the acute trauma phase. Diaphragmatic hernias are commonly diagnosed either in emergency settings or as incidental findings during laparotomy, occurring months or even years after the initial trauma, with a high risk of life-threatening complications, including visceral perforation, strangulation, and cardiovascular and respiratory failure. A CT scan can miss 30-50% of diaphragmatic ruptures during the initial evaluation (7).

Our case report illustrates the intricacies of a late presentation of a traumatic diaphragmatic hernia, a unique manifestation as gastric herniation. Notably, diaphragmatic rupture was not initially suspected in the acute setting due to the masking effect of associated injuries. The delay in diagnosis prompts us to consider the latent phase theory proposed by Grimes et al. (8) regarding traumatic diaphragm rupture, where small defects may remain undetected initially and enlarge over time. These delayed presentations can lead to a spectrum of complications, including respiratory issues and the herniation of visceral organs such as the stomach, small intestine, colon, spleen, or pancreas. In some cases, these hernias further complicate into obstruction, incarceration, necrosis, and perforation (9).

The occurrence of delayed presentation of traumatic diaphragmatic hernia complicated by gastric herniation within this subgroup is rare, with reported rates ranging from 0.17% to 6%. A retrospective study by Kumar et al. (10) evaluated 276 cases of traumatic diaphragmatic hernia and found that only 8% presented delayed symptoms, and among them, only a small proportion developed complications such as gastric herniation.

In our case, the diaphragmatic defect was surgically managed using individual slow-resorbing sutures, with additional reinforcement of the suture line via an extension suture, while avoiding the use of synthetic materials. This approach aligns with the perspective of Hayder Al-Masari I et al. (11), which recommends the closure of small diaphragmatic defects using non-resorbable single sutures to mitigate potential adhesions with abdominal organs.

This case report holds significance on multiple fronts. Firstly, the uncommon delayed presentation of traumatic diaphragmatic hernia complicated by gastric herniation underscores the importance of considering diaphragmatic hernia in the differential diagnosis for any patient with a history of trauma, regardless of the time interval. The occurrence of intestinal obstruction and perforation is an unusual and challenging scenario. Moreover, the presence of a previous history of trauma, despite a significant time gap, reiterates the significance of considering traumatic diaphragmatic hernia in the differential diagnosis (12).

Radiological findings and subsequent CT scans play a pivotal role in confirming the diagnosis and facilitating timely surgical intervention to prevent complications (13). Given the rarity and complexity of cases like this, there is a compelling need for further documentation and research to advance our understanding and enhance clinical approaches.

CONCLUSION

Diaphragmatic hernia after blunt trauma is a diagnosis based on a high index of suspicion that must be confirmed by appropriate radiological imaging. Early diagnosis with early surgery is the cornerstone of its management. Awareness of post-traumatic diaphragmatic hernia and its initial treatment is necessary in order to avoid a wrong diagnosis and to set an indication for operative treatment in time in order to avoid late complications that can be life-threatening.

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Procalcitonin - a prognostic biomarker in pancreatitis

Prokalcitonin – prognostički biomarker kod pankreatitisa

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Introduction: acute pancreatitis is an acute inflammatory process of the exocrine part of the pancreas caused by premature activation of intracellular digestive enzymes which damages the pancreatic and peripancreatic tissue, resulting in an inflammatory response. Early diagnosis of severe acute pancreatitis is important for timely intensive supportive treatment initiation, early recognition of complications and transfer of patients to specialized centers. Literature review**:** it has a wide range of clinical manifestations, from a moderate self-limiting pathological process to the development of severe forms complicated by the development of local and systemic complications. In addition to being a significant cause of death, severe acute pancreatitis is associated with prolonged intensive care stays, long hospitalization, and slow rehabilitation. Severe acute pancreatitis is characterized by necrosis of pancreatic tissue, which, due to bacterial colonization, leads to infected necrosis. The severity of acute pancreatitis cannot always be reliably determined by a clinical approach at the time of admission to the hospital. For this purpose and determining the need for intensive treatment, various biochemical parameters, computerized tomography and certain scoring systems are used. Regarding markers, only CRP is used clinically. CRP values begin to rise significantly 48 hours after the onset of the disease and reach their peak level only 72 hours after the onset of symptoms. At the time of admission to hospital, the sensitivity of CRP is 47%, similar to clinical examination. CRP is not optimal for diagnosing severe cases of pancreatitis. Procalcitonin (PCT) is an inactive propeptide, of 116 amino acids, of the biologically active hormone calcitonin. In current clinical practice, procalcitonin (PCT) has developed into a promising new biomarker. Increased procalcitonin values are correlated with the patient's inflammatory response to infection. Serum procalcitonin is an early predictor of the development of local complications and multiorgan failure in acute pancreatitis. The levels are in the first 12-24 hours, significantly higher in severe forms. The sensitivity and specificity of procalcitonin is significantly higher than CRP during the first 24 hours. Measuring procalcitonin (PCT) is a way to distinguish infection from inflammation because levels rise rapidly in response to a proinflammatory stimulus of bacterial origin and normally fall after successful treatment. Procalcitonin is the most rapid general reactant of the acute phase. Conclusion: the procalcitonin level is a practical, simple parameter that can be measured both qualitatively and quantitatively in order to diagnose severe acute pancreatitis earlier and monitor the clinical prognosis of the disease in addition to the scoring system. Thanks to its exceptional sensitivity and specificity, it is today an almost ideal marker for monitoring the clinical course of acute pancreatitis and helps direct antibiotic therapy.

