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with International Participation

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Dear colleagues and friends,

The year 2020 has dramatically changed our lives and the face of the entire world. During the first wave of the coronavirus pandemic, our world came to a standstill, and so did our domestic and foreign gatherings. Unfortunately we were unable to hold the 5th Congress of Emergency Medicine, which would have brought together many experts. However, despite the constraints in 2021, our activities continued. We have organized numerous online webinars and shown that even under difficult conditions one can still work professionally. As a result of great effort and continuous work, you have before you a thematic issue of the journal Acta Clinica Croatica. It contains collected works from the 6th Croatian Congress of Emergency Medicine (with international participation), which took place in Vodice, Croatia from 3-5 June 2022.

The Croatian Society for Emergency Medicine of the Croatian Medical Association (HLZ-HDHM) is the organizer of this congress. The Croatian Congress of Emergency Medicine with international participation is the most important professional meeting of the society. It is held every two years. This year, the main topics of the congress include significant issues related to the care of emergency patients from polytrauma, cardiopulmonary resuscitation, pain, geriatric medicine, education and new projects in emergency medicine. Special emphasis has been placed on the past two years and the importance of emergency medical services during the coronavirus pandemic.

As in the organization of numerous professional meetings, symposia and congresses, our desire was to achieve a high professional and scientific level and one of the ways is to publish complete papers in one of the most respected and important Croatian journals, Acta Clinica Croatica. All papers have passed independent reviews, English proofreading, and thanks to the valuable comments of the reviewers, the thematic issue represents a significant and instructive reading in everyday clinical work. We would certainly like to point out the great value of the works of emergency medical specialists who frequently presented their first clinical experiences, and for most of them, this was an opportunity for their first publication.

As a sign of our efforts to improve the quality of the congress, it is important to emphasize that it was attended not only by Croatian experts in the field of emergency medicine, but also by many recognized international experts.

The education of doctors working in the emergency medical service is better today, and with the introduction of a specialization in emergency medicine, we are receiving fully educated doctors. However, there is still room for improvement. Therefore, this congress is a good platform for the exchange of experiences and opinions with one main goal - safer and better care for emergency patients.

Višnja Nesek Adam, MD, PhD
President of Croatian Medical Association
– Croatian Society of Emergency Medicine

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Original Scientific Paper

EFFECT OF THE INTRODUCTION OF EMERGENCY MEDICINE SPECIALISTS ON THE EMERGENCY DEPARTMENT PERFORMANCE INDICATORS: A RETROSPECTIVE DATA ANALYSIS

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SUMMARY – Patient management in the emergency department (ED) is evaluated by performance indicators, such as wait times (time to be seen by a physician), length of stay (LOS) and the number of diagnostic tests per patient. To improve the quality of care, dedicated emergency medicine (EM) specialists are employed to work in the ED. The aim of this study is to evaluate three performance indicators of patient management in the ED compared by specialty, internal medicine (IM) versus EM. Research was conducted in the ED of a large tertiary teaching hospital. A retrospective data analysis of the hospital information system was conducted for the period when only IM specialists were working as attendants, versus a period when two EM specialists joined the ED team. We calculated the percentage of patients seen within the recommended time per Australasian Triage system (AST) category and compared the average LOS and the average number of tests per patient, using data from June 2017 to January 2020. Means, standard deviation, standard error, 95% confidence interval were calculated, and the independent t-test was used to compare means. With the introduction of the EM specialists, the percentage of patients examined within the recommended time frame per AST category was higher. There was a significant reduction in LOS in the ED when comparing only IM specialists to IM specialists with two EM specialists ($p<0.001$). The IM physicians on average do more tests than EM specialists, which was statistically significant ($p<0.05$). There was a significant improvement in efficiency in the ED with the introduction of EM specialists which was manifested by shorter patient wait times and shorter length of stay in the Emergency Department and fewer diagnostic test orders.

Key words: *Quality Indicators, Healthcare; Emergency Service, Hospital; Attending Physicians, Hospital; Triage; Length of Stay; Time Management.*

Introduction

With an increase in patients in the emergency departments each year, overcrowding has become a serious problem worldwide in the last few decades that adversely influences patients' outcomes and the availability of care[1]. Emergency Department (ED) crowding is a serious problem faced by most emergency departments all around the world. It is defined as "a situation in which the identified need for the emergency service exceeds the available resources for patient care in the ED, hospital, or both."[2-4] It represents a major problem considering that prolonged stay in the emergency department is associated with poor health outcomes.[5]

To improve the quality of care, patient management in the ED is evaluated by appropriate performance indicators, such as length of stay (LOS), time from arrival to triage, time to be seen by a physician, percentage of patients who left without being seen, and many more.[3,4]

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According to the Australasian Triage system (ATS)[6], patients in the first category must be treated immediately, category 2 patients should be treated within 10 minutes, category 3 within 30 minutes, category 4 patients within 60 minutes, and triage category 5 patients should be treated within 120 minutes of arrival at the ED.[6] Performance indicators describe the minimum percentage of patients treated in the recommended time, depending on the ATS category, which is 100% for category 1, 80% for category 2, 75% category 3 and 70% for categories 4 and 5[7].

As a part of a state-wide restructuring of the emergency medical services, our hospital started a five-year emergency medicine specialty residency program in 2012. Consequently, the first two specialists joined the team of 18 internal medicine (IM) specialists in June 2019, rotating in shifts in the ED of a busy urban teaching tertiary level hospital with about 22,000 patient visits in 2019.

The aim of this study was to evaluate three performance indicators of patient management in the ED compared by specialty: internal medicine vs emergency medicine.

Methods

Study design and setting

A retrospective data analysis using the hospital's information system was performed for the period when there were only Internal Medicine specialists working as attendings (from June 2017 to August 2018), compared to June 2019 – January 2020 when two EM specialists started working as attending physicians. In February 2020, due to the Covid-19 pandemic, there were major organizational changes implemented in the ED, therefore, that later period was not eligible for comparison. A prospective survey was carried out on a convenience sample of on-call residents and nurses who worked in the emergency department of an urban teaching hospital and gave their informed consent. Permission to conduct this research was obtained from the ethics committee of the University Hospital Dubrava and the Medical School of the University of Zagreb. The percentage of patients seen within the recommended time per ATS category (efficiency), for each period was calculated. The average length of stay (LOS) for patients in the ED and the average number of tests per patient seen in the ED per physician were compared.

Data analysis

Means, standard deviation (SD), standard error (SE), 95% confidence interval (CI) were calculated. Student's t-test was used to compare means between groups since the distribution was normal. The p-value <0.05 was considered significant. To compare mean number of tests per physician the Student's t-test was used.

Results

We found that with the introduction of EM specialists, patients were seen more quickly, since the percentage of patients examined within the recommended time frame per ATS category was higher (Figure 1). For the second ATS category, there were 38.27% of patients seen within the recommended 15-minute time frame with only IM attending physicians working in the ED, whereas when compared with two EM attendings in the team, it was 52.58%. In the third ATS category, there were 66.06% patients seen on time with two EM specialists working, compared to only half of patients (51.27%) with only IM attendings in the ED. Both second and third categories fail to meet the advised minimal percentage of patients seen within the recommended time frame. A similar rise in the efficiency is seen in the fourth and fifth ATS categories.

When comparing the average length of stay in the ED (Table 1) there is a significant difference between groups ($p<0.001$).

When comparing LOS for only IM specialists to IM with 2 EM specialist, there is a significant decrease in LOS ($p<0.001$). Considering the number of tests per patient (Table 2), we found that IM physicians on average do more diagnostic and laboratory tests than EM specialists, ($p<0.05$).

The average number of tests per patient for all IM specialists is 6.34, while for EM specialists 6.07 tests per patient, ranging from 5.96 to 6.63 tests per patient for 18 IM specialists, and 6.02 and 6.12 for EM specialists. The comparison was made with only 2 EM physicians vs 18 IM physicians as these two EM physicians attended to 33% of all patients seen in the examined period.

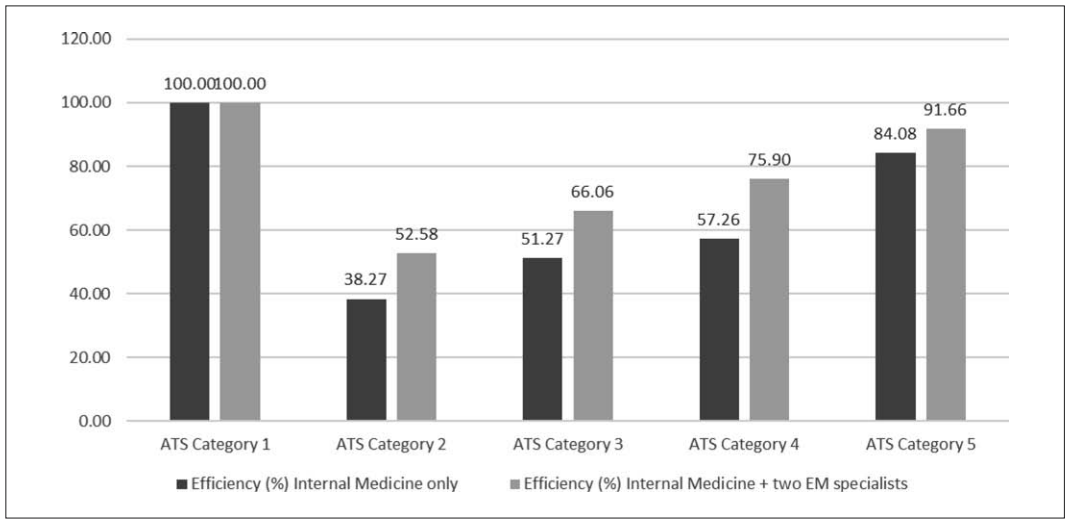

Figure 1 Efficiency in the ED by ATS Category and specialty of the attending physician.

Table 1 Student's t-test comparing mean length of stay for patients in the Emergency department depending on the attending physician.

		N	Mean	Std. Deviation	95% Confidence Interval		p
Length of stay	Only Internal Medicine	31135	4,05	2,59	0,29	0,36	**<0.001**
	Internal Medicine + Emergency Medicine	14841	3,32	2,37			

Table 2 Results of the Student's t-test comparing the average number of tests per patient per physician Internal Medicine Specialists vs Emergency Medicine Specialists.

		Mean	Std. Deviation	95% Confidence Interval		p
Average number of tests per patient per physician	Internal Medicine Specialists	6,341	0,168	0,015	0,529	**0,04**
	Emergency Medicine Specialists	6,069	0,072			

Discussion

The efficiency of the ED by ATS Category, the average length of stay and the average number of diagnostic tests per patient in the ED was evaluated by specialty. The wait time to be seen by a physician was shorter in every ATS category of patients with the introduction of EM specialists. This is supported by other studies that found that emergency clinicians rapidly process large numbers of high-need patients[8]. When comparing the work of internal medicine specialists to a combination with emergency medicine specialists, there was a significant shortening of LOS when two EM specialists worked together on a daily basis in the ED. Traditionally, internal medicine patients often exceed the four-hour stay in the ED,[9] which was also supported by our data. Driesen et al. have shown that 76- percent of LOS prolongation is organizational and only 22 percent is patient or disease-related, with 94 percent of the organizational factors outside the influence of the ED.[10] The above facts indicate a greater need for EM specialists since it has been shown that they can reduce LOS to an optimal four-hour target, that has been recommended by health authorities to decrease the LOS in ED.[11] Therefore, a significant factor in the ED that can be addressed is the introduction of EM specialists.

As already demonstrated, better coordination of care and faster decision making after completion of all diagnostics greatly decrease LOS[9,12,13] which may be

the advantage of EM specialists compared to other physicians.

Furthermore, we found that a statistically significant difference in the number of tests ordered by internal medicine or ED physicians, suggesting a more rational approach by the EM physicians. Unnecessary testing is time and labor consuming, involves pain and discomfort for the patient, possible adverse effects and unreasonable exposure to radiation, prolongs LOS, increases costs, which is why a rational goal-directed approach to testing is preferred in the ED[14].

Quality of the medical treatment, as well as LOS in triaged patients, is influenced by many factors such as the number of procedural formalities until the examination, the availability of acute hospital and ED beds and connection with other diagnostic points in the hospital, the complexity of certain conditions and other comorbidities of patients presented in the ED. Therefore, it is recommended to have as simple an approach in the treatment of emergency patients as possible, with a focus on the acute health problem. Overall, the results emphasize the need for specialist training in emergency medicine as well as the need for an adequate number of professional and skilled physicians in the ED.

Limitations

The main drawback of this study is the lack of evidence of treatment outcome. Another limitation, and a feature which had an impact on the results, is the timing of the implementation of high-sensitive Troponin in the ED which is the same as the introduction of EM specialists. Therefore, the shortened LOS can partially be attributed to that.

With the introduction of EM specialists there was a significant reduction in LOS for patients in the ED, significant reduction in wait times to be seen by a physician and fewer diagnostic test were ordered. Further improvements are necessary since urgent patients still do not meet the triage target time. Drawing on the results, we suggest implementing more EM specialists in the ED.

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Sažetak

UTJECAJ UVOĐENJA SPECIJALISTA HITNE MEDICINE NA POKAZATELJE UČINKOVITOSTI BOLNIČKE HITNE SLUŽBE – RETROSPEKTIVNA ANALIZA

Maša Sorić, Diana Špoljar i *Mia Golubić*

Zbrinjavanje bolesnika u bolničkoj hitnoj službi (BHS) ocjenjuje se pokazateljima učinkovitosti kao što su vrijeme čekanja (vrijeme čekanja na pregled liječnika), duljina boravka i prosječan broj dijagnostičkih pretraga po pacijentu. Kako bi se poboljšala kvaliteta skrbi, u BHS se specifično zapošljavaju specijalisti hitne medicine (HM). Cilj ove studije je ocijeniti tri pokazatelja učinkovitosti zbrinjavanja pacijenata u BHS u usporedbi prema specijalnosti, interna medicina (IM) u odnosu na HM. Istraživanje je provedeno u hitnoj internističkoj službi tercijarne nastavne bolnice. Provedena je retrospektivna analiza podataka bolničkog informacijskog sustava za razdoblje kada su kao liječnici radili samo specijalisti IM u odnosu na razdoblje kada su se pridružila dva specijalista hitne medicine. Izračunali smo postotak pacijenata pregledanih unutar preporučenog vremena po kategoriji australoazijskog trijažnog sustava (ATS), usporedili prosječnu duljinu boravka i prosječan broj testova po pacijentu, koristeći podatke od lipnja 2017. do siječnja 2020. godine. Izračunate su aritmetička sredina, standardna devijacija, standardna pogreška te 95% interval pouzdanosti, a za usporedbu srednjih vrijednosti korišten je nezavisni t-test. Uvođenjem specijalista HM postotak pregledanih pacijenata u preporučenom vremenskom okviru po ATS kategoriji bio je veći. Došlo je do značajnog smanjenja duljine boravka bolesnika u BHS kada se uspoređuju samo specijalisti IM sa IM specijalistima s dva HM specijalista ($p<0,001$). Liječnici IM u prosjeku rade više pretraga od specijalista EM, što je statistički značajno ($p<0,05$). Došlo je do značajnog poboljšanja učinkovitosti u BHS uvođenjem specijalista HM što se očitovalo kraćim čekanjem pacijenata i kraćim trajanjem boravka u bolničkoj hitnoj službi te manjim brojem narudžbi za dijagnostičke pretrage.

Ključne riječi: *pokazatelji kvalitete; hitna služba, trijaža; duljina boravka; specijalisti hitne medicine.*

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Original Scientific Paper

BLOOD PRESSURE IS ASSOCIATED WITH DIABETIC RETINOPATHY IN TYPE 1 BUT NOT IN TYPE 2 DIABETES

Tomislav Bulum[1,2], Martina Tomić[1], Romano Vrabec[1], Miljenka Martinović Bošković[1], Spomenka Ljubić[1,2] and Ingrid Prkačin[2,3]

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SUMMARY – The aim of this study was to investigate the role of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the development of diabetic retinopathy (DR) in type 1 and type 2 diabetes and to determine the differences between these two types of diabetes. This cross-sectional study included 84 patients with type 1 diabetes (T1DM) and 107 patients with type 2 diabetes (T2DM). Ophthalmologic retinal examination included indirect slit-lamp fundoscopy, color fundus photography according to EURODIAB (EUROpe and DIABetes) protocol and optical coherence tomography. Blood pressure was measured with a mercury sphygmomanometer after a 10-minute rest period. In T1DM, DR was positively associated with SBP ($p = 0.035$), $HbA1c_{median}$ ($p < 0.001$) and hypertensive retinopathy ($p < 0.001$), while in T2DM DR was positively related only to $HbA1c_{median}$ ($p = 0.021$). Binary logistic regression analysis (no DR/DR) showed that diabetes duration and $HbA1c_{median}$ were the main predictors of DR in both types of diabetes. In contrast, SBP (OR = 1.05, $p = 0.045$) and hypertensive retinopathy (OR = 3.75, $p < 0.001$) were the main predictors/indicators of DR only in T1DM. In conclusion, blood pressure is associated with DR in type 1 but not in type 2 diabetes.

Keywords: blood *pressure, type 1 and type 2 diabetes, retinopathy, risk factors*

Introduction

The prevalence of diabetes mellitus is rapidly increasing and is now the most common non-communicable disease, globally projected to affect over 700 million people by 2045.[1]

Diabetic retinopathy (DR), a microvascular complication of diabetes, is one of the leading causes of visual impairment and blindness in patients with type 1 (T1DM) and type 2 (T2DM) diabetes.[2] T1DM is an autoimmune disease that result from autoimmune β-cell destruction with absolute insulin deficiency and accounts for 5-10% of diabetes, while T2DM occurs more frequently, comprising more than 90% of all diabetes cases. It is associated with insulin resistance and metabolic syndrome components (obesity, hypertension, and dyslipidemia)[3]. Prospective studies identified hyperglycemia, diabetes duration and blood pressure as the most important risk factors for development of DR in T1DM and T2DM[4-7]. Besides diabetes duration, hyperglycemia and hypertension are modifiable risk factors.[8]

In patients with diabetes, high blood pressure increases blood flow and hypothetically damages the retinal capillary endothelial cells.[9] The results from the large and prospective United Kingdom Prospective Diabetes Study (UKPDS) showed that the incidence

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of DR was associated with systolic blood pressure (SBP) in T2DM.[10] T2DM in the highest tertile range with SBP over 140 mmHg had almost a three times higher risk of development of DR compared to subjects in the lowest tertile range with SBP below <125 mmHg. In contrast, results from the 25-year follow-up of the WESDR (Wisconsin Epidemiologic Study of Diabetic Retinopathy) study, which included T1DM, found that diastolic blood pressure (DBP) was a significant predictor of the progression of DR.[11] However, in the same study neither SBP nor DBP at baseline were associated with the incidence and progression of DR in T2DM.[12] We previously observed that SBP is a risk factor for the development and progression of DR in T1DM, but in patients with normal renal function and normoalbuminura.[13] In contrast, we previously observed that DBP is a risk factor and predictor for cataract development in T2DM[14].

The aim of this study was to investigate the role of SBP and DBP in the development of DR in T1DM and T2DM.

Subjects, materials and methods

This cross-sectional study included 84 T1DM and 107 T2DM patients at the Department of Ophthalmology and the Department of Diabetes of the Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases in Zagreb over a six-month period. The study was performed in accordance with the Helsinki Declaration and approved by the hospital's ethics committee. The patients included in the study received both written and oral information about the study and signed a consent form. T1DM and T2DM were defined according to the ADA classification.[3] We excluded from the study all illnesses that may affect eye function and blood pressure, such as therapy with corticosteroids or cytostatics, immunological and acute infectious inflammatory diseases, pregnant women and patients with other eye diseases. At the inclusion visit, consent forms were signed, blood samples were collected for laboratory analyses, and complete clinical and ophthalmologic retinal examinations were performed.

All subjects were examined the morning after an overnight fast to determine HbA1c, serum lipids and serum creatinine. Basic anthropometric measurements were performed on all study subjects, including body mass index (BMI). HbA1c was determined at the beginning of the study from a single venous blood sample. $HbA1c_{median}$ was obtained by a statistical analysis of data from the National Registry for Diabetes (CroDiabNet) and used as a marker of long-term glycemic control. The statistical analysis included HbA1c values from venous blood samples taken from each patient at 3-4-month intervals over the past three years. SBP and DBP were measured with an ambulatory mercury sphygmomanometer after a 10-min rest period, and a mean of three measurements was used.

The ophthalmologic retinal examination included indirect slit-lamp fundoscopy, color fundus photography, and optical coherence tomography (OCT) of the macula after mydriasis with eye drops containing 0.5 % tropicamide. Color fundus photographs of two fields (macular field, disc/nasal field) of both eyes were taken with the standard 45° fundus camera (Visucam NM/FA, Carl Zeiss Meditec) according to the EURODIAB retinal photography methodology[15]. Two medical retina specialists independently graded the photographs and assigned a DR level. The final diagnosis for each patient was determined from the level of DR of the worse eye using EURODIAB criteria.[15] OCT of the macula of both eyes was performed by Spectral Domain OCT (SD-OCT Copernicus REVO NX, Optopol Technology), and diabetic macular edema (DME) was defined by the proposed international clinical DR and diabetic macular edema disease severity scales.[16] Hypertensive retinopathy was defined and graduated using the Keith-Wagner-Barker classification.[17] Patients with active proliferative DR and active DME were not included in the study.

Statistical analysis was performed with the Statistica software package, version 14.0 (TIBCO Inc., USA). The normality of data distribution was evaluated by the Kolmogorov-Smirnov test and the homogeneity of variance by the Leven test. The results of the descriptive analyses were expressed as means ± SD or medians (min-max) for continuous variables and as numbers and percentages for categorical variables. Differences between continuous data were determined by t-test or a Mann-Whitney test. A nonparametric test was used when the assumption of homogeneity of variance for tested variables was not met. Differences among categorical data were evaluated by the Chi-square test. The Pearson's and Spearman rank correlation tests were used. ANOVA with two main factors

Table 1. Basic characteristics and clinical parameters of type 1 and type 2 diabetic patients included in the study.

	T1DM (n=84)	**T2DM** (n=107)	**t[a] Chi[b] Z[c]**	**p**
Age (years)*	41.54±7.58	66.74±8.01	-14.976[a]	**<0.001**
Gender (m/f)**	36/48	40/67	0.281[b]	0.596
Diabetes duration (year)†	15.5 (8-35)	15 (7-25)	1.289[c]	0.159
SBP (mmHg)*	123.75±21.15	142.34±23.03	-3.864[a]	**<0.001**
DBP (mmHg)*	78.39±11.39	81.07±12.53	-1.026[a]	0.307
HbA_1c (%)*	6.77±1.37	6.50±1.11	1.111[a]	0.268
HbA_1c_{median} (%)*	7.25±1.11	6.80±0.84	2.124[a]	**0.038**
Diabetic retinopathy**	33 (39.3)	42 (39.2)	0.000[b]	0.997
Hypertensive retinopathy**	27 (32.1)	40 (37.4)	0.264[b]	0.608

* mean ± SD ** number (percentage) † median (min-max) [a] t-test [b] Chi-square test [c] Mann-Whitney test
T1DM = type 1 diabetic patients; T2DM = type 2 diabetic patients; SBP = systolic blood pressure; DBP = diastolic blood pressure; HbA_1c = glycated hemoglobin value determined at the beginning of the study from a single venous blood sample; HbA_1c_{median} = glycated hemoglobin value obtained by statistical analysis of data from the National Registry for Diabetes (CroDiabNet).

and their interaction was used to compare the analyzed variables according to the type of diabetes and the DR status. Binary logistic regression analysis was used to assess the strength and independence of the associations between DR and the risk factors. In all analyses, $p < 0.05$ was considered statistically significant.

Results

This study included 84 (48 male/36 female) T1DM and 107 (67 male/40 female) T2DM. Their basic characteristics and clinical parameters are presented in Table 1. T2DM were significantly older ($p < 0.001$) and had significantly higher SBP ($p < 0.001$), while T1DM had significantly higher $HbA1c_{median}$ ($p = 0.038$). No significant differences in gender, diabetes duration, DBP, HbA1c, and number (percentage) of patients with diabetes and hypertensive retinopathy were found between the patients with different types of diabetes.

According to the DR status, patients were divided into two groups: Gr 1 (patients without DR; type 1 n=51, type 2 n=65) and Gr 2 (patients with DR; type 1 n=33, type 2 n=42). Table 2 presents the clinical parameters of T1DM and T2DM divided into two DR groups. T1DM with DR had significantly higher SBP than patients without DR ($p = 0.035$), while no significant difference in SBP in T2DM with and without DR was observed ($p = 0.062$). Also, the two DR groups in both types of diabetes did not significantly differ in DBP, and HbA1c determined at the beginning of the study, but $HbA1c_{median}$ was significantly higher in patients with DR than those without DR in T1DM ($p < 0.001$) and T2DM ($p = 0.021$). T1DM with DR had significantly more frequent signs of hypertensive retinopathy than those test subjects without DR ($p < 0.001$), although no significant difference in the number (percentage) of patients with and without DR and concomitant hypertensive retinopathy was found in T2DM ($p = 0.079$) (Table 2, Figure 1). Figure 2 presents the macular field of the left and right eye of one T1DM with non-proliferative DR and concomitant hypertensive retinopathy Gr. 3/2.

In T1DM DR was positively associated with SBP ($p = 0.035$), $HbA1c_{median}$ ($p < 0.001$) and hypertensive retinopathy ($p < 0.001$), while in T2DM it was positively related only to $HbA1c_{median}$ ($p = 0.021$) (Table 3).

The differences in SBP and DBP according to the type of diabetes and DR status were evaluated by ANOVA with two main factors and their interaction (Table 4, Figure 3). The among-group differences in SBP were observed according to the type of diabetes ($p < 0.001$) and DR status ($p = 0.009$), but no significant difference in SBP was found in the interaction between the type of diabetes and DR status ($p = 0.378$). For DBP, no differences were observed among-group according to the type of diabetes ($p = 0.451$) and DR status ($p = 0.904$) or in the interaction of the type of diabetes and DR status ($p = 0.253$).

Table 2. Clinical parameters of type 1 and type 2 diabetic patients divided into two groups according to the diabetic retinopathy status.

	T1DM (n=84)				T2DM (n=107)			
	DR		t[a] Chi[b]	p	DR		t[a] Chi[b]	p
SBP (mmHg)*	Gr 1 Gr 2	117.06±18.12 134.09±22.12	-2.228[a]	**0.035**	Gr 1 Gr 2	139.00±22.97 147.50±22.42	-1.887[a]	0.062
DBP (mmHg)*	Gr 1 Gr 2	77.06±12.75 80.45±9.07	-0.765[a]	0.451	Gr 1 Gr 2	82.15±12.89 79.40±11.90	1.109[a]	0.269
HbA_1c (%)*	Gr 1 Gr 2	6.57±1.49 7.07±1.16	-0.933[a]	0.359	Gr 1 Gr 2	6.42±1.06 6.62±1.18	-0.939[a]	0.349
HbA_1c_{median} (%)*	Gr 1 Gr 2	6.57±0.93 8.03±0.73	-4.384[a]	**<0.001**	Gr 1 Gr 2	6.65±0.81 7.03±0.83	-2.350[a]	**0.021**
Hypertensive retinopathy**	Gr 1 Gr 2	0 (0) 27 (81.8)	20.498[b]	**<0.001**	Gr 1 Gr 2	20 (30.8) 20 (46.6)	3.095[b]	0.079

* mean ± SD ** number (percentage) [a] t-test [b] Chi-square test
T1DM = type 1 diabetic patients; T2DM = type 2 diabetic patients; DR = diabetic retinopathy; Gr 1 = patients without DR (type 1 n=51; type 2 n=65); Gr 2 = patients with DR (type 1 n=33; type 2 n=42); SBP = systolic blood pressure; DBP = diastolic blood pressure; HbA_1c = glycated hemoglobin value determined at the beginning of the study from a single venous blood sample; $HbA_{1cmedian}$ = glycated hemoglobin value obtained by statistical analysis of data from the National Registry for Diabetes (CroDiabNet).

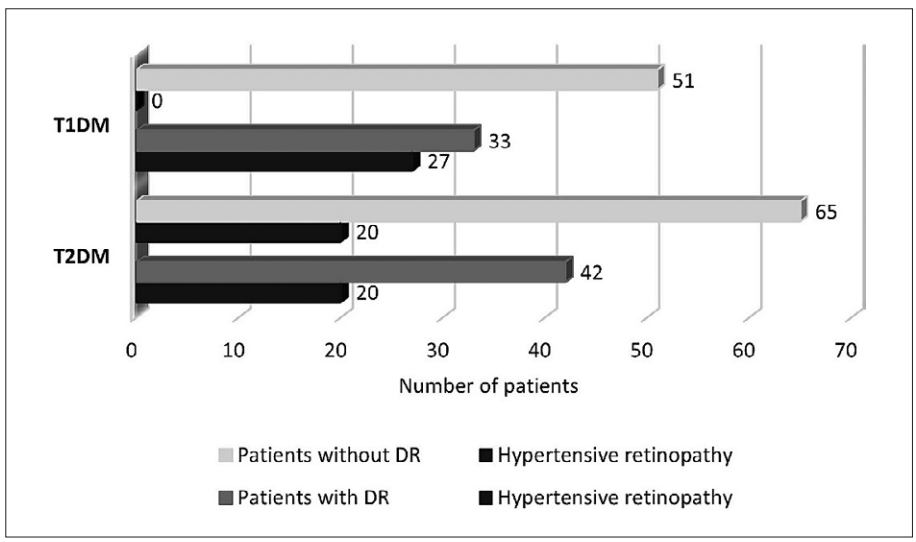

Fig. 1. Proportion of type 1 and type 2 diabetic patients with and without diabetic retinopathy and concomitant hypertensive retinopathy.

Binary logistic regression analysis (no DR/DR) showed that diabetes duration and long-term poor glycemic control, presented by $HbA1c_{median}$, were the main predictors of DR in both types of diabetes (Table 5). In contrast, SBP (OR = 1.05, p = 0.045) and hypertensive retinopathy (OR = 3.75, p < 0.001) were the main predictors/indicators of DR only in T1DM. Using the same logistic regression analysis, no significant association between DR and other analyzed variables were observed.

Discussion

The results of our study showed that in T1DM DR is positively associated with SBP, $HbA1c_{median}$ and hypertensive retinopathy, while in T2DM DR is posi-

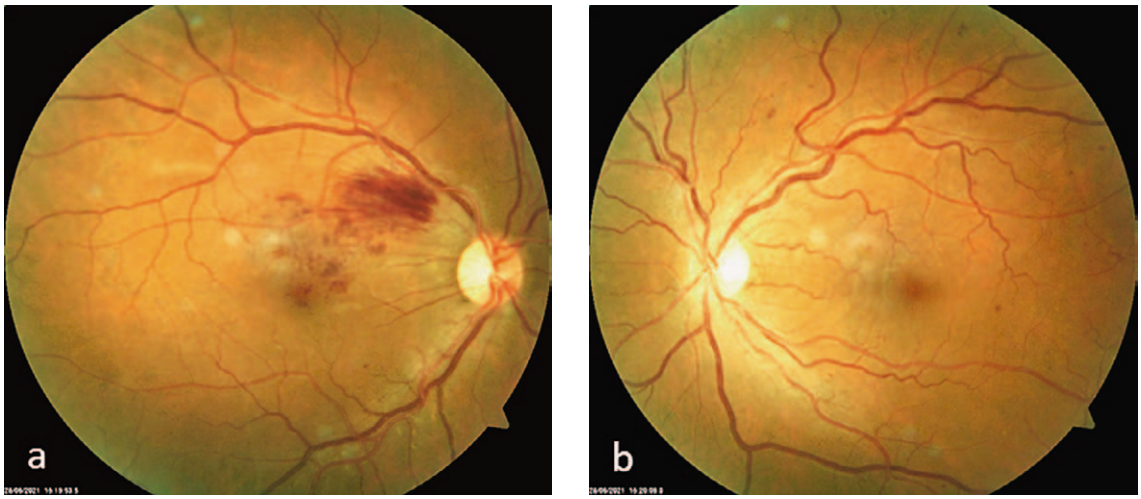

Fig. 2. Macular field of right (a) and left (b) eye of type 1 diabetic patient with nonproliferative diabetic retinopathy and concomitant hypertensive retinopathy Gr 3/2.

Table 3. Correlation between diabetic retinopathy and clinical parameters in type 1 and type 2 diabetic patients included in the study.

	Diabetic retinopathy					
	T1DM			**T2DM**		
	r^2	**t**	**p**	**r^2**	**t**	**p**
SBP	0.160	2.228	**0.035**	0.033	1.887	0.062
DBP	0.022	0.765	0.451	0.012	-1.109	0.269
HbA_1c	0.032	0.933	0.359	0.008	0.939	0.349
HbA_1c_{median}	0.425	4.384	**<0.001**	0.049	2.350	**0.021**
	Spearman R	t(N-2)	p	Spearman R	t(N-2)	p
Hypertensive retinopathy	0.856	8.428	**<0.001**	0.170	1.768	0.079

T1DM = type 1 diabetic patients; T2DM = type 2 diabetic patients; SBP = systolic blood pressure; DBP = diastolic blood pressure; HbA_1c = glycated hemoglobin value determined at the beginning of the study from a single venous blood sample; HbA_1c_{median} = glycated hemoglobin value obtained by statistical analysis of data from the National Registry for Diabetes (CroDiabNet).

tively related only to $HbA1c_{median}$. Binary logistic regression analysis (no DR/DR) showed that diabetes duration and $HbA1c_{median}$ were the main predictors of DR in both types of diabetes (Table 5). In contrast, SBP (OR = 1.05, p = 0.045) and hypertensive retinopathy (OR = 3.75, p < 0.001) were the main predictors/indicators of DR only in T1DM. Using the same logistic regression analysis, no significant association between DR and other analyzed variables was observed. Elevated blood glucose is a well-established risk factor for macrovascular and microvascular complications in patients with diabetes. The large prospective DCCT (Diabetes Control and Complications Trial) that included T1DM, as well as a UKPDS trial that included T2DM, showed that tight glycemic control significantly reduces the risk of the development and progression of DR and blindness.[18,19]

SBP and DBP are additional important modifiable risk factors for DR that have been documented in many trials. The ABCD (Appropriate Blood Pressure Control in Diabetes) and UKPDS are large, prospective trials that included T2DM and observed that strict blood pressure control can prevent and/or limit DR and visual dysfunction.[20,21] In ABCD study there were no significant differences in SBP and DBP between DR groups in T2DM. Similar to our results, blood pressure was similar in normotensive normoalbuminuric T2DM patients with and without DR[22].

Table 4. Results of two-way ANOVA for the differences in systolic and diastolic blood pressure according to the type of diabetes, diabetic retinopathy status, and their interaction.

		SBP		DBP	
	df	F	p	F	p
DM type	1	13.431	**<0.001**	0.571	0.451
DR	2	7.006	**0.009**	0.015	0.904
DM type & DR	3	0.782	0.378	1.317	0.253

DM type = type of diabetes mellitus; DR = diabetic retinopathy status; SBP = systolic blood pressure; DBP = diastolic blood pressure.

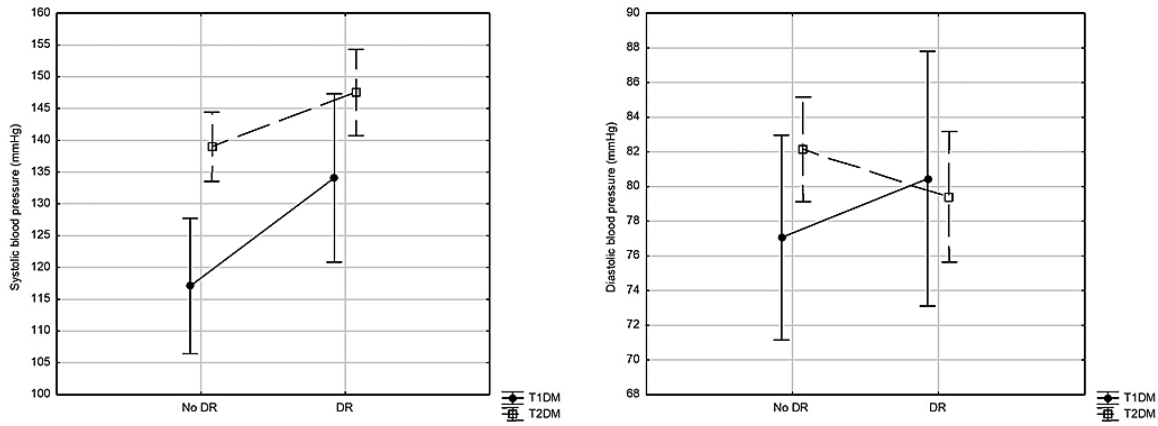

Fig. 3. Differences in systolic and diastolic blood pressure according to the type of diabetes and diabetic retinopathy status

Table 5. Predictors and indicators of diabetic retinopathy in type 1 and type 2 diabetes using binary logistic regression analysis.

	T1DM		T2DM	
	OR (95% CI)	p	OR (95% CI)	p
Diabetes duration	1.20 (1.05-1.38)	**0.005**	1.17 (1.08-1.27)	**<0.001**
SBP	1.05 (0.99-1.10)	**0.045**	1.02 (0.99-1.04)	0.065
DBP	1.03 (0.95-1.10)	0.438	0.98 (0.95-1.01)	0.269
HbA_1c	1.32 (0.72-2.41)	0.351	1.18 (0.83-1.68)	0.348
HbA_1c_{median}	6.92 (1.58-30.17)	**0.007**	1.75 (1.07-2.87)	**0.024**
Hypertensive retinopathy	3.75 (1.78-7.89)	**<0.001**	2.05 (0.91-4.61)	0.081

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; SBP = systolic blood pressure; DBP = diastolic blood pressure; HbA_1c = glycated hemoglobin value determined at the beginning of the study from a single venous blood sample; HbA_1c_{median} = glycated hemoglobin value obtained by statistical analysis of data from the National Registry for Diabetes (CroDiabNet).

High blood pressure in T1DM has been shown to significantly increase the risk of proliferative DR in the Wisconsin Epidemiology Study.[23] Another study that also included T1DM indicated that each increment of 5 mmHg in night-time SBP and DBP increase the risk of DR up to 40% even in T1DM without hypertension.[24] In contrast, it has been documented that normoalbuminuric T1DM with hypertension had no higher prevalence of DR compared to normoalbuminuric normotensive patients[25]. Another study that in-

cluded normoalbuminuric T1DM found higher only night blood pressure in patients with DR compared to those without retinopathy.[26] The results from the EURODIAB Prospective Complications Study, which included T1DM, found that DBP is a significant risk factor for DR after adjusting for nephropathy, while nighttime 24-hour ambulatory SBP was associated with the presence and severity of DR in T1DM without nephropathy and hypertension.[6,27] In our study, only SBP was associated with DR, which is in line with our previous study in which we observed that SBP is a risk factor for the development and progression of DR in T1DM with normal renal function and normoalbuminuria, and with the prospective UKPDS study, which also found higher relative risk for the incidence of DR with higher SBP in T2DM.[13,28] However, the methods used for diagnosis of blood pressure in our study (single standard sphygmomanometer not 24-hour ambulatory blood pressure) may influence the final results of our investigation and make a comparison between studies difficult.

In T1DM treatment with the ACE-inhibitor lisinopril resulted in a statistically significant 50% reduction in the progression of DR and an 82% reduction in the progression to proliferative DR even after an adjustment for glycemic control.[29] In the Diabetes Remission Clinical Trial (DIRECT) 5 years of ACE-inhibitor candesartan treatment in T1DM reduced the incidence of DR in severity by 18% and reduced the incidence of DR progression by 35%.[30] ACE-inhibitors have a beneficial hemodynamic effect, reduce endothelial dysfunction via enhancement of nitric oxide and blocking vascular endothelial growth factor receptors, and improve the blood-retinal barrier.[31] The beneficial effect on DR is observed even in T1DM with blood pressure in the "normal range," which is also observed in UKPDS, where researchers reported that there was no evidence of a threshold effect of SBP for the incidence of microvascular complications in T2DM.[28] It should be stressed that the majority of our T1DM were not on antihypertensive therapy and that the mean SBP and DBP was within the normal range for patients with diabetes (mean blood pressure 123/78 mmHg).