Keywords: pancreatitis, procalcitonin, CRP, biomarkers

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Transverse myelitis (letm c3 -c7-mri verf) after holiday trip to exotic country – case report

Transverzalni mielitis (letm c3 -c7-mri verf) nakon putovanja u egzotične zemlje – prikaz slučaja

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Introduction: transverse myelitis is a neurological disorder characterized by spinal cord inflammation, which can associate myelin damage and causes bilateral sensorimotor dysfunction. It is diagnosed with presence of a sensory level, an inflammatory profile of the cerebrospinal fluid (CSF) and disease progression. The incidence is one to four cases per million people, and it is classified according to the clinical severity and the radiological extension of the spinal cord injury. For the diagnosis, it is important to rule out other causes of spinal cord compression such as malignancies, and the etiology of LETM can be demyelinating, autoimmune, infectious, or paraneoplastic. Some of the infectious etiologies include cytomegalovirus, herpes viruses, influenza virus, echovirus, HIV, hepatitis A and rubella viruses. We report the case of a woman who developed LETM secondary to HSV infection. The patient was a 51-year-old woman who developed acute transverse myelitis and was admitted to Clinical Center University of Sarajevo due to weakness in the extremities and high temperature. Three days before her admission to the hospital, the patient felt weakness in her legs with a high temperature up to 39°C. An emergency CT scan of the brain was performed, which was normal, and a lumbar puncture showed: proteins 0.8, cells 134, Cl 123, rare Rbc. She was referred to the neurology clinic under diagnose Sy Guillian Barre, where an MRI of the brain and an MRI of the spine were performed. On the MRI of the cervical spine: from the level of C3 to C7, an inhomogeneous change in the hypersignal zone that is monitored at a length of 70 mm, post-contrast does not increase the signal intensity and is an open etiology. Due to deterioration of the general condition, she was transferred to the Intensive Care Unit at the Clinic for Anesthesia and Resuscitation. Patient informed doctors that the she returned from a trip to Bali 10 days ago, and states that she is allergic to penicillin. After the prescribed fully described therapy (pulse, plasmapheresis, immunoglobulins), the general condition stabilizes, and the patient is weaned from the ventilator and after decanimlaman is transferred to physical treatment. Conclusion: although inflammatory demyelinating etiologies account for a high proportion of acute myelopathies, other diagnoses need to be excluded. The chance of recurrence should be considered and preventative treatments should be initiated. The proportion of idiopathic inflammatory myelitis is likely to decline with the increasing availability of newer autoimmune markers, imaging techniques, and microbiological tests capable of defining a specific etiology for an acute myelopathy. This case highlights the fact that HSV-2 infection may cause serious infections even in an immunocompetent host.