In diabetic mouse models, hypertension significantly increases the thickness of the basement membrane and permeability to albumin.[32] The frequency of acellular capillaries, the morphological gold-standard marker for DR, is doubled in diabetic rats with hypertension compared to those without hypertensionin.[33] Depositions of advanced glycation end products-proteins in the retinal vasculature activated with hypertension induced development of DR in that study. Othe studies also suggested that hypertension could induce oxidative stress and inflammation, risk factors strongly implicated in the pathogenesis of DR, and contributed to the development of DR.[34] In animal models with diabetes and genetic susceptibility to hypertension, inflammation processes in the retina are present before the establishment of full hypertension.[35] It seems that the coincidence of hyperglycemia and hypertension can accelerate inflammation and oxidative stress, which are pathological processes involved in DR development and progression.

The present study has a number of potential limitations. First, its design was cross-sectional and sample size in subgroups was small, which limited our ability to infer a causal relation between DR and blood pressure. Second, ambulatory blood pressure measurement is more useful than causal or office blood pressure measurement, and the methods used for diagnosis of DR and blood pressure may have an influence on the final results, making comparisons of the findings between studies difficult.[36] Third, our analyses were based on a single measurement of blood pressure that may not reflect the relation over time. Fourth, this cohort had little racial/ethnic diversity and our data would be primarily relevant to a white European population.

In conclusion, our results suggest that diabetes duration and $HbA1c_{median}$ are the main predictors of DR in both types of diabetes. However, SBP and hypertensive retinopathy were the predictors/indicators of DR only in T1DM, indicating that blood pressure is associated with tDR in Type 1 but not in type 2 diabetes. This points to the need for close monitoring of blood pressure in T1DM aimed at preventing or limiting the progression of DR.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

The authors state that this manuscript has not been published previously and is not currently being assessed for publication by any journal other than the Acta Clinica Croatica. The authors did not receive any

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Sažetak

KRVNI TLAK JE POVEZAN S DIJABETIČKOM RETINOPATIJOM KOD BOLESNIKA SA TIPOM 1 ALI NE I KOD TIPA 2 ŠEĆERNE BOLESTI

T. Bulum, M. Tomić, R. Vrabec, M. Martinović Bošković, S. Ljubić i *I. Prkačin*

Cilj ovog istraživanja bio je istražiti povezanost sistoličkog krvnog tlaka (SKT) i dijastoličkog krvnog tlaka (DKT) te dijabetičke retinopatije (DR) kod šećerne bolesti tipa 1 i tipa 2 te utvrditi razlike između ova dva tipa šećerne bolesti. Ova presječna studija uključila je 84 bolesnika sa šećernom bolešću tipa 1 (ŠB1) i 107 bolesnika sa šećernom bolešću tipa 2 (ŠB2). Oftalmološki pregled uključivao je neizravnu fundoskopiju, fotografiju fundusa u boji prema EURODIAB (EUROpe and DIABetes) protokolu i optičku koherentnu tomografiju. Krvni tlak izmjeren je živinim tlakomjerom nakon 10-minutnog mirovanja. Kod ŠB1 DR je bila pozitivno povezana sa SKT ($p = 0,035$), $HbA1c_{medijanom}$ ($p < 0,001$) i hipertenzivnom retinopatijom ($p < 0,001$), dok je u ŠB2 DR bila pozitivno povezana samo s $HbA1c_{medijanom}$ ($p = 0,021$). Analiza binarne logističke regresije (bez i sa DR) pokazala je da su trajanje šećerne bolesti i $HbA1c_{medijan}$ glavni prediktori DR u oba tipa šećerne bolesti. Međutim, SKT (OR = 1,05, $p = 0,045$) i hipertenzivna retinopatija (OR = 3,75, $p < 0,001$) bili su glavni prediktori/indikatori DR samo u ŠB1. Zaključno, krvni tlak je povezan s DR kod tipa 1, ali ne i kod tipa 2 šećerne bolesti.

Ključne riječi: *sistolički krvni tlak, šećerna bolest tip 1 i tip 2, retinopatija, čimbenici rizika*

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Original Scientific Paper

ARTERIAL HYPERTENSION FOLLOWING COVID-19: A RETROSPECTIVE STUDY OF PATIENTS IN A CENTRAL EUROPEAN TERTIARY CARE CENTER

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SUMMARY – The aim of this study was to determine the frequency of newly verified or worsened existing hypertension in patients who had coronavirus 2019 (COVID-19).

To be categorized as a COVID-19 patient, a positive reverse-transcription polymerase chain reaction test at a single point in time was required. The patients' age, history, laboratory values and antihypertensive therapy of patients were recorded.

In one year, 32 of 199 patients studied had either newly verified (15) or worsened existing (17) arterial hypertension. Among those patients, the median time from a verified infection to the onset of symptoms was 3 months. When the patients were divided into groups, 4 were in the acute, 11 in the sub-acute, 8 in the chronic and 9 in the "long COVID" group. Compared to the rest of the study population, patients presenting with arterial hypertension had significantly higher systolic (median 141 mmHg vs 130 mmHg, p<0.001) and diastolic (median 93 mmHg vs 80 mmHg, p<0.001) blood pressure and were significantly younger (median 51 vs 59 years, p 0.032).

Arterial hypertension following COVID-19, either newly verified or worsened existing, is a relatively common occurrence (16% of our patient pool), indicating that more effort should be directed at evaluating the blood pressure values of patients following COVID-19.

Keywords: arterial *hypertension, COVID-19 infection, post-Covid*

Introduction

Deep into the second year of the pandemic, having made great advancements in the diagnosis and treatment of coronavirus 2019 (COVID-19) in both outpatient and inpatient settings, the focus of research questions is slowly starting to shift toward the long-term consequences of infection with severe acute respiratory syndrome coronavirus (SARS-CoV-2). On February 11, 2020, the World Health Organization officially changed the name of the disease caused by SARS-CoV-2 to (COVID-19). With most of the research focus of the biomedical scientific community on researching the epidemiology, etiology, diagnosis and treatment of COVID-19, the actual global pandemic, much new information about the disease is now being obtained on a daily basis.

While it has been both hypothesized and proven that COVID-19, a virus with a strong tropism for ACE2 receptors, which are present in most of the organ systems of the human body, causes lasting changes on both a molecular and macroscopic level, the exact epidemiologic dynamics and clinical manifestations of post-COVID have not been sufficiently researched. Of all the post-COVID manifestations and symptoms described in the literature, arterial hypertension seems to have gotten the short end of the stick. Despite being a risk factor for nearly every adverse cardiovascular

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event, renal disease and end organ damage known, the threat and significance of arterial hypertension are often underestimated by clinicians. This pattern of overseeing one of the deadliest silent killers of today is unfortunately also noticeable in post-COVID research. While it has been established that COVID-19 can both cause "de novo" onset hypertension and worsen existing ones by interacting with both the RAAS[1] and endothelin[2] systems, a review of the literature describing the clinical aspects of the phenomenon produced sparse results, with the authors finding only a single survey[3], a retrospective review[4], and a case study[5] regarding hypertension related to COVID-19. The aim of this paper, therefore, is to provide a window into this under-researched topic by describing a patient population suffering from post-COVID hypertension seen and treated by the authors, describing both their general attributes (age or gender) and specific clinical entities (arterial blood pressure, laboratory values, antihypertensive therapy, and other clinical conditions with which they are affected).

Methods

In this retrospective study, which lasted from January 2021 to January 2022, 199 patients (92 males, 107 females, with a mean patient age of 57.3 years) who have had COVID-19 were analyzed at the Emergency Department and Hypertension Clinic in Clinical Hospital Merkur, a tertiary care center in Zagreb, Croatia.

According to the accepted definitions of COVID-19 and its manifestations in regard to the time from a positive reverse-transcription polymerase chain reaction (PCR) test, the patients were divided into two groups: acute COVID patients (PCR test positive <30 days ago) and post-acute COVID patients (PCR test positive >30 days ago). Additionally, the post-acute group was subdivided into the following groups: subacute (30-90 days from a positive PCR test), chronic (90-180 days from a positive PCR test) and "long COVID" (>180 days from a positive PCR test to symptom onset).[6]

The patients' laboratory test values, blood pressure, previous medical history, current therapy and history of COVID-19 were recorded and entered into a database. The inclusion criteria was a positive PCR test for COVID-19 at a single point in time, with a medical report of the test result required as proof. The authors excluded patients with an incomplete medical history, an inaccurate timeline of the course of their COVID-19 disease course progression and consequences, and patients with symptoms of a respiratory infection or other infection without a report of a positive PCR test.

The data was statistically analyzed in JASP, an open-source statistics software package using distributive statistics and independent variable t-tests, to determine the similarities and differences between patients presenting with arterial hypertension and those presenting with other manifestations of post-COVID.

Results

A total of 199 patients with symptoms and manifestations related to COVID-19, with proof of a positive COVID-19 or SARS-CoV-2 PCR test, were analyzed. Among these patients, 32 of them (16.08%) had either new onset arterial hypertension (15 patients) or a worsening of an existing hypertensive condition (17 patients) related to COVID-19. In the hypertensive group, there were 18 (56.25%) female and 14 (43.75) male patients with a mean age is 51 years. Regarding the time of symptom onset, the patients were divided into two groups: acute (4 patients, 2%) and post-acute COVID patients : sub-acute (11, 5.52%), chronic (8, 4%) and "long COVID" (9 patients, 4.52%). When comparing the hypertensive and non-hypertensive pa-

Table 1. Demographic data, median time from COVID diagnosis to symptom onset and blood pressure of patients from patient pool

	Male (n=92)	**Female** (n=107)	**Mean**
Age (years, median)	59	56	57.3
Number of hypertensive patients	14	18	16%
SBP (mmHg)	130	133	131.5
DBP (mmHg)	80	85	82.5
T2DM	10	12	11%
Time from positive PCR (months)	2	2	2

number (percentage).
SBP = systolic blood pressure; DBP = diastolic blood pressure; T2DM = type 2 diabetic patients, PCR = real-time reverse-transcription polymerase chain reaction, positive value determined at the beginning of the study from a single sample.

Table 2. Statistically significant different variables between the hypertensive and non-hypertensive patient group

	Hypertensive (n=32, 56.2 % F)	**Non-hypertensive** (n=167)	**p value**
Age (year)*	51.54±4.58	59.64±8.01	0.032
Time from positive PCR (months)*	3	1	0.014
SBP (mmHg)*	141.75±21.16	130.14±20.01	<0.001
DBP (mmHg)*	93.39±11.35	80.07±12.51	<0.001
Erythrocyte**	4.98	4.66	0.026
Hematocrit**	0.432	0.400	0.015

* mean ± SD ** number (percentage)
SBP = systolic blood pressure; DBP = diastolic blood pressure; PCR =real-time reverse-transcription polymerase chain reaction, time from positive test to symptom onset, value determined at the beginning of the study from a single sample. Erythrocyte = count ($*10^{12}$/L). Hematocrit (L/L).

tient groups, statistically significant differences were found for systolic blood pressure (median 141 mmHg HTN group vs 130 mmHg non-HTN group, p<0.001) and diastolic blood pressure (median 93 mmHg HTN group vs 80 mmHg non-HTN group, p<0.001), for age (median 51 years for hypertensive (HTN) vs 59 years for non-hypertensive (non-HTN), p 0.032), erythrocyte count ($4.98*10^9$ cells in HTN group vs $4.66*10^9$ cells in non-HTN group, p 0.026), and hematocrit (0.432 L/L in HTN group vs 0.40 L/L in non-HTN group, p 0.015). There were no significant differences between the groups in other laboratory parameters, diabetes (only type 2) or other medical history and body mass index (BMI). In patients with existing hypertension (17 patients) 82% (15/17) had antihypertensive therapy in combination with angiotensin-converting enzyme inhibitors (ACEI) and calcium channel blockers or ACEI/diuretic. Only 12% patients (2/17) had monotherapy with ACEI.

Time from a positive PCR test to symptom onset was a median 3 months in HTN group vs 1 month in non-HTN group.

Discussion

We are well acquainted with the fact that hypertension is a "silent killer," meaning that its consequences and severity are only felt in its late stages when end-organ damage has already ended, settled and become irreversible. We find it important to stress once again the necessity of follow-up exams for all patients following COVID-19. [7,8] Considering the high infectivity rate of the virus and the number of people testing positive on both rapid antigen (RATs) and PCR tests daily, the question of the need for a post-COVID follow-up arises. The papers found during the authors' literature search on the topic of post-COVID hypertension estimated the incidence of arterial hypertension following COVID-19 to be between 9 and 12% [5,9]. Our results suggest that, in a sample of 200 patients, the incidence is about 16%, and it is a relatively common occurrence. More effort should be directed to evaluating patients' blood pressure values following COVID-19 to make a timely diagnosis and start proper treatment as early as possible.

To generalize the results in this paper for the general population, approximately 1 in every 7 people infected by Covid-19 is at risk of developing either new onset hypertension or having an exacerbation and worsening of an existing hypertensive condition. Even if we consider that one of the departments included in this study is a hypertension clinic (even though less than one-fourth of our patient data came from that clinic), which we expected to skew mildly the results in favor of a larger incidence of hypertension, there is a real possibility that more than 10% of the general population is going to be affected by post-COVID hypertension, many of them undetected, especially among patients with no prior conditions in their medical histories. Since the mean time from a positive PCR test to the onset of hypertension in our studied population was approximately four and a half months, and the mean time to the onset of all other manifestations is three months, we suggest that follow-up physical ex-

ams, preferably by the patient's primary care practitioner (PCP), including measuring blood pressure, blood glucose values and serum creatinine, be done 30, 90 and 180 days after a positive PCR test.

Giménez-Miranda, et al. propose to measure endothelial function 6–12 months after an acute Covid-19 infection in hypertensive patients, especially if they have other vascular disease.[10] Pulse wave velocity is the measure of arterial stiffness, which is directly connected to cardiovascular risk and hypertension-mediated organ damage. In future research on the detection of endothelial disfunction in Covid-19 patients, we recommend measure pulse wave velocity, which we carried in patients with a hypertensive crisis.[11]

In conclusion, post-COVID arterial hypertension is a real and serious consequence of a COVID-19 infection, affecting 1 in every 6 patients in our studied population, most often among women. While we found no laboratory markers that we can confidently use to predict arterial hypertension following COVID-19, we hope that the time frames provided in this paper - especially that for a positive PCR test to the onset of post-COVID symptoms - can help to provide a framework for sensible and adequate follow-up patient examinations after acute COVID-19, in order to make a timely diagnosis of any post-COVID sequelae and begin treatment before they develop into more serious conditions and syndemic problems.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

The authors state that this manuscript has not been published previously and is not currently being assessed for publication by any journal other than the Acta Clinica Croatica. The authors disclose that they did not receive any financial support for the study. No proprietary interest was involved in the study.

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Sažetak

ARTERIJSKA HIPERTENZIJA VEZANA UZ COVID-19 INFEKCIJU; RETROSPEKTIVNA STUDIJA U SREDNJE EUROPSKOM TERCIJARNOM CENTRU

Đ. Delalić, J. Jug i *I. Prkačin*

Pojavnost novoverificirane hipertenzije ili pogoršanje postojeće u pacijenata koji su preboljeli Covid-19 cilj je ove studije. Kako bi potvrdili da je pacijent bio kategoriziran kao Covid pacijent, morao je imati pozitivan PCR test.

Pacijenti su podijeljeni u grupe akutni i postakutni Covid. Analizirani su podaci vezani uz dob, indeks tjelesne mase, laboratorijske parametre, raniju medicinsku dokumentaciju te postojeću antihipertenzivnu terapiju.

U periodu od godinu dana obrađeno je 199 pacijenta koji su imali sve uključne kriterije. Od njih je u 32 (16%) utvrđena hipertenzija: u 15 s novoverificiranom hipertenzijom a u 17 pacijenata s pogoršanjem postojeće hipertenzije. Pojavnost hipertenzije bila je prema medijanu 3 mjeseca nakon potvrđene Covid-19 infekcije. Kada smo podijelili pacijente prema grupama: 4 pacijenta je bilo unutar akutnog perioda, 11 u subakutnom, 8 u kroničnom, a 9 pacijenata s hipertenzijom je bilo u grupi dugog (long) COVID-a. Populacija s hipertenzijom u odnosu na one koji nisu imali hipertenziju, imala je značajno viši sistolički (median 141 mmHg prema 130 mmHg, p<0.001) i dijastolički (median 93 mmHg prema 80 mmHg, p<0.001) krvni tlak. Utvrđena je statistički značajna razlika i prema dobi između skupine hipertoničara i nehipertoničara (median 51, prema 59 godina, p 0.032). Pojavnost hipertenzije nakon Covid-19 infekcije nije rijetka.

Ključne riječi: *arterijska hipertenzija, COVID-19 infekcija, post Covid*

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Professional Paper

DIAGNOSTIC VALUE OF CARDIAC ULTRASOUND IN ESTIMATING THE DURATION OF ARTERIAL HYPERTENSION

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SUMMARY – The aim of the study was to assess the correlation between the degree and duration of arterial hypertension and the hypertrophy of the left ventricle and the ejection fraction of the heart, with cardiac ultrasound. Our prospective study included 50 patients with arterial hypertension as leading diagnosis. All 50 patients were consecutively examined in the Emergency Department and then referred to the Cardiac clinic of the Clinical Hospital "Sveti Duh" for further evaluation. The inclusion criteria were male and female aged 18 and older and arterial hypertension as leading diagnosis during Emergency Department visit. Exclusion criteria were pathological conditions that alter myocardial architecture and impair contractility. Measurement of the left ventricle thickness based on the thickness of the intraventricular septum and the posterior wall of the left ventricle, and the ejection fraction was ultrasonically determined. The highest proportion of subjects was with the first degree of arterial hypertension, followed by subjects with a third degree. The average duration of arterial hypertension was 6.14 years. Of the total number of subjects, 28% did not take any antihypertensive drugs. A statistically significant association was found between the degree and duration of arterial hypertension with the development of left ventricular hypertrophy. Significant association wasn't found between the degree or duration of arterial hypertension and the heart ejection fraction. Our study have shown strong correlation between the degree and duration of arterial hypertension and the development of left ventricular hypertrophy and ultrasound could be a useful method in the evaluation of some patients with arterial hypertension in the emergency department.

Key words: *arterial hypertension, left ventricular hypertrophy, ejection fraction, ultrasound, emergency department*

Introduction

Arterial hypertension (AH) is one of the leading public health problems and a major independent risk factor for cardiovascular morbidity and mortality[1]. According to the latest classification criteria of the European Society for Arterial Hypertension (ESH) and the European Society of Cardiology (ESC) from 2018, arterial hypertension is defined by values of systolic arterial pressure ≥ 140 mmHg and/or diastolic arterial pressure ≥ 90 mmHg measured by calibrated mercury pressure gauge[1,2,3]. The total prevalence of arterial hy-

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pertension is about 30-45% of the total population, and it grows proportionally with the increase in age[1]. HBP is thought to be responsible in 18% of all deaths[4]. In most of the cases (85-95%) it is essential hypertension with a previously unknown cause, while in 5-15% of the cases it is secondary hypertension[2]. Hypertension is usually asymptomatic until complications develop on the target organs[5,6]. Diagnosis of arterial hypertension involves taking an detailed history-anamnesis, physical examination and laboratory tests. We can divide the diagnostic procedure itself into three steps: determining the height of the blood pressure, assessing the total cardiovascular risk and detecting secondary causes of hypertension[7]. High blood pressure (HBP) is the main risk factor for coronary heart disease, cerebrovascular disease, peripheral artery disease and chronic and final stage kidney disease[2,3]. Therefore, the height of blood pressure (BP) and the duration of arterial hypertension are important[4]. Arterial hypertension of the systemic bloodstream causes pressure load and left ventricular hypertrophy (LVH). LVH represents an important clinical entity because it is associated with an increased risk of cardiac failure, ventricular arrhythmias, development of myocardial infarction, reduction of ejection fraction (EF), sudden cardiac death, dilatation of aortic root and cerebrovascular event occurrence[8,9]. The LVH echocardiographically established and the reduced ejection fraction (EF) are independent predictors of adverse cardiovascular events[10]. Hypertension is considered a lifelong disease and a unique therapeutic problem. If the conservative approach (hygienic-dietary measures, lifestyle changes) proves ineffective, it is switched to pharmacological treatment[11].

Subjects and methods

A prospective study included 50 patients with arterial hypertension as leading diagnosis. All 50 patients were consecutively examined in the Emergency Department and then referred to the Cardiac clinic of the Clinical Hospital "Sveti Duh" for further evaluation. The inclusion criteria were male and female aged 18 and older and arterial hypertension as leading diagnosis during Emergency Department visit. Exclusion criteria were pathological conditions that alter architecture and impair heart contractility (dilative cardiomyopathy, severe aortic stenosis, myocarditis, primary amyloidosis, etc.). The research was approved by the Ethics Committee of the Clinical Hospital "Sveti Duh".

We measured the left ventricle wall thickness (LVWT), based on the thickness of the intraventricular septum (IVS) and the thickness of posterior wall of the left ventricle (LVPW) expressed in centimeters (cm) and the ejection fraction (EF) with the cardiac ultrasound GE Vivid E9. With the specified ultrasonic indicators we compared the degree and the duration of arterial hypertension.

Statistical methods

The statistical package SPSS 23.0 (IBM Corp., Armonk, NY) was used for data analysis. The distribution of subjects is presented using descriptive statistics, i.e. arithmetic environments with the corresponding standard deviations and the lowest and highest achieved result. Categorical variables are presented as frequencies at the corresponding percentages. To calculate the correlations of continuous variables, the Pearson correlation coefficient was used, while Spearman coefficient was calculated on data of ordinal nature. Statistical inference was carried out at levels 5% and 1%.

Results

A total of 50 participants participated in the survey, twenty-six were female (52%). The average age of the participants was 58.70±13.37 years. The average duration of HBP was 6.14±5.50 years. According to the degree of classification of arterial hypertension[1,2], the highest proportion were subjects with the first degree of hypertension (44%), followed by subjects with a third degree (36%), and the smallest have the second stage of arterial hypertension (20%). Of the total number of subjects, 14 of them or 28% did not take any antihypertensive drugs, respectively. In terms of ultrasonic indicators, the ejection fraction in our study averaged 64.20±8.07. According to the classification criterion, this value is normal if it is 55% or more[12], and in our study 47 subjects of 50 (94%) had a normal ejection fraction. According to clear cardiac criteria, the thickened IVS wall is > 1.2 cm for men, or > 1.1 cm for women[12], and in our study it was found that the IVS wall is thickened in just over half of our subjects (N=27). According to the same cardiac criteria, we found that 30% of our sample (N=15) had a thickened posterior wall of the left ventricle, or 41.7% of men

compared to 19.2% of women (Table 1.). From the table of correlations (Table 2.), we note that there is a statistically significant but weak negative correlation of the ejection fraction with the thickness of the left ventricle IVS (r=-0.29, p<0.05). The value of IVS showed a significant statistical correlation with the degree of arterial hypertension (r=0.27, p<0.05), with the thickness of IVS and growing with a higher degree of HBP. Furthermore, a moderate significant correlation between the variables LVPW and the duration of arterial hypertension have shown that a higher thickness of LVPW is associated with a longer duration of arterial hypertension (r=0.34, p<0.05). There is significant positive interdependence between left ventricular hypertrophy (LVH) and LVWT IVS (r=0.74, p<0.01) and LVWT LVPW (r=0.66, p<0.01). HBP therapy (defined solely as exists/does not exist), is moderately highly associated with duration of HBP (r=0.47, p<0.01). There is a statistically significant positive correlation between grade of arterial hypertension and the development of left ventricular hypertrophy (r=0.30, p<0.05). The probability of developing LVH increases with an increase in BP. There is no statistically significant association between the degree of arterial hypertension or the duration of HBP with the heart ejection fraction (p>0.05).

Discussion

The study has shown that arterial hypertension is more common in females (52% vs. 48% in men), what correlates with the literature[3,4]. Regarding age distribution, our research results are consistent with the searched literature[2,3]. Our research has shown that a higher proportion of patients is with high blood pressure levels. A higher proportion of persons with a third degree of HBP, i.e. pressure values ≥ 180/110 mmHg could be explained by the fact that a small number of people are aware of their disease. A study conducted in 2003 in Croatia showed that more than 50% of patients were unaware of their illness, 48.4% received treatment, and in only 14.8% of patients achieved satisfactory pressure value[13]. There is a clear correlation between grade of arterial hypertesion and its duration with the onset of cardiovascular diseases and incidents,

Table 1. Indicators of LVWT IVS and LVWT LVPW according to cardiac criteria

	LVWT IVS category number of patients N (%) thickened	LVWT LVPW category number of patients N (%) thickened
altogether	27 (54%)	15 (30%)
males (N=24)	12 (50%)	10 (41.7%)
females (N=26)	15 (57.7%)	5 (19.2%)

LVWT – left ventricular wall thickness, IVS – intraventricular septum, LVPW – left ventricular posterior wall.

Table 2. Correlations EF, LVWT IVS, LVWT LVPW, degree, duration and therapy of HBP

	EF (%)	LVWT IVS	LVWT LVPW	duration of HBP	degree of HBP	LVH	therapy of HBP
EF (%)	1	-0.29*	-0.22	-0.04	-0.13	-0.12	0.05
LVWT IVS		1	0.839**	0.23	0.27*	0.74**	0.03
LVWT LVPW			1	0.34*	0.21	0.66**	0.16
duration of HBP				1	-0.08	0.13	0.47**
degree of HBP					1	0.30*	-0.25
LVH						1	0.05
therapy of HBP							1

* p<0.05; ** p<0.01
EF-ejection fraction, LVWT-left ventricular wall thickness, IVS-intraventricular septum, LVPW-left ventricular posterior wall, HBP-high blood pressure/arterial hypertension, LVH-left ventricular hypertrophy

while the value of blood pressure and the duration of arterial hypertension is important[4,10,14]. Our research shows that the degree and duration of HBP led to an increase in the left ventricle wall thickness. Those data are important since the literature states that LVH is one of the most important predictors of adverse cardiovascular events[10]. The prevalence of LVH in hypertensive patients ranges from 36 to 41%[15] which is slightly lower than our score, according to which 54% of subjects had LVH. According to the Framingham Heart Study[16], LVH is often found in the early stages of the disease, which was also observed in our study where the average duration of HBP with signs of LVH was 6.14 years. The study showed that thickening of the left ventricle wall is directly related to the progression of hypertension, and the authors conclude that ultrasonic measurement of LV wall thickness could help determine patients in need of antihypertensive therapy[16]. Laufer E[17] points out in his paper that ultrasonic measurement of LV wall thickness alone can prove LVH in 80% of patients with newly discovered hypertension, although more significant is calculation of the mass of LV in the assessment of patients with left ventricular hypertrophy. The results of our study have shown strong correlation between the degree and duration of arterial hypertension and the development of left ventricular hypertrophy.

As a conclusion, ultrasound could be a useful method in the evaluation of some patients with arterial hypertension in the emergency department. However, this research should continue and be carried out on a larger number of subjects in order to increase the statistical and clinical significance of the use of ultrasound as a fast method of assessing the two indicators investigated (LVWT and EF) in the emergency department.

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Sažetak

DIJAGNOSTIČKA VRIJEDNOST ULTRAZVUKA SRCA U PROCIJENI TRAJANJA ARTERIJSKE HIPERTENZIJE

N. Kočet, D. Rošić, V. Nesek Adam, M. Matolić, M. Svetec i *A. Simić*

Cilj istraživanja je bio uz pomoć ultrazvuka srca procijeniti povezanosti između stupnja i duljine trajanja arterijske hipertenzije te razvoja hipertrofije lijeve klijetke i istisne frakcije srca. Provedeno je prospektivno istraživanje koje je uključivalo 50 bolesnika sa arterijskom hipertenzijom kao vodećom dijagnozom. Svih 50 bolesnika je uzastopno pregledano u Objedinjenom hitnom bolničkom prijamu, a nakon toga upućeno u kardiološku ambulantu Kliničke bolnice „Sveti Duh" na daljnju obradu. U istraživanje su bili uključeni bolesnici stariji od 18 godina, oba spola, s vodećom dijagnozom arterijske hipertenzije postavljene u Objedinjenom hitnom bolničkom prijamu dok su iz istraživanja bili isključeni bolesnici s patološkim stanjima koja mijenjaju arhitekturu i narušavaju kontraktilnost srca. Ultrazvučno se određivala debljina stijenke lijeve klijetke sačinjena od debljine intraventrikularnog septuma i stražnje stijenke lijeve klijetke te istisna frakcija. Najveći udio ispitanika bio je s prvim stupnjem, a slijedili su ih ispitanici s trećim stupnjem arterijske hipertenzije. Prosječno trajanje arterijske hipertenzije iznosilo je 6.14 godina. Od ukupnog broja ispitanika, 28% nije uzimalo nikakve antihipertenzivne lijekove. Pronađena je statistički značajna povezanost između stupnja i duljine trajanja arterijske hipertenzije s razvojem hipertrofije lijeve klijetke. Nije pronađena značajna povezanost stupnja niti duljine trajanja arterijske hipertenzije s istisnom frakcijom srca. Naša studija pokazala je snažnu povezanost između stupnja i duljine trajanja arterijske hipertenzije i razvoja hipertrofije lijeve klijetke, a ultrazvuk bi mogao biti korisna metoda u procjeni nekih bolesnika s arterijskom hipertenzijom u hitnoj službi.

Ključne riječi: *arterijska hipertenzija, hipertrofija lijeve klijetke, istisna frakcija, ultrazvuk, hitna služba*

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Professional Paper

DIAGNOSIS OF PULMONARY EMBOLISM IN THE EMERGENCY DEPARTMENT

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SUMMARY – The aim of this study was to determine the association of clinical presentation, the Wells scoring system and D-dimer values with MSCT pulmonary angiography. A case control study was conducted in the Emergency Department of the Clinical Hospital Sveti Duh throughout 2019. Patients with a referral diagnosis of a pulmonary embolism were included in the study. Patients were divided into two groups. The first group consisted of patients diagnosed with pulmonary embolism by MSCT pulmonary angiography or *postmortem*, and the second group consisted of patients excluded from pulmonary embolisms. For the Wells score, D-dimers, troponin, respiratory rate and peripheral blood oxygen saturation, statistically significant differences were found between groups of patients with confirmed or excluded pulmonary embolism ($p < 0.001$). For heart rate, chest pain, syncope, and hemoptysis, no statistically significant differences were found between these two groups of patients. Deep venous thrombosis of the lower extremities was found by ultrasound in > 70% of patients with massive a pulmonary embolism. Pulmonary embolism was confirmed in all patients for whom a high risk was calculated according to the Wells score. In conclusion, a low degree of clinical probability (according to the Wells score), along with a normal concentration of D-dimer, are a sure strategy in excluding pulmonary embolism.

Keywords: pulmonary *embolism, Wells score, D-dimers, MSCT pulmonary angiography, emergency medical service*

Introduction

Venous thromboembolism is a clinical entity that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Pulmonary embolism is an emergency caused by sudden obstruction of the pulmonary circulation by a blood clot. It represents a serious diagnostic - therapeutic challenge in emergency and intensive care units. It is the third most common cardiovascular disease with an estimated incidence of 100 – 200: 100.000 inhabitants.[1,2] Thromboembolus most commonly originates from the veins of the lower extremities and pelvis. A thrombus forms in a vein, and when mobilized it travels through the venous system and the right heart and reaches the pulmonary arteries, where it partially or completely clogs one or more branches. The clinical presentation depends on the degree of involvement of the pulmonary circulation, and patients are most often presented with dyspnea, tachypnea, chest pain, fainting or complete loss of consciousness.[3–5] PE may remain unrecognized and undiagnosed due to a nonspecific clinical presentation.[6] In addition to the anamnesis and physical examination, which are most important in establishing clinical suspicion of PE, we also used the calculation of the Wells scoring system and the laboratory value of D-dimer. There are

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diagnostic algorithms that assess the risk of suspected pulmonary embolism and determine further diagnostic and therapeutic procedures. The final diagnosis is made by MSCT pulmonary angiography, which is the diagnostic gold standard. Ultrasound of the right heart and/or ultrasound detection of deep vein thrombosis in the veins of the lower limbs or pelvic veins also play an important role.[7,8] Treatment is initiated by correction of hypoxemia and hypovolaemia and anticoagulant or thrombolytic therapy, depending on the clinical presentation of PE. If treatment is with anticoagulants, unfractionated or low-molecular-weight heparin and vitamin K antagonists or direct oral anticoagulants are most commonly used.

Subjects and methods

The study included patients with a pulmonary embolism, who were examined in the ED (Internal Medicine Clinic) of the Clinical Hospital Sveti Duh from January to the end of December 2019. A case control study was conducted and patients were divided into two groups based on the findings. After the anamnesis was taken and a physical examination conducted, the patients had an electrocardiogram, blood was taken for laboratory tests, and they were then sent for X-rays of the heart and lungs. Based on the clinical presentation, Wells scoring system, and elevated D-dimer values, PE was suspected in 305 patients. The final diagnosis of pulmonary embolism was confirmed by MSCT pulmonary angiography. Ultrasound diagnostics was performed with the aim of detecting deep venous thrombosis. The research was approved by the Ethics Committee of Clinical Hospital Sveti Duh.

Statistical methods

SAS 9.1 software, licensed for the University Computer Center (SRCE, site: 0082452005), was used in the analysis. Distributions of quantitative data analyzed for normality by the Smirnov-Kolmogorov test showed that the distribution is not normal, except for heart rate data. Therefore, nonparametric and parametric analytical procedures were used in the analysis for heart rate data (conventional measures of descriptive statistics and t-test). Distributions are described by standard measures of descriptive statistics (median (M) minimum (min) and maximum value (max) and interquartile range (IQR)). They were analyzed by the Kruskall-Wallis test. Distributions of qualitative data were analyzed by $\chi 2$ test and Fisher 's exact test. The results were interpreted at the 5% level of significance.

Results

During 2019, 22.252 patients were examined at the Emergency Department (internal medicine clinics) of the Clinical Hospital Sveti Duh; and 305 of them were suspected of having a pulmonary embolism. In 149 patients, a diagnosis of PE was made, which is a frequency of 0.7%. In the remaining 156 patients, the diagnosis of PE was ruled out. The majority of patients (> 80%) were over 60 years old. Approximately 60% of the patients were female.

For the Wells score, D-dimers, troponin and respiratory rate, statistically significant differences were found between the groups of patients who were confirmed or excluded from the diagnosis of PE ($p < 0.001$) (Table 1). Peripheral blood oxygen saturation was statistically significantly lower in the group of patients with confirmed PE (Table 2). Regarding heart rate, no statistically significant difference was found between the examined groups. The most significant risk factors for pulmonary embolism in our study were: immobilization (32.89%), malignancy (17.45%), major surgery (8.72%) and previous DVT / PE (5.37%). Deep venous thrombosis of the lower extremities was also

Table 1. Review of examined indicators and their statistical significance

Indicators	**confirmed PE**	**excluded PE**	**p**
	median (25th and 75th)	median (25th and 75th)	
Wells score	5,5 (4,5-7)	1,5 (0-2,5)	<0,001
D-dimers	4264 (4189-4327)	4078 (1654-4327)	<0,001
troponin	60 (17-239)	27 (10-104)	<0,001
respiratory rate	91 (86-95)	94 (90-97)	<0,001

Table 2. Distribution of examined clinical signs / symptoms

	Pulmonary embolism	
	Confirmed	**Excluded**
chest pain	72 (48,32%)	65 (41,67%)
syncope	34 (22,82%)	32 (20,51%)
hemoptysis	2 (1,34%)	7 (4,49%)
SpO2 < 90%	72 (48,32 %)	39 (25%)

Table 3. Incidence of pulmonary embolism according to Wells score

		Proven pulmonary emboly		
	Risk	**Yes**	**No**	**Total**
WELLS score	<2 low	3	117	120
	2-6 medium	108	39	147
	>6 high	38	0	38
Total		149	156	305

found by ultrasound in > 70% of patients with massive pulmonary embolism. In all patients (100%) for whom a high risk was calculated according to the Wells score (> 6 points), PE was confirmed, while in 97.5% of patients who were excluded from the PE, the Wells score showed a low risk (<2 points). The differences found were statistically significant ($\chi 2$ (2) = 178.19, p <0.001; $\chi 2$ test) (Table 3). The odds ratio (OR) showed that patients with medium and high Wells scores were 47 times more likely to develop pulmonary embolism than the low score group, OR = 47.77, p <0.001 (95% CI: 22, 28, 102.44).

In 48.85% of patients (149/305) MSCT pulmonary angiography confirmed the diagnosis of PE, which is almost every second patient who is suspected of PE based on the clinical presentation, Wells score and D-dimer.

Discussion

The obtained results showed a frequency of PE of 0.7%, which corresponds to the literature data. A retrospective analysis based on several international databases found a prevalence of PE of less than 1%. According to Valle et al., the incidence of PE in the emergency department was 1.01 per 1,000 patients.[9] In our study, > 80% of the patients were over 60 years old and about 60% of them were women, while the results of the same authors show that the average age of respondents was 72 years, and 58% were women. As many as 72% of respondents were over 65 years old. [9,10] Among the conclusions of the searched literature, it is stated that PE is more often diagnosed in women and elderly patients due to associated diseases and risk factors that increase with age. The calculation of the Wells scoring system and the value of D-dimer proved to be a good diagnostic strategy in the exclusion of PE. However, in our study, as evidenced by the literature, D-dimers did not prove effective in differentiating the severity of the clinical picture.[11] The group of authors states that the negative predictive value of D-dimer (<500 ng / ml) was 93.7%, and in combination with the Wells score (for risk ≤ 4) 100%.[12,13.14] According to Pasha et. al. the incidence of low-risk PE morbidity based on the Wells score and normal D-dimer concentration is 0.34% with a negative predictive value of 99.7%.[14,15] The sensitivity of D-dimers is 95%, while their specificity is about 50%. MSCT pulmonary angiography is the diagnostic gold standard, with a sensitivity of 83% and a specificity of 96%.

According to the literature, the most common symptoms/signs of the disease were also dyspnea, chest pain and syncope. However, in our study syncope was a more frequent sign of suspected PE (20%: 9%). [9,15–17] According to Akbas et. al. the mean value of respiratory rate was 28/min, the mean value of blood oxygen saturation was 88% (without oxygen compensation), while the mean value of the heart rate was 88.5/min.[18] For heart rate, no statistical significance was shown in our study in relation to the group of patients who were excluded from the diagnosis of PE. According to the literature consulted, dyspnea was present in more than 70% of patients in our study. Regarding risk factors, malignancy, immobilization, major surgery and previous PE were most often mentioned, which is evident from our research.

Thus, the diagnosis of PE is often difficult due to non-specific clinical presentation and it is extremely important to set the initial suspicion of this disease in time. A detailed clinical examination and anamnesis, supplemented by the calculation of the Wells score and the laboratory value of D-dimer, can establish the clinical suspicion of PE.

Ultrasound also plays an important role in the early and rapid detection of patients with signs of shock.

In conclusion, low risk according to the Wells score together with normal D-dimer concentration is a reliable strategy in excluding pulmonary embolism.

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Sažetak

DIJAGNOSTIKA PLUĆNE EMBOLIJE U OBJEDINJENOM HITNOM BOLNIČKOM PRIJAMU

D. Rošić, N. Kočet, A. Simić, I. Prkačin i V. Nesek Adam

Cilj rada je bio utvrditi povezanost kliničke slike, Wellsovog bodovnog sustava i vrijednosti D-dimera s MSCT plućnom angiografijom. Provedena je studija istraživanja parova u Objedinjenom hitnom bolničkom prijamu Kliničke bolnice „Sveti Duh" tijekom cijele 2019. godine. U istraživanje su bili uključeni bolesnici sa uputnom dijagnozom plućne embolije. Bolesnici su podijeljeni u dvije skupine. U prvoj su skupini bili bolesnici kojima je dijagnoza plućne embolije potvrđena MSCT plućnom angiografijom ili *post mortem*, a drugu skupinu su činili bolesnici kod kojih je isključena plućna embolija. Za Wellsov skor, D-dimere, troponin, frekvenciju disanja i perifernu zasićenost krvi kisikom nađene su statistički značajne razlike između skupina bolesnika s potvrđenom, odnosno isključenom plućnom embolijom ($p<0,001$). Za frekvenciju srca, bol u prsima, sinkopu i hemoptizu nije nađena statistički značajna razlika između ove dvije skupine bolesnika. U >70% bolesnika s masivnom plućnom embolijom ultrazvučno je nađena duboka venska tromboza donjih ekstremiteta. Kod svih bolesnika kojima je prema Wellsovom bodovnom skoru izračunat visok rizik potvrđena je plućna embolija. Zaključno, niski stupanj kliničke vjerojatnosti (prema Wellsovom bodovnom skoru) zajedno s normalnom koncentracijom D-dimera sigurna su strategija u isključenju plućne embolije.