Keywords: transverse myelitis, inflammatory demyelinating, infection

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Advanced therapies in ARDS in trauma patient

Savremeni pristup liječenja ARDS-a kod traumatskih pacijenata

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Introduction: trauma remains a leading cause of mortality worldwide. Complications associated with trauma such as systemic inflammation, pneumonia, and sepsis will frequently give rise to subsequent respiratory failure. It is estimated that 5%-20% of all mechanically ventilated patients will develop acute respiratory distress syndrome (ARDS) with the majority demonstrating moderate to severe forms of the disease. Aim: severe ARDS in the trauma patient continues to have a reported mortality rate as high as 60% despite appropriate and aggressive supportive care. Despite widespread acknowledgment that excessive plateau pressures contribute to associate lung injury, variable implementation of ventilator strategies promoting lung protective ventilation may exist. Evidence to support the use of different advanced therapies frequently used in ARDS such as airway pressure release ventilation (APRV), extracorporeal membrane oxygenation (ECMO), and high frequency oscillatory ventilation (HFOV) is deficient.
Materials and methods: use of ECMO as a temporary rescue for trauma patients with hypoxic respiratory failure has been reported in multiple case reports during the last 15 years. Despite the associated risks of prior massive blood loss, coagulopathy, coexisting solid organ or traumatic brain injury, trauma patients placed on ECMO (with or without systemic anticoagulation) have improved survival with minimal complications or long-term morbidity. Results: in studies trauma patients were placed on ECMO typically within 2 days of diagnosis of severe ARDS; ECMO then facilitated substantial reductions in ventilator volumes and pressures with less associated volutrauma and barotrauma, respectively. When trying to analyze timing of escalation of therapy, it becomes important to balance risks of the therapy versus potential benefits, both in the short and long term. Future research should evaluate the timing, risks, and benefits of all adjunctive therapies for trauma patients with severe ARDS. Conclusions: management of patients with severe ARDS remains a challenge. Outside of lung protective ventilation there are few therapies that improve patient mortality. Numerous studies are published on this topic but conclusions drawn regarding the appropriateness of these therapies are conflicting. Thus, substantial variation in clinical practice remains common. In particular, for trauma patients with severe ARDS, even less data exists to guide clinical practice.

Keywords: trauma, ARDS, ECM

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Morbus moyamoya

Morbus moyamoya

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Introduction: Mb. Moyamoya is a condition in which certain brain arteries are narrowed. Blood flow is blocked by their constriction and by forming blood clots. Collateral circulation develops around blocked blood vessels to compensate blockage, but the collateral vessels are small, weak and prone to bleeding from aneurysms and thrombosis. On the usual angiography, these collateral blood vessels have the appearance of puff of smoke (described as もやもや (mojamoja) in Japanese. When a disease is diagnosed by itself, without underlying correlative conditions, it is diagnosed like moyamoya disease. Usually, occlusion of the distal internal carotid artery occurs and performed angiography shows the appearance of puffs of smoke. The treatment of choice is surgical bypass. Case report: a patient borne in 1999 was received at Clinic for Infectious disease at KCUS because of elevated body temperature of unknown origin, high blood pressure and severe headaches. The standard diagnostics procedures and lumbar puncture are performed (cerebral fluid findings are normal). During hospitalization, the patient condition worsened. The transfer to Intensive care unit for continued treatment is indicated by anesthesiologist. On admission, a patient was in extremely severe general condition, disorientated, communication was difficult, extremely hypertensive. Due to the complexity of the general status of patient, an expert council consisting of a neurologist, an infectious disease specialist, a cardiologist, a nephrologist, a radiologist, an immunologist is held and additional diagnostic tests are performed. The laboratory tests showed a drop in the red blood count with a pronounced thrombocytopenia, persisting despite the administration of blood derivatives of the appropriate blood group. It was also followed by an increase in nitrogenous substances. The nephrologist indicated hemodialysis treatment, which was carried out in more cases on occasion. Due to worsening of the general condition and the signs of respiratory insufficiency and altered status of consciousness, endotracheal intubation was performed and mechanical respiratory support was started with continuous analgosedation. During the entire hospitalization, the patient had severe persistent hypertension despite continuous infusion of antihypertensive drugs with other specific resuscitation therapy and constant monitoring of cardiologist. The patient was initially treated with: Metoprolol with continuous Ebrantyl but increase in values of blood pressures were still extremely high so antihypertensive therapy was changed to Amlodipine, Spirinolactone, Carvediol. Neurological status showed: horizontal nystagmus, bilaterally positive Babinski. Therapy with Dexamethasone was started and according to the renal parameters, with Mannitol. Head CT scan on admission showed inflammatory encephalic changes with bleeding zones, diff. dg. changes caused by hypertension/hypertensive encephalopathy. Brain MRI pointed to a cortical and subcortical zone with altered signal intensity bilaterally can possibly correspond to PRESS with a small bleeding zone. On the sixteenth day after hospitalization, cardiac arrest occurs. Conclusion: early recognition of disease symptoms, detailed radiological diagnostics, as well as timely neurosurgical treatment of revascularization, is considered the current choice of treatment.