Ključne riječi: *plućna embolija, Wellsov skor, D-dimeri, MSCT plućna angiografija, hitna medicinska služba*

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Professional Paper

OUTPATIENT TREATMENT OF PULMONARY EMBOLISM – A SINGLE-CENTER EXPERIENCE

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SUMMARY – *Background:* Pulmonary embolism (PE) is a common diagnosis in an emergency department. It also represents a large share of patients admitted to hospital wards. Patients with PE can be risk-stratified and discharged early from the emergency department. This results in better availability of hospital beds for other patients and a significant reduction of treatment costs for the healthcare system. This paper aims to describe the protocols used in our emergency department, with special emphasis on risk stratification, for adverse events and bleeding risk, treatment strategies, and outcomes for this type of protocol.

Materials and methods: This paper is a retrospective analysis of patients discharged from the emergency department in a of two-year period (2020-2021) with a low-risk pulmonary embolism.

Results: We have included in this study 42 patients discharged after a short-term observation from the emergency department (<24h) or short-term hospitalization; <24h). Ninety-one percent of patients were discharged with direct oral anticoagulant as a treatment for PE. We did not notice any adverse events (hemorrhage, progression of PE, or major cardiovascular issues).

Conclusion: In the cohort of patients with PE, early discharge and outpatient treatment was safe and effective, with lower healthcare costs and almost no adverse events for patients

Key words: *pulmonary embolism, emergency department, early discharge, outpatient treatment*

Introduction

Pulmonary embolism (PE) is a common diagnosis encountered by physicians working in the emergency department. In the United States, approximately two million patients are diagnosed with pulmonary embolism or deep vein thrombosis each year[1]. There is no clear data on the incidence in the literature in Croatia. Until recently, every patient with deep vein thrombosis and pulmonary embolism was admitted to the inpatient ward. In the last six years, in most cases (78.6%), patients with deep vein thrombosis have been discharged for outpatient treatment at the University hospital center Zagreb[2]. Such treatment strategy can lead to significant savings for the health care system and has reduced the average costs at the emergency department (ED) of UHC Zagreb for the treatment of patients with DVT by approximately 50%[2]. Diagnostic procedures and treatment of pulmonary embolism are also a major burden on the health system, and the diagnosis itself has almost always been an indication for hospitalization[3]. In the last few years, there have been more and more papers describing the safety and usefulness of PE treatment in outpatient settings, although this concept has been known for more than the last 20 years. In the last 8 years, with studies that have proven the safety of treating pulmonary embolism with direct anticoagulants, and after introducing the recommendation of such treatment in the ESC guidelines, more and more centers have adopted such a treatment protocol. Various validated clinical tools are used to assess the risk of pulmonary embolism: HESTIA score[5]; simplified pulmonary embolism severity score (sPESI)[6] and pulmonary embolism severity score (PESI)[7]. Meta-analyzes have confirmed that

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outpatient treatment of pulmonary embolism is safe for patients[4].

This study aims to describe the population, diagnostic process, risk assessment, therapeutic options, and complications of outpatient treatment of pulmonary embolism at ED UHC Zagreb.

Methods

We retrospectively analyzed patients discharged from the emergency department or hospitalized for a maximum of one day in one of the departments of the University Hospital Center Zagreb, in the period from 1.1.2020. until 31.12.2021. The average annual number of patient visits at ED UHC Zagreb is about 100,000. The patients included in this analysis are adults (> 18 years of age) who were either examined in the emergency department and discharged with a diagnosis of pulmonary embolism after short-term observation (up to 24 hours) or were hospitalized in one of the hospital wards and discharged to home care within 24 hours of admission to the hospital. Patients excluded from the analysis were patients who were treated for a long time in the wards of UHC Zagreb or died during emergency treatment, or we could not obtain data on patients. Patient data from the Hospital Information System (BIS) of the University Hospital Center Zagreb were analyzed. The process itself was structured so that one researcher sought data on patients who could be included in the analysis, and another, a senior researcher, checked the data and made an analysis of the data obtained. The data included in the analysis were previously agreed upon and standardized before the beginning of the analysis. The data we analyzed were general patient data, clinical features of the disease, diagnostic procedures, risk quantification process for potential outpatient treatment, complications, and returns to the emergency department after discharge, for up to a total of two years after the first patient was discharged. All patients who entered this analysis underwent CT pulmonary angiography as a method of confirming the diagnosis of pulmonary embolism, in ED itself; or patients reported to ED with CTA report. The risk assessment tools - HESTIA score, PESI score, sPESI score, and the VTE-BLEED bleeding risk assessment tool - were also retrospectively analyzed. In addition, the therapy prescribed to the patient upon discharge was registered as well as potential complications that occurred after the patient was discharged from the hospital, for a total of up to 6 months after discharge.

All analyzes were performed in MedCalc 14.1. The results are presented as absolute and relative frequencies and median with interquartile range (IQR).

Results

Demographic characteristics of patients

This analysis included 42 patients who were discharged from the University Hospital Center Zagreb and treated according to the protocol for the treatment of pulmonary embolism in outpatient settings. The total number of patients diagnosed with pulmonary embolism in the two years was 457. 9.2% of patients were treated in outpatient settings. The mean age of the patient was 54 years, ranging from 42-72 years, and the proportion of women was 57.1%. Of these patients, 19 (45.2%) had a history of COVID-19 infection. Other demographic data, as well as previous diseases that are important in the treatment of these patients, are listed in Table 1.

Table 1. Demographic characteristics of patients

Variable	Number	Percentage
Age (in years)	54 (42-72)	/
Female sex	24	57.1%
Male sex	18	42.9%
Previous history of pulmonary embolism	8	19%
Previous history of deep vein thrombosis	9	21.4%
Hypertension	17	40.5%
Coronary heart disease	7	16.7%
Heart failure	6	14.3%
History of malignancy	12	28.6%
History of COVID-19	19	45.2%

Clinical characteristics of the patients

The predominant symptom experienced by the patients included in the study was shortness of breath, which occurred in 47.6% of patients. Patients had a normal heart frequency (median pulse 81/min (range 75-94) and normal respiratory rate (respiratory rate 16/min (range 12-18 / min). Oxygen saturation was nor-

Table 2. Clinical characteristics of patients

Variable	Number	Percentage
Chest pain	19	45.2%
Shortness of breath	20	47.6%
Elevated body temperature	6	9.5%
Swelling of the leg	4	6.5%
Syncope	2	4.8%
Palpitations	5	11.9%
Heart rate (min-1)	81 (75-94)	/
Respiratory rate (min-1)	16 (12-18)	
Blood pressure (systolic value)		
<100mmHg	3	3.14%
100-120mmHg	9	21.43%
120-140mmHg	14	33,33%
140-160mmHg	11	26,19%
>160mmHg	5	11.9%
Oxygen saturation (%)	97 (96-97)	/
D-dimers	2.4 (1.6-4.6)	/
NTproBNP	156 (117-509)	/
Troponins (hsTnI)	5 (3-11)	/
CT angiography of the lungs		
Large vessels	2	4.76%
Lobar branches	6	14.29%
Segmental branches	15	35,71%
Subsegmental branches	12	28,57%
Bilateral pulmonary embolism	7	16.67%
Ultrasound of the heart		
Significant RV disfunction	0	0
Mild RV disfunction	7	16.67%
No RV disfunction	35	83,33%
Ultrasound of the leg veins		
Proximal DVT	2	4.76%
Distal DVT	11	26,19%
Without DVT	29	69,05%
Arterial blood gas analysis		
Normal findings	40	95,24%
Respiratory alkalosis	2	4.76%

mal in all patients. The median d-dimer level in patients was 2.4 micromoles / mL (range 1.6-4.6 micromoles / mL) The median NTproBNP level was 156 pg/mL (ranging between 117 and 509.) All patients analyzed were diagnosed with CT pulmonary angiography, 35.71% of patients had a segmental pulmonary embolism. It was interesting to note that 7 (16.67%) patients had a bilateral pulmonary embolism. All patients underwent cardiac ultrasound, which was normal in 83.33% of patients. All patients were examined with color doppler of leg veins, in 4.76% of patients we found proximal deep vein thrombosis, and in 26,9% of cases distal deep vein thrombosis. Analysis of arterial blood gases in the majority of patients was normal. Clinical characteristics of patients are shown in Table 2.

Assessment of severity of pulmonary embolism and assessment for the risk of bleeding

Several validated tools were used to assess the severity of pulmonary embolism and to assist. The HESTIA score was negative in all patients. The SPESI score in 14 patients (33.33%) indicated a high risk for outpatient treatment. The PESI score showed a very low or low risk of pulmonary embolism severity in 73% of patients. The VTE-BLEED score in 14 patients (33.33%) indicated a high risk of bleeding during treatment with direct oral anticoagulants. Other risk assessment data are listed in Table 3.

Table 3. Assessment of the severity of the PE and assessment of the risk of bleeding

Variable	Number	Percentage
HESTIA score	42	100%
sPESI score		
Low risk	28	66,67%
High risk	14	33,33%
PESI score		
Very low risk	23	54,76%
Low risk	8	19.05%
Medium-high risk	7	16.67%
High risk	4	9.52%
Very high risk	0	0
VTE-BLEED score		
Low risk of bleeding	28	66,67%
High risk of bleeding	14	33,33%

Treatment and complications after discharge from hospital

The majority (78.6%) of patients were discharged from the emergency department after observation for

Table 4. Treatment and complications

Variable	Number	Percentage
Type of discharge:		
Patients discharged from ED	33	78.6%
Patients discharged after hospitalization <24h	9	21.4%
Medication for treatment:		
Rivaroxaban	33	78.6%
Dabigatran	0	0
Apixaban	4	9.5%
Edoxaban	1	2.3%
Warfarin	1	2.3%
Dalteparin	3	7.1%
Complications		
Bleeding	0	9.52%
Thrombosis progression	0	
Major cardiovascular event	0	
Return to ED	4	

up to 24 hours, and 21.4% of patients were discharged from inpatient wards within 24 hours from admission. The medication predominantly started for outpatient treatment was rivaroxaban (78.6% of patients). Bleeding, progression of pulmonary embolism, or major cardiovascular event, including death, has not been observed in any patient. Four patients returned to the ED after discharge from the ED or hospital. First patient returned to the emergency department due to chest pain, his workup was fine, and the patient was discharged from the emergency department. Second patient developed pericarditis, as part of the non-recognized immune disease, he was hospitalized, and after stabilizing the condition with high doses of nonsteroidal antirheumatic drugs, he was discharged home. The third patient came to the emergency room due to symptoms of respiratory infection, with workup we found pneumonia in the territory of the vessels affected by pulmonary embolism, and the patient was discharged to home care with a recommendation for antibiotic treatment. A fourth patient was admitted to the emergency room due to symptoms of acute exacerbation of chronic obstructive pulmonary disease and was discharged home with a recommendation for treatment with steroids and antibiotics. We would like to point out a patient that was diagnosed with deep vein thrombosis of the arm and pulmonary embolism in the emergency department, which was also successfully treated in outpatient conditions without complications. In table 4 the types of treatment and complications after discharge are shown.

Discussion

Our retrospective analysis examined the demographic, clinical-diagnostic, and therapeutic characteristics of patients treated for pulmonary embolism in an outpatient setting. It is interesting to note that the greatest risk factor for the development of pulmonary embolism in the last two years was COVID-19 infection. The protocol used in ED UHC Zagreb requires adequate workup before the decision for discharge. This protocol includes the use of CT pulmonary angiography as a method of confirming pulmonary embolism, analysis of highly sensitive troponins and NT-PROBNP to rule out biochemical signs of right heart loading, orientational cardiac ultrasound to rule out signs of right ventricular stress, and leg vein ultrasound to confirm or exclusion of the existence of deep vein thrombosis. In addition, the risk assessment of the severity of the clinical picture is determined using the HESTIA score, and the PESI or sPESI score. These tools can adequately identify patients at low risk of mortality and morbidity within 30 days of discharge[8,9,10]. In addition, part of the protocol is to assess the risk of bleeding in the patient. For this purpose, we used the VTE-BLEED score[11], a clinical tool developed to assess the risk of bleeding in patients receiving anticoagulant therapy for the first time. Unlike the HAS-BLED clinical tool, which is most often used in clinical practice, the VTE-BLEED score was designed and subsequently validated in the group of patients with venous thromboembolic disease, while the HAS-BLED score was validated for the group of patients with nonvalvular atrial fibrillation. In addition, the VTE-BLEED score has been studied in patients receiving direct oral anticoagulant therapy and is therefore specific for bleeding that may occur during treatment with these drugs. As can be seen in the analysis, even patients with higher VTE-BLEED scores (> 2) can be treated safely and without complications with DOAC in an outpatient setting. More than 90% of patients were discharged from the emergency department with DOAC therapy, in most cases with rivaroxaban. Rivaroxaban is a drug that has been validated multiple times in the outpatient treatment of

pulmonary embolism[12]. The HOT-PE study[13] showed that rivaroxaban changes were safe and effective, with a very low risk of bleeding (1.6%) and an extremely low risk of thrombosis progression (0.6%), which is why the study was discontinued earlier than necessary because the null-hypothesis was statistically satisfied[14]. Finally, our analysis showed that low-risk pulmonary embolism outpatient treatment is safe. There were no cases of thrombosis progression, bleeding, or major cardiovascular events. The reason for this may be that this is a group of patients who are already at low risk for adverse events, but this does not change the fact that this analysis shows that the treatment protocol is safe for patients. Adverse events in terms of returning the patient to the emergency department were treated without hospitalization, were not serious, or were unrelated to pulmonary embolism, disease complications, treatment with direct oral anticoagulants, or treatment complications. The limitations of this study are primarily evident from the design itself. Namely, it was a retrospective analysis, and the cohort of patients was not large (42 patients). In addition, we studied complications of the disease or treatment if the patient came back to our hospital. The study also included patients who were hospitalized for a short time but who were discharged within 24 hours of treatment. The hospitalized patients were predominantly patients with bilateral pulmonary embolism, and although the protocol did not state that this was a contraindication for outpatient treatment, for patient safety they were still hospitalized for a short time. To correct the limitations of this retrospective analysis, it is necessary to do additional research, but still, monitor the cohort of patients who were treated in this way. Therefore, a prospective study is planned to study outpatient treatment of pulmonary embolism at OED UHC Zagreb.

Conclusion

In this retrospective analysis of patients who were discharged from the University Hospital Center Zagreb after short-term treatment (up to 24 hours) with a diagnosis of pulmonary embolism, it is evident that this is a safe and effective method of treatment. No patient had a disease complication (thrombosis progression), no treatment complication (bleeding), or any other major cardiovascular event. Outpatient treatment of pulmonary embolism with such a protocol could be implemented in the work of other health care institutions in the Republic of Croatia.

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Sažetak

IZVANBOLNIČKO LIJEČENJE PLUĆNE EMBOLIJE – ISKUSTVA JEDNOG CENTRA

Jasmin Hamzić i *Ivan Gornik*

Uvod: Plućna embolija (PE) predstavlja jednu od čestih dijagnoza u svakodnevnom radu hitnog prijema i dovodi do velikog broja prijema u bolnicu, što nije uvijek nužno. Pošto se pacijenti na temelju obrade i stratifikacije rizika mogu obraditi i otpustiti iz hitnog prijema, to može dovesti do rasterećenja bolničkih odjela, te smanjenja troškova u sustavu zdravstva. Cilj ovog rada je opisati protokol koji se koristi u našem centru, koji uključuje obradu stratifikaciju rizika za kompliciranu kliničku sliku i krvarenje, terapijske opcije i neželjene događaje ovakve vrste liječenja

Materijali i metode: Ovo je retrospektivna analiza pacijenata koji su u razdoblju od dvije godine (2020 i 2021 godina) otpušteni iz hitnog prijema kao plućna embolija niskog rizika.

Rezultati: U studiju je uključeno 42 pacijenata koja su otpuštena iz OHBP KBC Zagreb nakon kratkotrajne opservacije (do 24h) ili su otpuštena iz bolnice nakon kratkotrajne hospitalizacije (do 24h). U 91% slučaja je pacijentu u terapiju uveden direktni oralni antikoagulans. Kod niti jednog pacijenta nije bilo neželjenih događaja (krvarenje, progresija tromboze ili veliki kardiovaskularni incident)

Zaključak: U ovoj kohorti jasno se vidi da je rani otpust pacijenata sa plućnom embolijom niskog rizika siguran način za liječenje ove bolesti, te da dovodi do većeg zadovoljstva pacijenata, manjeg boja hospitalizacija, manjih troškova za bolnice, te zanemarivog broja neželjenih učinaka liječenja.

Ključne riječi: *plućna embolija, hitni prijem, izvanbolničko liječenje, rani otpust*

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Professional Paper

VENOUS THROMBOEMBOLISM IN THE EMERGENCY DEPARTMENT – SINGLE-CENTER EXPERIENCE

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SUMMARY – Given the importance of early recognition of acute venous thromboembolism (VTE) and the nonspecificity of its symptoms and signs, it is essential to follow the guidelines for diagnostic and therapeutic decisions. Ultrasound examination of the entire lower extremity is currently the standard diagnostic method for symptomatic patients with a clinical probability of deep vein thrombosis (DVT) according to the Wells scoring system. The aim of this study is to show the demographic structure and analyze the number of patients in the emergency department with suspected venous thrombosis. In the past 10 years, 2,022 patients with DVT and 686 with pulmonary emboli have been diagnosed. Despite adherence to the diagnostic protocol, nearly two-thirds of patients require early ultrasound diagnosis. One-fifth of patients had thrombosis of the superficial venous system of the leg or arm. Thrombus was present in the veins of the lower leg in 37% of patients with DVT. The presence of thrombi above the knee, involving the deep femoropopliteal venous system, was found in as much as one-third of patients. These findings and current guidelines suggest that there is a paradigm shift toward more frequent use of DOAC in patients with DVT. However, greater educational efforts may be needed for many physicians to become comfortable with the use of DOAC in the outpatient management of patient populations at low risk for pulmonary embolism.

Key words: *venous thrombosis, pulmonary embolism, venotromboembolism, emergency medicine*

Introduction

Acute venous thromboembolism (VTE) refers to deep vein thrombosis (DVT) and pulmonary embolism (PE), potentially fatal conditions with a one-year mortality rate of 9% to 23%.[1,2] The incidence of DVT is approximately 1-2 ‰ annually[3,4,5]. One-third of patients with untreated DVT develop clinically significant PE, and the mortality rate of PE patients admitted to the emergency department exceeds 20%[3]. In 95% of pulmonary emboli, the origin of the embolus is DVT, including 85 to 90% of lower extremity emboli[4]. Despite significant improvements in the diagnosis, prophylaxis, and treatment of these conditions, the incidence of VTE has remained the same in recent years[3,4]. Accurate and timely diagnosis of DVT determines immediate and long-term patient outcomes. Because the signs and symptoms of DVT are not specific, clinical assessment alone is not a reliable tool for diagnosis[5]. Laboratory determination of serum D-dimer levels is important for the diagnosis of DVT, but exclusively with negative predictive value and unsatisfactory specific values[6]. Although contrast venography is considered the "gold standard" of diagnosis in patients with suspected DVT, this test has been replaced by compression color Doppler ultrasound due to its invasiveness and complications, both in clinical practice and as a reference test for clinical trials[6,7].

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Ultrasound examination of the entire lower extremity is currently the standard diagnostic method for symptomatic patients with clinical probability of DVT according to the Wells scoring system[6,7].

Materials and method

A retrospective analysis of the database of visits to the Emergency Department of University Hospital Sveti Duh from January 1, 2011, to December 31, 2021, included all patients with suspected DVT. In addition, data from the radiological database of confirmed pulmonary emboli were included. The aim of this study is to show the demographic structure, the number of patients in the emergency department with suspected venous thrombosis, the localization of the thrombus confirmed by ultrasound, the presence of concomitant diseases, the treatment, and early outcomes of VTE. Continuous data is provided as median ± interquartile range. Categorical data are given as n / N (%).

Results

In the period from January 1, 2011 to December 31, 2021, 6,509 cases of suspected venous thrombosis of the extremities in 5,349 patients were treated in the emergency department of the University Hospital Sveti Duh, 256 patients were excluded from the analysis due to incomplete data (Figures 1).

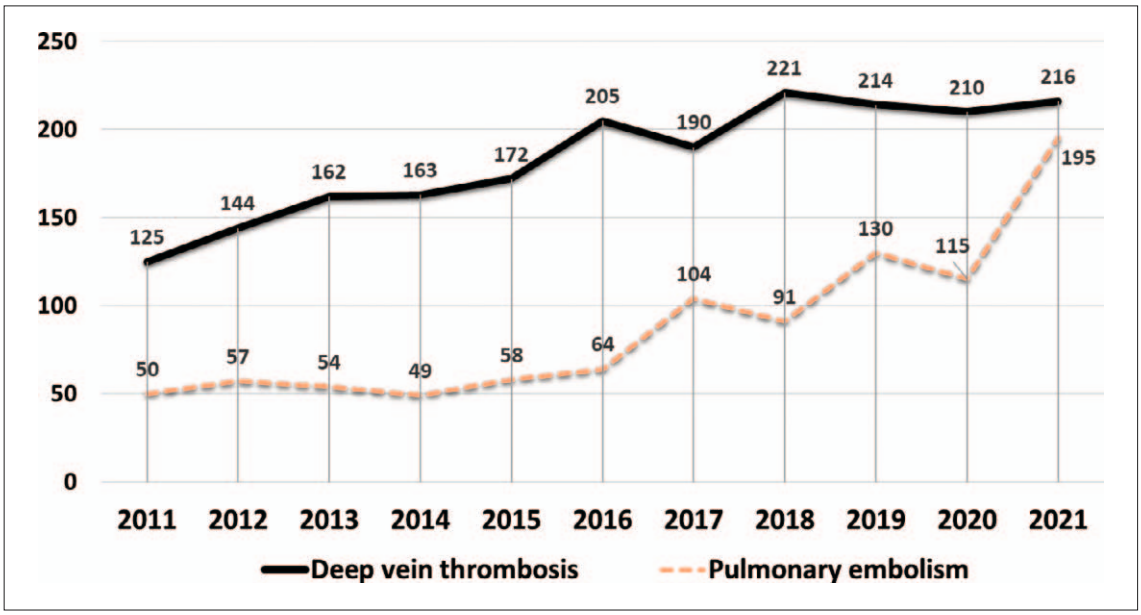
Of the 5,093 patients, DVT was excluded in 1,420 (27.9%) because the risk was low according to the Wells scoring system and D-dimer levels were within the reference range. Ultrasound diagnosis of DVT was excluded in 1,651 (32.4%) and confirmed in 2,022 (39.7%) patients. The median age was 62.18 years (49.2-73.5 IQR) and 56.43% were female. Six hundred sixty-one patients (32.7%) with DVT were hospitalized. There were 686 hospitalizations, 50.7% of which were female, the median age was 67.7 years (53.1-77.1 IQR), 67% were over 60 years old, and the median hospital stay seven days (5-9 IQR).

During the observation period, 967 cases of pulmonary embolism were registered: 60.9% female and 60% older than 65 years old. Of the patients hospitalized for pulmonary embolism (92%), 74 patients (7.65%) died at the time of hospitalization, the median age was 73.96 years (64.0-81.1 IQR), 80% were older than 60 years. Fibrinolysis therapy was performed in 94 cases.

The most common concomitant diseases in patients with VTE were arterial hypertension (47%), hyperlipidemia (12%), diabetes (14%), active tumor disease (13%), recent trauma (11%), and renal injury (4%). Each of the prolonged conditions was more common in patients with PE than in patients with DVT alone. Estrogen therapy was noted in 7.6% of women with VTE. Patient histories included data on previous VTE, which was significantly more common in the DVT group than in PE (24.2% vs. 16.5%).

The median time from onset of symptoms to first medical contact was longer in the DVT group (median three days, IQR 2-5) than in PE (median one day, IQR 0-10). The most common symptoms and signs in patients with DVT were pain (88.7%), limb swelling (75%), and local extremity warmth (34%). The most common symptoms in PE were dyspnea (79.1%), chest pain (34.5%), rapid heart rate (21%), and syncope (5%). Forty-five percent of patients with suspected DVT were examined during working hours from 8 a.m. to 4 p.m., with an average treatment time of 169 minutes; 82.1% in the period from Monday to Friday, without major variations in the number of inputs by month. In 90% of the cases, the time from patient admission to ED to radiological findings suggestive of pulmonary embolism was within three hours.

One-fifth of patients, 21%, had thrombosis of the superficial venous system of the leg or arm. Thrombus was present in the veins of the lower leg in 37% of patients with DVT, which was localized in the posterior tibial veins in 31% of cases, in the peroneal veins in 60%, and in the muscular veins (gastrocnemius or soleus) in 29%. The presence of thrombi above the knee involving the deep femoropopliteal venous system was found in 38% of patients and was evenly distributed among the common femoral, superficial femoral, and popliteal venous segments. The presence of thrombus in the iliac region was less frequent, in 10% of patients on ultrasound. Thrombus in the femoropopliteal segment was found in all patients with external iliac thrombosis, and 60% also had thrombosis in one or more tibial veins. Deep vein thrombosis in the arms was present in only 4.7% of patients. Isolated lower leg thrombosis was more often associated with leg pain (60% vs. 40%) and less often with subjective leg swelling (20% vs. 60%).



Figures 1. Annual incidence of venous thromboembolism in the emergency department.

Among patients with nonthrombotic findings, the most common diagnoses were edema (34.9%), Baker cysts (22.6%), and unspecified fluid collections (16.3%).

Hospitalization was elected for 95% of proximal DVT. For distal DVT, hospitalization increased from 20% in patients aged 18 to 40 years to 70% in patients aged 60 years.

A total of 95% of patients were treated in the emergency department, prophylactically until diagnostic exclusion of thrombosis, or therapeutically in hospitalized patients with DVT with anticoagulants, mostly low-molecular-weight heparin (enoxaparin, dalteparin).

Discussion

Patients with suspected deep vein thrombosis and pulmonary embolism report to the emergency department almost daily.

The symptoms and signs of deep vein thrombosis are nonspecific, and several other pathologic conditions may mimic them, such as Baker cyst, thrombophlebitis, lymphadenopathy, subcutaneous edema, chronic deep vein thrombosis, fluid collection, hematoma, and muscle tears.

The clinical onset of symptoms and the timing of diagnostic tests were different in patients with DVT and PE, with a shorter duration in the latter group. This difference is to be expected since PE is the more severe form of VTE.

Despite adherence to the diagnostic protocol, nearly two-thirds of patients require early ultrasound diagnosis, which is increasingly accepted by physicians, especially in emergency medicine. However, CDUV is not available in certain situations, requiring time and the availability of trained medical personnel.

Nearly half of patients with deep vein thrombosis report to the emergency department between 4 p.m. and 8 a.m., when ultrasound diagnosis is performed with limited exclusion of distal thrombosis. Alternatively, if ultrasound diagnosis of the veins is not available, empiric anticoagulation is required, most commonly with low-molecular-weight heparin, until DVT is definitively confirmed or excluded[8,9].

The sensitivity of US diagnosis for proximal DVT (above the knee) has been reported to be 97% but is much lower for isolated distal DVT[9].

Isolated calf vein thrombosis is common, accounting for 28% to 70% of all lower extremity DVT diagnosed by ultrasound[10,11]. These findings are consistent with other reports, as we found in our series that 37% of thromboses diagnosed by full-duplex ultrasonography at the initial examination were isolated calf vein thromboses. This suggests that an initial ultrasound examination performed with a limited range (from the groin to the popliteal fossa) misses nearly one-third of

DVT cases. We found that isolated deep vein thrombosis of the calf was more commonly associated with leg pain than proximal deep vein thrombosis. It is generally believed that acute DVT triggers an inflammatory response and that the pain associated with DVT is primarily due to inflammation of the vein wall around the clot.

Isolated calf thrombosis was less frequently associated with subjective leg swelling and objectively measured circumferential difference. One explanation for this finding is that in most patients there is a single iliac, femoral, and popliteal vein for each leg. Thrombosis in these veins therefore results in occlusion of all deep venous outflow at this level. In contrast, there are multiple deep veins in the calf. In most cases of isolated calf vein thrombosis, one or some of these veins are occluded, leaving other deep calf veins open.

Although the clinical significance of isolated distal DVT is unclear, up to 25% of these thrombi may spread to proximal veins, increasing the risk of PE and post thrombotic syndrome[10], guidelines recommend anticoagulant therapy for isolated distal DVT in patients with severe symptoms or with risk factors for spread[8,12].

The location of the primary DVT influenced the decision of emergency department physicians for hospitalization. Hospitalization was chosen more frequently in patients with proximal DVT than in patients with distal DVT.

In addition, the approach to patients with DVT changed significantly after the introduction of new forms of direct-acting oral anticoagulants (DOACs). In the last two years, the shift in prescribing ambulatory therapy has reversed in favor of DOACs, with the possibility of switching to warfarin therapy for socioeconomic reasons, contraindications, and patients with active tumor disease. The same trend is not seen in patient groups requiring hospitalization, and heparin remains the first choice of therapy. No change was observed in the number of hospitalizations or choice of therapy for pulmonary embolism, even in the patient groups with low risk of mortality and severity of complications according to the PESI scoring system.

Conclusion

Given the importance of early recognition of deep vein thrombosis and pulmonary embolism, the non-specificity of symptoms to and signs, and the congestion of hospital emergency departments, it is necessary follow guidelines for diagnostic and therapeutic decisions. Diagnosis of isolated calf vein thrombosis is particularly difficult in the ED when the definitive diagnostic test, whole-leg ultrasonography, is not available. These findings and the current guidelines suggest that there has been a paradigm shift toward more frequent use of DOAC in patients with DVT. However, greater educational efforts may be needed for many physicians to become comfortable with the use of DOAC in the outpatient management of patient populations at low risk for pulmonary embolism complications.

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Sažetak

VENSKA TROMBOEMBOLIJA U HITNOJ MEDICINSKOJ SLUŽBI – ISKUSTVA JEDNOG CENTRA

I. Jurić i *V. Nesek Adam*

Venski tromboembolizam označava duboku vensku trombozu i plućnu emboliju, a uzevši u obzir važnost ranog prepoznavanja, nespecifičnosti simptoma i znakova, neophodno je pridržavanja smjernicama prilikom donošenja dijagnostičkih i terapijskih odluka. Ultrasonografija je trenutno standardna dijagnostička metoda za simptomatske bolesnike s kliničkom vjerojatnosti VTE prema Wellsovom bodovnom sustavu. Cilj rada je prikazati demografsku strukturu i analizirati broj bolesnika u hitnoj službi sa sumnjom na vensku trombozu. Unazad 10 godina, dijagnosticirano je 2022 bolesnika s DVT i 686 plućnih embolija. Unatoč protokolu, u gotovo dvije trećine bolesnika neophodna je rana ultrazvučna dijagnostika, sve više prihvaćena od strane liječnika, posebno u uvjetima hitne medicinske pomoći. U petine bolesnika, 21%, utvrđena je tromboza površinskog venskog sustava noge ili ruke. U 37% bolesnika s DVT tromb je bio prisutan u venama potkoljenice. Prisutnost tromba iznad razine koljena, uz zahvaćenost femoropoplitealnog dubokog venskog sustava, dokazan je u 38% bolesnika. Rezultati istraživanja i trenutne smjernice sugeriraju da je došlo do promjena u izboru antikoagulacijske terapije kod bolesnika s DVT, u prilog DOAK-a. Međutim, možda će biti potrebni veći napori kako bi se liječnici odlučili za DOAK u vanbolničkim uvjetima liječenja bolesnika s plućnom embolijom.

Ključne riječi: *venska tromboza, plućna embolija, venotromboembolizam, hitna medicina*

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Preliminary Communication

SYSTEMIC INFECTION WITH SINGLE OR MULTI-ORGAN DAMAGE CAUSED BY INADEQUATELY MANAGED CHRONIC WOUNDS: A CASE SERIES

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SUMMARY – Chronic wounds are often underestimated condition with increasingly growing inpatient and outpatient treatment costs. Since the patient population affected by chronic wounds is heterogeneous and includes diabetes, chronic venous insufficiency and peripheral artery disease patients, with additional differences in gender, age, previous medical history, treatment of chronic wounds is highly personalized and dependent on a variety of factors. This paper aims to highlight the problems that the chronic wound patient population is facing during the COVID-19 pandemic: from higher probability of an undesirable disease outcome to the fact that many of them have limited access to primary care providers and to the regular and continuous care that their condition demands.

This paper describe three patients with chronic wounds. Each of the patients had a significant worsening of their chronic wounds during the COVID-19 pandemic: either following an active SARS-CoV-2 infection or due to the limited access to primary care.

The cases described here highlight the necessity of providing proper and regular care for all patients during the COVID-19 pandemic, regardless of the current state of the healthcare system and the adversities and hurdles it currently faces, to prevent the pandemic from becoming a syndemic.

Keywords: chronic *wounds, care, COVID-19 pandemic*

Introduction

Chronic wounds are an often underestimated issue, even though there is data showing that they negatively impact the quality of life of 2.5% of the total US population and present a significant economic burden on the healthcare system.[1] With the advent of the novel coronavirus (SARS-CoV-2) pandemic, patients with chronic wounds are at an even greater risk, with the risk factors related to chronic wounds (hypertension, vascular disorders, diabetes) being some of the most important predictors of severe presentations and lethal outcomes of COVID-19. Having all the listed factors in mind, it is easy to see why proper, regular and timely chronic wound care is a priority. Adding to that point is the fact that the lack of regular visits to a wound care clinic can increase hospitalization rates by up to 20 times.[2] In this case series, we present three patients unfortunately affected by a combination of the sequelae of a SARS-CoV-2 infection, lack of regular visits to a wound care clinic and an ineffective bureaucracy, the sum of which presents itself as serious infections with single or multi-organ damage.

Case 1

A 77-year-old female came to the Clinic for Chronic Wounds at KB Merkur, a tertiary care facility in Zagreb, Croatia. She had a history of arterial hypertension of more than 10 years, a past SARS-CoV-2 infection after being vaccinated and a cholecystectomy 10 years ago. At the time of the examination, she had chronic ulcers on both shins, which had been treated

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with various dressings for months. She was taking ciprofloxacin 500mg pills BID for a presumed infection at the site of the ulcers, prescribed for 10 days. In her therapy, the patient also had acetylsalicylic acid, bisoprolol, oxazepam, indapamide and lisinopril. The patient interview during the examination revealed that the patient had been demoed the dressings prescribed at the clinic, citing a guideline of the Croatian Bureau of Health Insurance (HZZO) to discontinue a dressing if it did not improve the status of the wound within 28 days. A physical examination revealed five ulcers (three on the right shin and two on the left) with a large volume of green secretion resembling pus. The patient's vital signs were stable, with a blood pressure of 110/70 mmHg, a pulse of 61 beats/min, 15 respirations/min. Her oxygen saturation was 95% on room air. A lavage with H2O2 and sterile saline solution was carried out, along with a dressing of 10% NaCl and 10% iodopovidone. The patient was prescribed tramadol 50mg hard capsules for pain from the ulcers and was sent to the emergency internal medicine clinic for further workup following complaints of dyspnea, a dry cough and diarrhea.

An electrocardiogram (ECG) and blood laboratory tests were made. The ECG showed a sinus rhythm with 61 beats per minute and a deviation of the electrical axis to the left, along with a left bundle branch block. The laboratory results showed a prominent leukocytosis of 39.90*10^9 leukocytes, microcytic anemia (Hb 73 g/L, MCV 69.0 fL), high neutrophile to lymphocyte ratio (NEU% 90, LYM% 4.9), hypocoagulable state (PT 0.35), hyperkalemia (6.5 mmol/L), hyponatremia (132 mmol/L), elevated urea (62.9 mmol/L) and creatinine (467 umol/L), elevated liver enzymes (AST 75 U/L, ALT 201 U/L, GGT 100 U/L), elevated CRP (123.3 mg/L) and high-sensitivity troponin I (26 ng/L). An arterial blood gas (ABG) test was also performed and showed an acidosis (pH 7.246) with hypocapnia (pCO2 2.65 kPa), hypobicarbonatemia (HCO3 8.6 mmol/L) and a base excess of -18.7 mmol/L. The patient was hospitalized with a diagnosed infection with multiorgan damage, acute kidney failure (AKF), hepatic damage, cardiac damage, coagulation breakdown), and administered a blood transfusion, antibiotics (piperacilin/tazobactam 4.5mg i.v.) and i.v. fluids (500mL of 5% glucose with 8 units of fast-acting insulin because of hyperkalemia with loop diuretics (due to hyperkalemia a dose of furosemide was 80 mg iv). A chest X-ray and an abdominal ultrasound were also made. The X-ray showed an enlarged heart with a cranial redistribution of circulation. The abdominal ultrasound showing no abnormalities.

Case 2

This patient is a 42-year-old male who came to the emergency clinic with a primary complaint of erythema, pain and edema of the right foot. After taking a medical history, it has been established that the patient had been suffering from multiple conditions for more than 10 years, including arterial hypertension, hyperlipidemia, type II diabetes mellitus, and chronic ulcers on both feet. He had had no medication allergies in the past and reported taking bisoprolol, alogliptin, metformin, ramipril, amlodipine, hydrochlorthiazide, atorvastatin and glargine during his therapy. He had also had COVID-19 at one point in time, with a positive PCR test. Upon examination, the patient's right foot was edematous, red and painful, with pus secreted out of the wound. The foot was missing a second digit, which had been previously amputated. The sole of the foot was red, and the skin looked macerated. Arterial pulses were palpable femorally, but not distally. An emergency doppler ultrasound of the right leg vasculature showed no significant atherosclerotic changes and the flow through the large lower extremity arteries was satisfactory. The deep veins of the leg were compressible, anechoic, without signs of deep venous thrombosis (DVT). Blood samples were taken for laboratory analysis and the laboratory test results showed a prominent leukocytosis of 23.33 *10^9 leukocytes/L, an elevated neutrophile to lymphocyte ratio (90.5%/3.9%) indicative of severe inflammation, hyponatremia with a sodium value of 127 mmol/L, hyperglycemia with a blood glucose level of 19.8 mmol/L, a high-sensitivity C-reactive protein (hs-CRP) level of 267.6 mg/L and kidney damage with a serum creatinine value of 273 umol/L. A swab of the wound was taken and sent for microbiological testing. The patient was admitted to the vascular surgery ward and given intravenous antibiotics. Following a 2-week hospitalization, the patient was discharged with instructions to come for control visits and redressing the wound every second day, either at the chronic wound clinic or his primary care provider (PCP). After several weeks of not showing up for control visits and wound redressing, the patient showed up at the emergency ward complaining of right food erythema, edema and pain. The wound

had severely worsened, and a swab was again taken. It came back positive for Klebsiella pneumoniae and type B beta hemolytic streptococcus. The patient was once again admitted to the hospital and a reamputation of the second digit was deemed necessary.

Case 3

This patient is a 68-year-old male who came to the emergency ward complaining of pain and erythema on the left foot and erythema, pain, edema on the right shin. The patient had a medical history of type II diabetes mellitus for more than 20 years, glaucoma, diabetic retinopathy, arterial hypertension, hyperlipidemia and chronic ulcers of both feet. He stated a previous allergic reaction to penicillin and was taking rapid acting insulin, glargine, amlodipine, phenofibrate, atrovastatin, ramipril, hydrochlorthiazidem acetylsalicylic acid, dorzolamide and timolol in his chronic therapy. Upon physical examination, the right leg was erythematous and swollen and the left food was erythematous with a large number of purulent and necrotic deposits inside the wound. A vascular murmur over the carotids was also noted. A wound swab was taken and sent for microbiological testing. The results came back positive for vancomycin sensitive Enterococcus faecalis. A doppler ultrasound of the leg arteries showed diffuse atherosclerotic changes without isolated significant stenotic changes – the finding was deemed overall satisfactory, with a control exam and regulation of risk factors recommended. Blood samples were drawn and sent for analysis. The laboratory test results showed pronounced inflammation with a hs-CRP of 121 mg/L, a hypokalemia with a serum potassium level of 3.3 mmol/L and significant acute kidney injury with a serum creatinine of 306 umol/L. The patient was admitted to the endocrinology ward.