Keywords: moyamoya, brain arteries, nitrogenous substances, thrombocytopenia

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Analgosedation in brachytherapy

Analgosedacija u brahiterapiji

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Introduction: the number of non-invasive and minimally invasive medical procedures that are performed outside the operating room, in outpatient settings, has shown an exponential growth in recent decades. With the introduction of short-acting sedatives, opiate analgesics, as well as antagonists of these drugs, the use of anesthetics with a quick onset and a short period of action and with the use of non-invasive monitoring, analgosedation can be performed safely in various hospital or outpatient conditions. Materials and methods: analgosedation is defined as the technique of administering sedative or dissociative anesthetics, with or without analgesia, so that the patient is able to tolerate unpleasant procedures, while maintaining unchanged cardiorespiratory function. It enables a decrease in the patient's level of consciousness with adequate oxygenation and airway protection. For the performance of therapeutic interventions and diagnostic procedures, only sedation or only analgesia is sufficient, and in some cases there is a need for analgosedation. Analgosedation is used to perform non-invasive and invasive diagnostic and therapeutic procedures. Radiological procedures belong to non-invasive diagnostic procedures that are painless and where sedation aims to bring the patient to a calm state without movements, which could reduce the success of diagnostic procedures. In order to achieve the desired immobilization of the patient, deep sedation or minimal anesthesia is sometimes required. Brachytherapy (internal, cavitary radiation) involves the use of a source of radioactive radiation in the tumor itself or in its immediate vicinity. The brachytherapy process itself is not painful, but the placement of the applicators through which the radiation sources are subsequently introduced is extremely painful. Conclusion: application of analgosedation during brachytherapy is an important part of this oncological treatment, which facilitates the process itself. It implies enabling a more efficient performance of the procedure by the oncologist, as well as the elimination of intra-procedural and post-procedural pain in patients, with benefit from the psychological aspect.

Keywords: analgosedation, brachytherapy, pain

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Unilateral spinal anesthesia during operative management of hip fracture in patients with a markedly increased perioperative risk

Unilateralna spinalna anestezija kod operativnog zbrinjavanja frakture kuka kod pacijentice sa izrazito povišenim perioprativnim rizikom

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Introduction: fractures of the proximal part of the femur are among the most common diseases of elderly patients, with an annual incidence of 110–130 cases per 100,000 residents, and for patients over 65 years of age, 650–900 cases per 100,000 residents. Unilateral spinal anesthesia is a cost-effective and rapidly performed anesthetic technique. An exclusively unilateral block only affects the sensory, motor and sympathetic functions on one side of the body and offers the advantages of a spinal block without the typical adverse side effects seen with a bilateral block. Case report: a 97 years old patient suffered a hip fracture at home, than she was treated conservatively in another medical institution. She was admitted to the Clinic of Orthopedics and Traumatology of the Clinical Center University of Sarajevo for further evaluation and treatment. After the initial and internist treatment, the patient was transferred to low-molecular weight heparin. Among accompanying comorbidities, there are HTA and dementia. It is stated, in medical history, that patient previously had hysterectomy. Denies drug allergies. During the preoperative examination, the patient is conscious, has difficulty communicating due to poor hearing, and complains of pain in her right hip. The risks of anesthesia and surgery are explained in detail to the patient and the family member, who is the legal guardian, after which they agree to the same. On the day of the surgery, the patient was premedicated with 4 mg of Dexamethasone. Upon arrival to the operating room, the patient was placed on continuous non-invasive monitoring of vital parameters and oxygen support via a nasal catheter. Ketamine is administered, in an analgesic dose of 30 mg intravenously. After achieving the analgesic effect, the patient is carefully placed in the right lateral position for spinal anesthesia. Lumbar puncture is done at the level L4/L5 with a spinal needle 29G, pencil point, a clear cerebrospinal fluid is obtained and 0.8 ml of 5% Levobupivacaine + 1 ml of 40% Glucose is prescribed, after 15 minutes the patient is placed in the supine position. The patient breathes spontaneously, sufficiently. Intraoperatively, 1850 ml of crystalloid and 245 ml of erythrocyte concentrate of appropriate blood group and Rh factor are prescribed. Relative hemodynamic stability is maintained by intermittent administration of Noradrenaline 50+10+10 mcg. A partial endoprosthesis of the right hip (PEP) is implanted. After the operation, the patient is transferred to the intensive care unit of the Clinic for Orthopedics and Traumatology. Two hours after the operation, the patient is conscious, communicative, as well as possible, oriented, hemodynamically relatively stable, respiratory sufficient. Conclusion: movement and sensibility of the lower extremities are normal. During discharge from the hospital, patient was recommended to walk with the help of a walker or crutches, and with the help of another person, with dosed support on the operated leg. Operative treatments of hip fractures have a high operative risk, which requires appropriate management. Postponing surgery for non-medical reasons leads to a worse prognosis.