Discussion

The patients presented here were affected by either the reduced regularity of visits to the wound care clinic due to the COVID-19 pandemic or an ineffective and unforgiving bureaucracy that failed to recognize the need of chronic wound patients for regular reapplication of dressings specifically designed to prevent infection. It has been shown that regular visits to the wound care clinic play an extremely important role in preventing infection, One study determining the success of simple mechanical debridement in reducing bacterial activity inside and peripheral to the wound using fluorescence imaging has shown that a single debridement reduces bacterial activity inside the wound by 99.4% and peripherally by 64.3% (before using antiseptic)[3]. Wound care clinics are also important because of the psychological effects that procedures such as changing dressings and interviewing the patient about their experience regularly allows for a more personalized approach to each patient, which has been shown to improve the psychological state of patients and the time needed to complete wound healing[3,4]. In addition to the obvious benefits listed above, regular visits to the wound care clinic also allow for a timely diagnosis of wound infection. Several analyses have shown that there are reliable risk factors for the development of chronic wound infection, most of which can only be evaluated by regular physical examination of the wound: wound area >10 cm^3, new, increased or altered wound pain, malodor, increased wound area, erythema, increased wound temperature[4] and heavy exudate from the wound[5]. It is also important for family physicians and bureaucratic entities providing health insurance to recognize and respect the expertise and importance of the wound care surgeon's opinion and findings in order to provide adequate multidisciplinary care to the patient, even outside the wound care clinic and ensure that the same level and quality of care is provided both in the inpatient and outpatient settings. Two of the three patients described in this case series had a history of COVID-19, after which their chronic wounds clinically increased in severity. It is therefore important to discuss the treatment of chronic wound patients infected with SARS-CoV-2, to ensure proper wound care during the acute infection phase, when patients are supposed to be in isolation for 1-2 weeks, and to provide adequate aftercare in the form of more frequent follow-up exams, as it has been shown that not only are chronic wound patients more susceptible to unfavorable COVID-19 outcomes, but that their chronic wounds (and other chronic conditions) can also rapidly progress into their later, more severe stages in the midst of an infection with SARS-CoV-2, which has been known to interact with important molecular mechanisms regulating blood vessel tone, integrity and other important properties, so some researches describe this situation as a "pandemic within a pandemic" [6,7].

In conclusion, in the wake of the COVID-19 pandemic, many healthcare topics have gone under the

radar, including chronic wound care. Since patients with chronic wounds are at risk of being exposed to z lack of regular care due to the increased load on the healthcare system and having significantly worse COVID-19 outcomes if infected, it is important to recognize the role of multidisciplinary care and proper communication between wound care specialists, family medicine specialists and insurance providers so that this sensitive group of patients will receive the best possible care, especially in these trying times of Covid syndemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Sažetak

SUSTAVNA INFEKCIJA S OŠTEĆENJEM JEDNOG ILI VIŠE ORGANA UZROKOVANIM NEADEKVATNO LIJEČENIM KRONIČNIM RANAMA: PRIKAZ SLUČAJEVA

Đ. Delalić, R. Roher, D. Mileta i *I. Prkačin*

Kronične rane predstavljaju podcijenjeno stanje koje je povezano sa značajnim rastućim troškovima bolničkog i ambulantnog liječenja. Znajući da je populacija pacijenata s kroničnim ranama vrlo heterogena te obuhvaća populaciju dijabetičara, pacijente s kroničnom venskom insuficijencijom, perifernom arterijskom bolesti, te uvažavajući dodatne razlike vezane uz spol, dob te prethodnu medicinsku dokumentaciju, liječenje kroničnih rana je visoko personaliziran postupak i ovisan je o nizu različitih čimbenika. U ovome radu naglašen je problem populacije s kroničnim ranama tijekom pandemije COVID-19 u smislu veće vjerojatnosti neželjenog ishoda bolesti primarno zbog ograničenog pristupa liječnicima primarne zdrastvene zaštite, kao i regularne skrbi zbog drugih prilažećih kroničnih stanja. U radu su opisani prikazi slučajeva tri bolesnika s kroničnim ranama koji su imali značajno pogoršanje uslijed pandemije COVID-19. Isto se moglo prevenirati pravilnom i regularnom brigom, stoga smatramo da za sve pacijente tijekom pandemije COVID-19, bez obzira na trenutno stanje zdrastvenog sustava i postojeća ograničenja, prepreke nisu nesavladive, u cilju nadzora ovih pandemijskih problema koji postaju sindemija.

Ključne riječi: *kronične rane, njega rana, COVID-19 pandemija*

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Review

PROTHROMBIN COMPLEX CONCENTRATE IN EMERGENCY DEPARTMENT

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SUMMARY – Coagulation abnormalities are common in bleeding or critically ill patient and hemostatic management remains a major challenge for the emergency physician. Management of bleeding patients consists of bleeding control, restoration of blood volume, and correction of any associated coagulopathy. Traditionally, the fresh frozen plasma (FFP) is used for correction of coagulopathy to manage and prevent bleeding, but today Prothrombin complex concentrates (PCCs) offer an attractive alternative because they offers a number of advantages over FFP, including lower infusion volume, rapid INR normalization, faster availability, lack of blood group specificity, and better safety profile. The aim of the present review is to provide an short overview about using PCC, their indication, efficacy and safety in different bleeding setting's.

Key words: *bleeding, emergency department, prothrombin complex concentrates*

Introduction

Although, fresh frozen plasma (FFP) contains all clotting factors at physiological concentrations and traditionally has been the blood component therapy of choice for the prevention and treatment of bleeding, today we have several different plasma products. These products include single coagulation factor concentrates, such as factor VIII concentrates for the treatment of hemophilia A and factor IX concentrate for the treatment of hemophilia B and prothrombin complex concentrates (PCCs). PCCs are human plasma protein concentrates that contain four vitamin K-dependent coagulation factors, factors II, VII, IX and X and therapeutically effective concentrations of thrombo inhibitors (proteins C and S). PCCs are indicated for the urgent reversal of acquired coagulation factor deficiency from warfarin-induced anticoagulation and can be used as an alternative to fresh frozen plasma (FFP) for emergency bleeding in patients who are not taking anticoagulants.

In this review, we will discuss PCCs and their indications and safety, focusing on use and effectiveness in an emergency department.

Prothrombin complex concentrates

Prothrombin complex concentrates were originally developed as a source of factor IX (FIX) for the treatment of hemophilia B[1], but in the 1990s, with the availability of high-purity plasma-derived recombinant Factor IX, PCCs are now rarely used in this indication. They come from the cryoprecipitate supernatant of large plasma pools after the removal of antithrombin and factor X[2]. Since the 1960s, different PCC products have been available, but today prothrombin complex concentrates contain either three-factor (i.e., factors II, IX and X) or four-factor (i.e., factors II, VII, IX and X) vitamin K-dependent coagulation factors in a concentration about 25 times higher

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than in normal plasma[3] and are standardized regarding their factor IX content. Due to the high concentration of coagulation factors and the prevention of their activation, most PCCs contain heparin. The half- life of coagulation factors is different. The half-life of factor II is 60-70 hours, which is much longer than other factors (6-24 hours). Factor VII has the shortest half-life, only 6 hours[3]. As a consequence, repeated dosing will lead to an accumulation of factors II and X and increase the risk of thrombotic complication.

PCCs are lyophilized and can be stored at room temperature for several years, allowing administration without warming.

Clinical indication

As mentioned before, PCCs were originally used to treat and prevent bleeding in patients with hemophilia B, but today they are most commonly used for rapid reversal of warfarin anticoagulation[4], although there is increasing interest in using it to treat other forms of abnormal coagulation. Urgent reversal of acquired coagulation factor deficiency induced by warfarin-induced anticoagulation in patients presenting with major acute bleeding (intracerebral hemorrhage-ICH) or a need for an urgent invasive surgery or procedure[5] was approved in the United States in 2013 and is the only FDA approved indication for PCCs.

However, off-label use of PCCs occurring in nearly 40% [6], mostly for the reversal direct oral anticoagulants (DOAC) induced coagulopathy, treatment or prophylaxis of bleeding in congenital deficiency of any vitamin K-dependent coagulation factors, pre-operative to decrease bleeding in patients not taking oral anticoagulants or in a trauma setting with massive transfusions[5].

Reversal of anticoagulants

Reversal of vitamin K antagonist

For many years, the vitamin K antagonist (VKA), warfarin has been the cornerstone for thrombosis prevention and treatment. The efficacy of warfarin for prevention and treatment of thrombosis has been studied in a number of clinical studies, but bleeding, particularly in the setting of over-anticoagulation, is still a major concern. The reported incidence of bleeding during therapy with VKAs is highly variable in published studies. The overall incidence of bleeding in anticoagulated patients during long-term VKA therapy is about 10%–17% per year, 2%-5% for major bleeding and 0.5% -1% for fatal bleeding[7]. Previously, FFP and vitamin K were the only options for reversing anticoagulation, but today PCCs offer several advantages over FFP. These advantages include more rapid INR normalization, lower infusion volume (a large volume of FFP is needed to reverse coagulopathy caused by vitamin K antagonism; 10 mL/kg-20 mL/kg), significantly higher amounts of the clotting factors compared to FFP (one dose of a PCC equals 8 to 16 units of FFP)[5], a lack of blood group specificity, a lower risk of viral transmission, since they undergo viral inactivation, and a better safety profile.

It is very important to point out that both FFP and PCCs need coadministration of vitamin K for warfarin reversal. The half-life of vitamin VII is only 6 to 8 hours, whereas warfarin has a half-life of several days. Although vitamin K is not a direct hemostatic agent, it is a cofactor for the activation of factors II, VII, IX, X, and the anticoagulant proteins C and S[8]. Administrations of vitamin K counteract the long half-life of warfarin. The usual dose is from 5 to 10 mg.

A meta-analysis of 13 studies comparing the use of PCCs and FFP for warfarin reversal showed that PCCs were associated with a significant reduction in all-cause mortality, more rapid INR reduction, (INR, odds ratio [OR] 10.80; 95% confidence interval [CI], 6.12–19.07) and the time to correction was shorter (mean difference – 6.50 h; 95% CI, –9.75 to –3.24), less volume overload (OR 0.27, 95 % CI; 0.13–0.58) and without an increased risk of thromboembolic events[9]. The 17 studies with a total of 2606 participants also showed that PCCs were more effective than FFP in all-cause 90-day mortality and INR reduction with a lower risk of adverse events[10]. A meta-analysis by Brekelman et al. showed that the INR within 1 h after PCC administration ranged from 1.4 to 1.9, and after FFP administration from 2.2 to 12 which means that PCC significantly reduced the time to reach INR correction in comparison with FFP[11].

The most seriously complication in patients taking oral warfarin is intracranial hemorrhage with still very high mortality. A prospective, observational study showed that PCC adequately corrected INR without any increase in adverse events compared to FFP and

was associated with less major hemorrhage and improved 3-month outcomes in patients with warfarin-associated intracranial hemorrhage[12].

American Heart Association guidelines from do 2010 not recommend any specific reversal protocol for warfarin-associated intraparenchymal hemorrhage[13] and state that "PCCs have not shown improved outcome compared with FFP but may have fewer complications compared with FFP and are reasonable to consider as an alternative to FFP" (Class IIa, Level B evidence)[13]. However, guidelines from do 2015 state that „PCCs may have fewer complications and the INR more rapidly than FFP and might be considered over FFP (Class IIb; Level of Evidence B)"[14]. The new recommendation is based on results from phase 3 randomized controlled trial performed on 202 patients with acute bleeding (24 of whom had intracranial hemorrhage)[15.] The study showed that PCC is an effective alternative to FFP for urgent reversal of vitamin K antagonist therapy in major bleeding. Rapid INR reduction was achieved in 62.2% of patients receiving PCC versus 9.6% receiving FFP [15].

Reversal of direct oral anticoagulants (DOACs)

Today, direct oral anticoagulants (DOACs) are the treatment of choice to prevent thromboembolic events because of their better overall risk–benefit profile, more predictable pharmacokinetics and pharmacodynamics and fewer interactions with other medications and food, compared to VKA. Their main disadvantage is currently the absence of a specific reversal agent and the fear of bleeding. Although, patients receiving therapy with DOACs have a lower risk of bleeding compared to VKA therapy, they also may present with serious bleeding or a need for unexpected emergency surgery or procedures[16]. Because of their very short half-lives compared to warfarin, most episodes of non-life-threatening bleeding can be managed with supportive measures, such as temporarily withholding drugs, blood product transfusions, etc. However, in a life-threatening bleed, and in patients with intracranial bleeding, additional strategies may be required. At present, the treatment of DOAC-associated hemorrhaging is limited. A specific reversal agent for dabigatran, idarucizumab, was approved by the US Food and Drug Administration (FDA) in 2015. In May 2018, andexanet alfa, the antidote for factor Xa (FXa) inhibitors, was also approved by the FDA to reverse apixaban and rivaroxaban in patients with life-threatening or uncontrolled bleeding[17]. However, these specific antidotes, particularly andexanet alfa, are very expensive and not widely available.

The recommendation for managing bleeding patients on DOACs was based on limited evidence[18 -22]**.** Several nonspecific therapeutic strategies have been developed as potential DOAC reversal agents. Treatment options include nonspecific agents, such as fresh frozen plasma, PCCs, recombinant activated factor VII, and antifibrinolytic agents. Evidence regarding the use of PCCs as a potential therapeutic option is increasing.

Data primarily from small case or cohort studies with PCCs in bleeding patients has suggested that PCCs are safe and efficacious in the management of Xa inhibitor bleeding.

The French Working Group on Perioperative Hemostasis (GIHP) in a prospective, cohort registry study of 732 patients treated with direct oral anticoagulants and hospitalized for severe bleeding showed that hemostasis was totally or partially achieved in 44% with 4F-PCCs and 37% with activated PCCs of those who received these agents[23]. The UPRATE study, which included two cohorts, one in Sweden[24] and one in Canada[25] also, found that the use of PCCs for the management of major bleeding in patients on rivaroxaban or apixaban is an effective strategy and supports the use of PCCs for the reversal of activated factor X inhibitors in bleeding patients. PCCs were effective in 69% of patients in the Sweden cohort and 68% in the Canada cohort.

Because specific reversal agents for DOACs are not widely available PCCs, in cases without access to these specific agents. and in situations where the anticoagulant agent is unknown, remain the cornerstones of therapy in patients with DOAC-associated bleeding.

Prothrombin complex concentrate in trauma patients

A resuscitation strategy in trauma bleeding patients have a common aim: to stop bleeding, reestablish hemostasis, restore normal perfusion pressure and prevent acute traumatic coagulopathy (ATC), and improve the outcome of severely injured patients requiring massive blood transfusion[26].

Although there is no high-quality study to evaluate the use of PCCs in trauma patients, guidelines in both

trauma and operative settings support the administration of PCCs in bleeding patients to reverse coagulopathy[27,28]. Several small studies have shown that coagulopathy in trauma patients can be effectively reversed with PCCs and also showed decreased blood product consumption[29,30] PCCs increase thrombin generation and may potentially be effective in facilitating hemostasis. A recent meta-analysis that included 17 studies reported similar findings. A resuscitation strategy using both PCCs and FFP transfusion was associated with reduced mortality when compared to a resuscitation strategy involving solely FFP. Also, PCCs reduced the need for RBC transfusions when compared with treatment strategies not involving PCCs[31]. According to recent evidence and discussions on the potential therapeutic role of PCCs in trauma bleeding patients, PCCs may be a good option in the management of hemodynamically unstable trauma patients. But it is important to point out that PCCs do not contain factor V and may not be sufficient as a single agent in traumatic cases requiring massive transfusions[5].

Conclusion

Data from the literature indicates that PCCs are the therapy of choice for rapid reversal of vitamin K antagonist anticoagulation, and also in situations requiring rapid reversal of anticoagulation by non-vitamin K antagonist, making PCCs a general antidote for oral anticoagulation. For trauma patients the use of PPCs can reduce transfusion requirements and the severity of hemostatic abnormalities, with more rapid restoration of hemostasis.

It has also been shown that not only do PCCs replace deficient clotting factors more rapidly than FFP, but they also minimizes the risk of fluid overload and risk of viral transmission. PCC treatment can be the therapy of choice in an emergency anticoagulant reversal setting and can be safely used for rapid hemorrhage control.

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Sažetak

KONCENTRAT PROTROMBINSKOG KOMPLEKSA U HITNOJ MEDICINSKOJ SLUŽBI

V. Nesek Adam i *I. Bošan-Kilibarda*

Poremećaji koagulaciji česti su u kritičnih bolesnika i u bolesnika s krvarenjem, te predstavljaju veliki izazov za sve liječnike koji su uključeni u rad hitne medicinske službe. Liječenje bolesnika s krvarenjem uključuje kontrolu krvarenja, nadoknadu volumena krvi i korekciju koagulopatije. Tradicionalno, za korekciju koagulopatije i sprječavanje krvarenja najčešće se koristi svježe smrznuta plazma (SSP), no danas se kao alternativa sve češće koristi koncentrat protrombinskog kompleksa (engl. prothrombin complex concentrates - PCC) zbog brojnih prednosti u odnosu na SSP, a koje uključuju primjenu manjeg volumena, bržu korekciju INR-a, bržu dostupnost, bolji sigurnosni profil, a također nije potrebna ni krvno grupna specifičnost. Cilj ovog rada je pružiti kratki pregled o osnovnim indikacijama, sigurnosti i učinkovitosti primjene PCC u stanjima krvarenja različite etiologije.

Ključne riječi: *Krvarenja, hitna medicinska služba, koncentrat protrombinskog kompleksa.*

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Review

VENOMOUS SNAKEBITES IN CROATIA, CLINICAL PRESENTATION, DIAGNOSIS AND TREATMENT

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SUMMARY – Venomous snake bites are recognized as a major public health problem, affecting mostly poor, underdeveloped areas in the tropical and subtropical areas. Every year, more than three million bite cases and about 100,000 deaths are registered worldwide. Over the past years, 632 people have been hospitalized in Croatia with only 3 deaths due to venomous snake bites. Favorable geographic position, warm climate and great biodiversity of Croatia have resulted in the development of a total of 15 species of snakes, of which only 3 are venomous: horned viper (*Vipera ammodytes*), the common European viper (*Vipera berus*) and meadow viper (*Vipera ursinii macrops*). Snake venom envenomation is called ophidism (greek ofis=snake). Snake venoms are complex mixtures of proteins and toxins that have a wide range of toxic effects. The clinical presentation of ophidism is due to hematotoxic, neurotoxic, myotoxic (cardiotoxic) and cytotoxic effects of venom. There is currently no test to identify patients with a systemic spread of the venom, the diagnosis is made by a combination of diagnostic tests, clinical symptoms and sings of systemic envenomation. Ophidism is a medical condition that requires urgent treatment. Following first aid given at the scene, the patient should be transported to the closest medical facility to assess the severity of the clinical presentation in a timely manner and take the necessary treatment measures.

Keywords: Croatia, *ophidism, epidemiology, diagnostics of ophidism, treatment*

Introduction

Venomous snake bites are emergencies that pose a clinical challenge due to a possible rapid fatal outcome. The group of venomous snakes with the highest medical importance, as defined by the World Health Organization includes species that are widespread in densely populated geographical areas where they cause bites resulting in high morbidity, disability and mortality, as well as species that are understudied but provide a strong indication of this that they could pose a significant risk to humans, and finally species whose bites, although rare, in principle result in severe and life-threatening systemic envenomation[1]. 2,500 to 3,000 species of snakes have been explored till now, and approximately 375 different species are considered venomous, of which 250 can cause severe systemic envenomation in humans[2,3]. Venomous snake bites are recognized as a major public health problem, affecting mostly poor, underdeveloped areas in tropical and subtropical regions.[4,5]. For this reason, the World Health Organization included venomous snake bite as a neglected tropical disease in June 2017, and in May 2019 launched a plan to double the reduction in number of deaths and disabilities by 2030, with particular emphasis on antidote development and their adequate availability in the most vulnerable countries[6]. Worldwide, the venomous snake bites more than three million people each year, while approximately 125,000 die[1]. In Europe, including the European part of Russia and Turkey, about 7,500 snake bites have been reported annually, 1,000 cases of severe clinical presentation of

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systemic envenomation with an average of four deaths[2,3]. According to statistics of the Croatian Institute of Public Health, a total of 632 people were hospitalized due to venomous snake bites in the period from 1998 to 2019. The highest number of hospitalizations was in 2001-58; 2000 - 57; 2018 - 40; 2019 - 18. In the last 20 years, only 3 snake bites deaths were recorded in the Republic of Croatia, in 2006, 2007 and 2013. Analyzed for this period, the mortality rate from venomous snake bites in Croatia is 0.2% per year[2,7]. It is believed that the number of snake bites is much higher because not all injured people seek medical help due to unavailability of health care or turn to the methods of traditional medicine. The number of venomous snake bites is on the rise, partly due to climate change, and due to the growing trend of keeping exotic venomous snakes as pets.