Keywords: fracture, femur, spinal anesthesia, unilateral anesthesia, geriatric population

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Regional anesthesia - TAP block

Regionalna anestezija - TAP blok

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Introduction: TAP (transversus abdominis plane block) is part of multimodal postoperative analgesia used in various gynecological, abdominal and urological surgeries. Transverse abdominis plane (TAP) block is a type of peripheral nerve block which involves the innervation of the nerves covering the anterior abdominal wall (T6-L1 anterior branch). It contains intercostal, subcostal, iliohypogastric, and ilioinguinal nerves. They are responsible for the innervation of the skin, muscles and parietal peritoneum of the anterior and posterior abdominal wall. As part of multimodal analgesia, it accelerates recovery and mobilization of the patient, reduces stress response, and significantly minimizes and eliminates the use of opioids in postoperative analgesia, thus reducing all their side effects (sedation, vomiting, reduced intestinal motility, negative effects during the infant breastfeeding). It is done preoperatively before surgical incision, or most often, at the end of surgical procedure, before the patient's awakening. Before the TAP block, the written consent of the patient should be obtained and the possible risks, benefits, alternatives of pain therapy should be discussed. Contraindications are absoule and they involve patient's refusal, allergy to local anesthetic, infection at the site of the block. Coagulopathy and surgery at the site of the block are relative. Materials and methods: the following is required for TAP block: ultrasound-linear probe (10-14Hz), sterile cover, gel. The aria is aseptically cleaned, sterile gloves are used, a local anesthetic, usually 0.25% of ropivacaine/bupivacaine/levobupivacaine, is loaded into a 20ml syringe, and with the help of 50-100mm (22-25G) block needles the prescribed dose for TAP block is administered. Monitoring is also required, as well as resuscitation equipment and lipid emulsion. Ultrasound identifies 3 muscles of the abdominal wall, externus obliqus (EO), internus obliqus (IO), transversus abdominis (TA). The method itself is simple; with the ultrasound quidance, the needle is placed between the IO and the TA, the fascia is pierced and a local anesthetic is applied. There are several approaches with respect to the anatomical location of the block: subcostal, lateral and posterior approache, which can subsequently be combined depending on surgical field, and thus we have unilateral blocks, dual and bilateral TAP blocks. Rare complications include: failure, bleeding (hematoma), infection, LA systemic toxicity, intraperitoneal injection, visceral injury (intestines, liver), transient nerve injury. Conclusion: TAP block as a multimodal analgesia is the most optimal when applied after a cesarean section, it significantly reduces postoperative pain, delays the time to the first, reduces the total consumption of analgesics, accelerates mobilization and facilitates breathing and expectoration. TAP block is an alternative to spinal morphine application for postoperative analgesia. Safe, with very few complications, efficient, easy to perform and inexpensive. Ultrasound increases the success of the block and minimizes complications!

Keywords: gynecology and obstetrics, regional anesthesia, TAP block

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Ultra sound guided regional anesthesia in orthopedics

Ultrazvučno vođena regionalna anestezija u ortopediji

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Introduction: regional anesthesia is a type of pain management for surgery that numbs a large part of the body. It is the use of medication to block pain in a part of the body such as an arm, leg or abdomen. The medication is delivered through an injection or small tube called a catheter and is used when a simple injection of local anesthetic is not enough, and when it's be for the patient to be awake. Literature review: regional anesthesia is an integral component of successful orthopedic surgery. Neuraxial anesthesia is commonly used for surgical anesthesia while peripheral nerve blocks are often used for postoperative analgesia. Patient evaluation for regional anesthesia should include neurological, pulmonary, cardiovascular, and hematological assessments. The choice of regional anesthesia is a unanimous decision made by the surgeon, the anesthesiologist, and the patient based on a risk-benefit assessment. The choice of the regional block depends on patient cooperation, patient positing, operative structures, operative manipulation, tourniquet use and the impact of post-operative motor blockade on initiation of physical therapy. Regional anesthesia is safe but has an inherent risk of failure and a relatively low incidence of complications such as local anesthetic systemic toxicity, nerve injury, falls, hematoma, infection and allergic reactions. Ultrasound should be used for regional anesthesia procedures to improve the efficacy and minimize complications. The use of ultrasound is the gold standard in performing regional anesthesia and analgesia techniques. The supraclavicular block is one of several techniques used to anesthetize the brachial plexus. The block is performed at the level of the brachial plexus trunks where almost the entire sensory, motor, and sympathetic innervation of the upper extremity is carried in just three nerve structures confined to a very small surface area. Consequently, this technique typically provides a predictable, dense block with rapid onset. A femoral nerve block is well suited for surgery on the anterior aspect of the thigh and for superficial surgery on the medial aspect of the leg below the knee. A femoral nerve block can also be used to supplement a sciatic or popliteal block to provide complete anesthesia of the lower leg and ankle. Distal sciatic nerve block (popliteal fossa block) is a very clinically valuable technique that results in anesthesia of the calf, tibia, fibula, ankle, and foot. Results: in the period from March 2022 to March 2023, 60 popliteal blocks, 50 femoral blocks, 30 supraclavicular blocks, 20 TAP, 10 PEG, 5 interscalene blocks were performed at the Clinic o Anesthesia and Reanimation of the Clinical Center University of Sarajevo. Conclusion: regional anesthesia has numerous advantages compared to general anesthesia, such as: better analgesia, greater efficiency, shorter length of hospitalization, earlier mobilization of the patient, lower incidence of postoperative nausea and vomiting, and thus greater patient satisfaction.

Keywords: orthopedic surgery, regional anesthesia, ultrasound, peripheral nerve blocks, upper extremity, lower extremity, supraclavicular block, femoral block, popliteal block, lumbar plexus, brachial plexus, complication, nerve injury

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Therapeutic hypothermia - case report

Terapijska hipotermija - prikaz slučaja

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Introduction: the stroke (stroke drop, apoplexy, cerebrovascular insult - CVI is an acute neurological disorder that occurs suddenly due to brain disorders circulation, and the consequence is insufficient Supplying certain parts of the brain oxygen and nutrients. Therapeutic hypothermia has been proven to be a controlled decrease in body temperature for therapeutic reasons and is one of the most challenging treatments that improve neurological recovery and treatment outcomes in patients with acute stroke. Hypothermia has shown a neuroprotective effect in cerebral ischemia and should be started as soon as possible in order to achieve maximum neuroprotection and effects of brain edema formation. Aim: to examine the effect of therapeutic hypothermia and the outcome of the neuroprotectiv effect at the cell level, and preserving a stroke. Materials and methods: a case report related to a patient bortn in 1985 where CT confirmed ischemic stroke. During the process of hypothermia we used Artic-San aparet to cool the body to the target body temperature from 34 °C to 35 °C for up to 24 hours. The outcome (survival or death) of the patient's treatment, the degree of disability and recovery from the resulting ischemic stroke were monitored. Results: after the therapeutic hypothermia, there were no previously verified ischemic changes. Conclusion: the therapeutic hypotermia proved to be neuroprotectiv for ishemic stroke.

Keywords: brain, metabolism, therapy

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Regional anesthesia - Caudal block

Regionalna anestezija - Kaudalni blok

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Introduction: regional anesthesia has become an integral part of most anesthesia protocols. It is included in the basic principles of regional anesthesia in childhood. It begins with adequately taken anamnestic data and good knowledge of anatomy and equipment. The application of regional procedures requires written consent from the parents. Before anesthesia is administred it is mandatory to revise theoretical part of each regional anesthesia, as it is important to administer an adequate dose and concentration of the drug. It should be taken into account that sometimes it takes more than thirty minutes for preparation, the block performance and analgesic efficasy. Always ensure adequate monitoring, and before performing the block, place an i.v. cannula, draw anatomical landmarks and determine the puncture site. Record any anatomical deviation and skin changes, follow the rules of asepsis and antisepsis. Resuscitation and ventilation equipment and the source of oxygen and suction must always be kept in the room where the block is performed. Contraindications are identical to those in adults, and they include the presence of infection at the puncture site, sepsis, children suffering from coagulopathy, thrombocytopenia or children on anticoagulant therapy, as well as lack of parental consent. Complications related to caudal block administration are: subarachnoid puncture and possible headache, visceral organs puncture, infection, intravascular administration, nerve damage, paresthesias, bleeding, spinal cord injury. There is a risk of developing a lumbar epidermoid tumor if needles with a mandrel are not used for puncture. Materials and methods: in order to reduce the pain during anesthetic injection, the drug should be warmed to room temperature and a syringe with a smaller volume should be used. There are two types of local anesthetics: amide (Bupivacaine, Levobupivacaine, Ropivacaine, Lidocaine) and ester local anesthetics (Tetracaine, Chloroprocaine). Given the toxicity of local anesthetics, it is mandatory to apply a test dose of local anesthetic in order to determine the unwanted effect of intravascularly applied anesthetic. Caudal block procedure is perfomed in the manner that the child is placed in a lateral decubitus or stomach position. The sacral hiatus is palpable as two bony ridges 0.5 to 1.0 cm apart. The L4-L5 intervertebral space is palpated, decending slowly along cauda to the sacral hiatus. Prefarably, a blunt short-bevel needle is used to avoid the risk of intravascular drug injection. Needles with mandrel reduce the possibility of introducing dermal tissue into the caudal space. The needle is introduced at an angle of 45-60 degrees through the skin, subcutaneous tissue and sacrocozygeal ligament to the caudal canal. The angle is than reduced to 30 degrees, and the needle is practically manuvered parallel to the patient's back. A characteristic "pop" is felt when passing through the sacrococcygeal ligament. The needle is then advanced one to two millimeters further and the anesthetic is administered. Aspiration is mandatory, do not inject air. The distance between the skin and the lumbar epidural space is approximately 1 mm per kg of body weight, but due to the increase in the number of obese children, this estimate has lost its significance. Bupivacaine, Levobupivacaine and Ropivacaine are used. The dose of the local anesthetic is determined by the volume, not by the concentration and the volume of the epidural space, which changes with age. Volume (ml) = 0.05 ml/kg/number of dermatomes we want to block. Case report: a child, of 10 kg body wight, blockage of T10 dermatome, should be given the volume: 0.05x10x10=5 ml. Recommended Bupivacaine concentrations for a single shot caudal block are from 0.125 to 0.25%. Bupivacaine 0.175% provides the best analgesia with fast recovery. Ivan, et al. (2003) indicate that the optimal concentration of Levobupivacaine for a single shot caudal block is 1ml/kg for with no additions (0.2% da li je ovo višak?). Conclusion: the effects of caudal anesthesia are of great importance in the application of well-balanced anesthesia and the reduction of intravenous anesthetics during surgery. Hemodynamic stability in children in relation to general endotracheal anesthesia. Reduction of postoperative pain.

Keywords: pediatric surgery, regional anesthesia, caudal block.

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Basic principles of ultrasound application in regional anesthesia

Osnovi principi primjene ultrazvuka u regionalnoj anesteziji

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Ultrasound-guided techniques have become the gold standard in the performance of regional (peripheral) blocks. The technique involves puncturing and guiding the needle through the tissues under ultrasound control, the possibility of monitoring anatomical structures and safe identification of nerves. The use of ultrasound shortened the time and increased the success of performing blocks. The total dose of local anesthetic is reduced, which reduces the risk of a toxic reaction. The incidence of unwanted events (puncture of blood vessels or pleura) is reduced and patient comfort and satisfaction are increased. Regional anesthesia under ultrasound control ensures excellent anesthesia for a wide range of surgical procedures. Postoperative analgesia is superior. Ultrasound has revolutionized the field of regional anesthesia.

Keywords: regional anesthesia, peripheral nerve blocks, ultrasound

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Introduction is a concise, short part of the article, and it contains purpose of the article relating to other published articles with the same topic. It is necessary to quote the main problem, aim of investigation, and/or main hypothesis which is investigated.

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