Species and geographic distribution of venomous snakes

We distinguish four families of venomous snakes: *Colubridae* (colubrids), *Elapidae* (elapids), *Viperidae* (vipers), and *Atractaspidae* (sub-terranean snake venoms of Africa and the Middle East). During evolution, *Colubridae* lost their venomous glands and only a few specimens are dangerous to humans. Their fangs are located at the back of the upper jaw, which prevents them from successfully biting their prey. The fangs of the Elapidae group are located in front of the upper jaw and cannot rotate or move. The vipers (*Viperidae*) have hollow venomous teeth that are located in front and through which the venom is expelled when bitten. The vipers (*Viperidae*) are divided into true vipers (*Viperinae*) and rattlesnake (*Crotalinae*)[8]. On all continents, except Australia, the number of non-venomous snake species is higher than the number of venomous snakes[7]. The most venomous snake species are in the tropical and subtropical zone, India, the Malay Archipelago, Brazil, Central America, the southern United States, and some parts of Africa. Among the few families of venomous snakes in Europe, only vipers (*Viperidae*), mainly the subspecies of the true viper (*Viperinae*). From the rattlesnake subfamily (*Crotalinae*), only Ancistrodon halys inhabits the extreme southeast of Europe. There are areas in the world where there are no venomous snakes at all. In Europe, these are Ireland, Iceland, the Balearics, Corsica and Sardinia[9]. Croatia is the area with the most widespread venomous snakes throughout Europe[10].

Snakes in Croatia

Favorable geographical position, warm climate and a great biodiversity of Croatia have conditioned the development of a total of 15 species of snakes, of which only 3 belong to the venomous ones. These are horned viper (*Vipera ammodytes*), the common European viper (*Vipera berus*) and meadow viper (*Vipera ursinii macrops*). Two species belong to the semi-venomous category, dragon (*Malpolon insignitus*) and the European ratsnake (*Telescopusfallax*), which cannot bite humans hard enough to inject venom, while the remaining species are non-venomous and harmless. In the south of Croatia, snakes are active from late winter to late autumn[6].

The horned viper (*Vipera ammodytes*) is the most dangerous European venomous snake, also the most important snake in Croatia, given the severity of the systemic envenomation it can cause and the outcome of which can be fatal[8]. Despite the complex taxonomic status and insufficiently uniform division of this species, two subspecies are considered significant: *Vipera ammodytes ammodytes* and *Vipera ammodytes meridionalis*[11]. In Croatia, the subspecies *Vipera ammodytes ammodytes* predominates, which is particularly common in Dalmatia, as it lives more often in dry and rocky areas than in lowland areas[8]. Its length reaches up to 90 cm, the head is extended at the nape of the neck, and at the tip of the nose is a soft horn covered with scales. It is ash gray in color that turns yellowish-brown and reddish-brown in some specimens, and both black and white specimens were found. A dark winding line extends along the entire body in the middle of the back. On the underside, the horned viper is whitish with black dots. The horned viper inhabits dry, rocky areas with bushes. It is mostly active at night. In cold areas, it goes into hibernation (winter sleep). In mountainous areas, it can be found at an altitude of 2500 m. It is widespread from South Tyrol and Carinthia to Asia Minor, and it is also found on larger Croatian and Greek islands[12]. In venom glands, adult specimens of horned viper have 10-45 mg of venom, and one bite can excrete as much as 20 mg of venom, which can be a lethal dose for a healthy adult, especially children, and chronically ill patients.

The common European viper (*Vipera berus*) is the most widespread snake in the world. There are two subspecies in Croatia: *Vipera berus berus*, in the area of Gorski Kotar, and *Vipera berus bosniensis*, in the area of floodplain meadows along the Sava, Drava and Danube river, and the mountains Triglav and Dinara. The length ranges from 60 to 80 cm, and large females reach up to 90 cm. The head is broad and triangular, the torso rounded, narrowed in the neck area. A characteristic sinuous dark line stretches in the middle of the back of the body. It is variable in color, from ashy gray to black (melanistic shape), but can also be reddish without a characteristic pattern and greenish. The common European viper bites are much rarer than the horned viper bites and are rarely fatal to a healthy adult[12].

The meadow viper (*Vipera ursinii macrops*) is our smallest and rarest venomous snake, about 50 cm long. It is light gray to yellow with a dark dashed pattern on the back[12]. Its bites are much rarer in our areas than the horned viper and the common European viper bites[10]. It is found on the southern, grassy slopes of Velebit, Dinara and Kamešnica[12]. The common European viper and meadow viper are strictly protected domestic species, while the horned viper is currently only a protected domestic species. In recent years, the number of venomous snakes in Croatia has increased significantly both in the Zagreb Zoo and among private individuals[13].

Snake venom

Snake venom envenomation is called ophidism (greek ofis=snake). Of all the venoms of natural origin, those produced by venomous snakes are considered the most complex, containing more than a hundred different bioactive molecules of variable toxicity and pathophysiological effects, acting individually and/or combined. From a biochemical point of view, snake venoms are complex mixtures of proteins and polypeptides that make up more than 90% of the total dry matter of the entire venom, and low molecular weight organic molecules, including amines, free amino acids and lipids, carbohydrates, citrates, nucleosides, and various inorganic ions. primarily sodium, zinc, and calcium[14,15]. According to the clinical symptoms of poisoning, the division of snake venoms into those with neurotoxic, hematotoxic, cytotoxic and myotoxic (cardiotoxic) effects is common. Snakes from the family *Viperidae* have venom of predominantly hematotoxic and necrotoxic effects, while snakes from the family *Elapidae* have primarily neurotoxic venom. Depending on the site of action, the components of venom can be divided into those with local and systemic action[14]. Snake venoms contain enzymatic and non-enzymatic proteins and peptides that are classified into different families according to their structure and function[16]. Enzymatically active proteins in snake venoms are: phospholipases A2 (PLA2), zinc-dependent metalloproteinases, serine proteinases, L-amino acid oxidases and acetylcholinesterases. Proteins isolated so far without enzymatic activity are three-finger toxins, α-neurotoxins, disintegrins, C-type lectins, natriuretic peptides, myotoxins, cysteine-rich secretory proteins, neuronal and vascular endothelial growth factors, cystatins and Kunitz-type protease inhibitors[16,17].

Previous research indicates that differences between snake venoms are due to the variable presence of protein components that exhibit (no) enzymatic activity and that the composition of snake venom can vary within genera and even species due to ontogenesis, geographic distribution, which can significantly change the clinical presentation and the course of symptom development and further complicate the treatment of venomous snake bites[18,19]. Snake venom PLA2 is one of the most researched components showing heterogeneous pharmacological effects, of which the most important are neurotoxic and myotoxic[20,21]. Three venomous phospholipases called amoditoxins have been found in vipers, the most venomous European snakes. Most PLA2 acts like β-neurotoxins, by binding to specific receptors on the presynaptic membrane irreversibly inhibits the release of acetylcholine in the neuromuscular junction, thus causing a complete disruption of signal transduction in motoneurons. Neurotoxicity is also manifested by phospholipase activity and blocking of voltage-dependent potassium channels[17,22]. In addition, PLA 2 can cause mitochondrial membrane disorders in respiratory muscles due to the hydrolysis of phospholipids[23,24], leading to acute neuromuscular weakness, followed by flaccid paralysis[25]. Snake venom PLA2 is known to cause local or systemic skeletal muscle necrosis. The myotoxic effect essentially manifests itself in the form of rapid, drastic and irreversible biophysical changes of the sarcolemma, which are attributed to disruption of its integrity, depolarization and finally, an increase in

permeability followed by loss of cytoplasmic markers, e.g. myoglobin, creatine kinase, and lactate dehydrogenase[16].

Zinc-dependent metalloproteinases account for about one-third of the total protein composition of the venom and are considered major toxins responsible for local tissue damage at the site of the bite. They are a common component of snake venom from the *Viperinae* family. Metalloproteinases have the ability to directly activate cells and release endogenous bioactive components directed to basement membrane proteins, coagulation factors, platelets, endothelial and anti-inflammatory cells[16,17,22].

Metalloproteinases and PLA2 are known to cause venom-induced expendable coagulopathy, which can be complicated by life-threatening bleeding. The procoagulant action of metalloproteinases, mediated by their repeated activation of coagulation factors, is most likely to be manifested as a marked depletion of available plasma fibrinogen concentrations which are required for efficient blood clotting in blood vessel injury[8]. PLA2 inhibits the process of blood clotting and platelet aggregation by hydrolysis of platelet phospholipids and thus acts on the sites where coagulation complexes are formed[26,27].

Some snake venoms have been researched in detail due to common envenomation that over time have led to the production of antidotes. Some components of the venom have been identified as beneficial due to their mechanism of action on the human body which has been used in the pharmaceutical industry for the production of drugs[15]. The first drugs produced on the basis of snake venoms were the antihypertensives captopril and enalapril, the antiplatelet drugs tirofiban and eptifibatide (Integrilin ®)[28].

The role of snake venom in the treatment of certain diseases has been intensively investigated in recent years, as the components of snake venom have been shown to have antitumor, anti-inflammatory and immunomodulatory properties.[30]

Clinical presentation of ophidism

The purpose of a snake bite is for food or defense, so we distinguish two types of bites, a bite for food or a bite for defense, based on the amount of venom injected into a victim or attacker[16,29]. In a snake whose purpose is to bite for food, the intention is to kill the victim, the snake bites the victim and injects a large amount of venom, and the prey is swallowed only after killing it. By biting in order to defend, the snake injects a smaller amount of venom into the victim because it tries to escape and thus defend itself. A bite in which the venom does not empty the venom glands is called a dry bite[29]. The dose of venom injected into the human body depends on the size of the snake, the location of the bite and the characteristics of the victim. Because of their relatively lower body weight, children receive a higher dose of venom per unit body weight. Although venomous snake bites in adults and children present a similar clinical presentation, the severity of the envenomation clinical presentation is more severe in children and complications of snake envenomation are more common in childhood[30,31].

The clinical presentation of ophidism is due to hematotoxic, neurotoxic, myotoxic cardiotoxic and cytotoxic effects of venom.

The common classification of snake bite envenomation which is often used in everyday clinical practice to show the severity of the clinical presentation of envenomation, is:

- Very mild reaction - the appearance of local edema, without general signs and symptoms, except the patient's fear
- Mild reaction - the appearance of local or widespread edema, with or without gastrointestinal signs and symptoms, but without the appearance of general symptoms
- Moderate reaction - the appearance of extensive edema, shock lasting less than two hours, and the appearance of other signs and symptoms of moderate envenomation
- Severe reaction - the appearance of shock lasting more than two hours or recurrent shock and the appearance of other signs and symptoms of severe systemic envenomation
- Fatal outcome - obvious signs of systemic envenomation ending in death[10,32].

The diagnostics of ophidism

Achieving timely diagnosis, and thus treatment of ophidism, is a challenge facing physicians around the world[33]. For years, much effort has been put into development of new diagnostic tools that would facilitate

the rapid diagnosis of venomous snake bites, particularly in rural areas of the tropics. Studies have shown that early treatment of patients after venomous snake bites is associated with faster recovery and shorter hospital stays[34,35]. On the other hand, delayed treatment has been found to increase the risk of severe and life-threatening complications (acute renal failure, respiratory muscle paralysis, bleeding due to consumable coagulopathy, cardiac arrhythmias) leading to prolonged hospital stays and increased treatment costs[36,37]. There is currently no test to identify patients with systemic envenomation, the diagnosis is made by a combination of available diagnostic tests and clinical symptoms of systemic envenomation. The availability of diagnostic tests available to clinicians varies from country to country, and the level of experience in diagnosing and treating venomous snake bites varies greatly among clinicians from different hospitals. To date, diagnostics has been based on techniques ranging from immunological tests (usually an ELISA test), through enzyme activity tests, to forensic genetic methods. Tests are used to detect the venom in the blood, to evaluate the effectiveness of the antidote used to neutralize the venom, to determine the type of snake. The downside is that most of the available tests last at least 3-4 hours and are not suitable for clinical use, but are used only for research purposes. Since venomous snake bites are an emergency where toxins are present within minutes, it would be useful to have a diagnostic device for clinical use that operates on a timescale of minutes rather than hours and is stable over a wide range of temperatures and ambient conditions[38].

The basic diagnosis of ophidism includes a detailed history of the patient, targeted examination and appropriate laboratory tests. Collection of a detailed medical history includes examining the circumstances of the bite (e.g. geographic area, time of the bite, number of bites), details of the snake (if seen, photographed), clinical manifestations of the venom (including onset time), first aid and previous illnesses (eg comorbidities, allergies, previous snake bites, medications)[38]. Laboratory tests include evaluation of the coagulation profile to check for venom-induced coagulopathy by repeated measurements of the international normalized ratio (INR) of blood coagulation, activated partial thromboplastin time (aPTT), D-dimer and/or fibrinogen degradation products. An acute decrease in hemoglobin and hematocrit may indicate internal bleeding, and a decrease in fibrinogen levels may indicate coagulopathy. Blood levels of creatine kinase, electrolytes, urea, and creatinine are also measured, which can be used along with analysis of urine (hematuria, proteinuria, urea levels, and urine excretion) to assess venom-induced rhabdomyolysis and associated complications, such as acute renal failure caused by myoglobulinemia, polyuria, oliguria, or anuria[39].

Treatment of ophidism

Epidemiological researches have shown that mortality from snake bites is not a major concern, and hospitalization and rapid diagnosis are crucial to determine the proper use of antidotes which is the only specific treatment for venomous snake bites[38]. Ophidism is a medical condition that requires urgent treatment. At the time of the bite, the victim should rest, the bite site should be cleaned, and in the case of a limb bite, the limb should be immobilized. No other form of alternative and local lay help or self-help is recommended on the ground. When providing first aid at the scene, the patient should be transported to the nearest medical facility to assess the severity of the clinical presentation in a timely manner and to take the necessary treatment measures[10]. In a hospital setting, the patient is monitored and in case of progression of local and/or general symptoms, symptomatic and specific treatment is applied. When a snake bites, the amount of venom injected may not be significant, and such a bite may not require the administration of an antidote. Therefore, constant monitoring of patients is required.

The use of anti-viper serum (antidote) is recommended in our area for the moderate and severe clinical presentation of envenomation, especially in children and pregnant women, as they represent a group with an increased risk of developing complications. Pregnant women are at risk for both mother and child, and in 50% of cases, intrauterine bleeding and/or miscarriage occurs[2,10,40]. The antidote is hyperimmune globulin obtained from an animal previously immunized with snake venom. It prevents or reverses the effect of snake venom[2]. It can be monovalent or polyvalent, depending on whether it is effective for the bite of one or more species of venomous snakes. The antidote for venomous snakes in Croatia was produced at the Immunological Institute in Zagreb. It is a polyva-

lent antidote that effectively neutralizes the venom of all three venomous snakes in our area[13]. As the last batch produced expired on November 30, 2019, currently, the supply of anti-viper serum in Croatia is provided by imports[10,41].

The antitoxin should be administered according to the manufacturer's instructions. It is used exclusively in hospital conditions because its use can cause serious reactions (allergic reaction, anaphylactic shock, serum sickness)[41]. After anti-viper serum, protection against tetanus should be given depending on the immune status of the tetanus patient. The prophylactic use of antibiotics is not recommended, only in cases of proven infection (based on the isolated causative agent and its sensitivity to the antibiotic). Corticosteroids are used only in the treatment of allergic reactions to serum, while some authors recommend the use of corticosteroids in "compartment" syndrome. If the patient is severely disturbed or in shock, treatment is carried out in the intensive care unit using crystalloid solutions, blood products, sedatives, anticonvulsants, mechanical ventilation, hemodialysis and other necessary measures. Surgical intervention is sometimes required for incision of a hemorrhagic bulla or abscess, necrectomy, fasciotomy, or amputation of part or all of the limb. It is very important to recognize the development of "compartment" syndrome in time, which requires urgent fasciotomy[42].

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Sažetak

UGRIZI ZMIJA OTROVNICA U HRVATSKOJ, KLINIČKA SLIKA , DIJAGNOSTIKA I LIJEČENJE

D. Tunjić Pejak, V. Nesek Adam i *I. Srzić*

Ugrizi zmija otrovnica značajan je javnozdravstveni problem koji uglavnom pogađa siromašna, nerazvijena područja u tropskim i suptropskim krajevima. Svake godine u svijetu bilježi se više od tri milijuna slučajeva ugriza i oko 100.000 smrtnih slučajeva. U zadnjih 20 godina zbog ugriza otrovnih zmija u Hrvatskoj hospitalizirano je 632 osobe sa samo 3 smrtna ishoda. Povoljan geografski položaj, topla klima i velika bioraznolikost Hrvatske uvjetovao je razvoju ukupno 15 vrsta zmija od kojih samo 3 pripadaju otrovnicama: poskok (*Vipera ammodytes*), riđovka (*Vipera berus*) i planinska riđovka tj. planinski žutokrug (*Vipera ursinii macrops*). Otrovanje zmijskim otrovom naziva se ofidizam (grč. ofis-zmija). Zmijski otrovi su složene smjese proteina i toksina koji imaju širok raspon toksičnih djelovanja. Klinička slika ofidizma posljedica je hematotoksičnog, neurotoksičnog, miotoksičnog (kardiotoksičnog) i citotoksičnog djelovanja otrova. Trenutačno ne postoji test kojim bi identificirali bolesnike kod kojih je došlo do sustavnog širenje otrova, dijagnoza se postavlja kombinacijom dijagnostičkih testova i kliničkih simoptoma sustavnog otrovanja. Ofidizam je medicinsko stanje koje zahtijeva hitno zbrinjavanje. Nakon pružene prve pomoći na mjestu događaja, bolesnika treba prevesti u najbližu zdravstvenu ustanovu kako bi se na vrijeme procijenila težina kliničke slike i poduzele potrebne mjere liječenja.

Ključne riječi: *Hrvatska, ofidizam, epidemiologija, dijagnostika ofidizma, liječenje*

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Review

SEPSIS DEFINITION: WHAT'S NEW IN THE TREATMENT GUIDELINES

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SUMMARY – Sepsis is a life-threatening organ dysfunction caused by an unregulated response of a host. Septic shock is its most severe form. It is manifested by a drop in blood pressure, which decreases tissue perfusion pressure, causing hypoxia that is characteristic of shock. Sepsis is still one of the leading causes of mortality worldwide. Its incidence has increased since the first consensus definitions were established in 1991. Raising sepsis awareness, its significance and the need for better treatment, has led to an improvement in in defining sepsis and the development of guidelines for its treatment. The first guidelines were published in 2004, the second 2008, the third 2013, the fourth 2016, and the last revised guidelines appeared in 2021. This paper will describe the previous and new definitions of sepsis and septic shock, the previous guidelines for the recognition and treatment, and the latest recommendations for treatment. Timely diagnosis is crucial for the outcomes for patients with sepsis and septic shock. The fact is that the sepsis care bundles have been modified to increasingly shorter time determinants, which emphasizes the importance of emergency physicians, who frequently first recognize and begin emergency treatment of septic patients.

Key words: *sepsis, septic shock, treatment, definition, bundles*

Introduction

Sepsis is often the immediate cause of death of critically ill patients in an intensive care unit (ICU). It is still one of the leading causes of morbidity and mortality in the world. The incidence of sepsis and septic shock has been steadily increasing since the first consensus definition in 1991. The appropriate definition of sepsis also plays a role in correct and rapid recognition. Research has shown that early identification and timely care of patients has the greatest impact on reducing mortality. Until recently, sepsis was defined as a clinical syndrome that manifests as a systemic inflammatory response syndrome (SIRS) to infection. However, there are no specific clinical, imaging or biochemical indicators to indicate this condition. The nonspecificity of the signs of SIRS, on which the definition of sepsis was based, was the reason for a significant discrepancy in the presentation of the incidence and mortality of sepsis in epidemiological studies. The latest redefinition of sepsis (2016), which highlights the host's inadequate response to infection, makes it easier to recognize sepsis in daily clinical practice. The results of scientific research demonstrate that the incidence of sepsis is increasing, but thanks to the efforts of the Surviving Sepsis Campaign (SSC) and the development of guidelines or recommendations in the form of bundles for the treatment of sepsis, there has been a reduction in mortality. However, the total number of deaths due to sepsis is still rising, as more people are getting sick. The sepsis care bundles are a set of evidence-based components that, if implemented togeth-

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er, can lead to a better treatment outcome than if applied individually.

How the definition of sepsis has changed over time

The first definition of sepsis dates to 1992 and was the result of an agreement among world experts in the field of intensive care. Sepsis is defined as the systemic immune response syndrome (SIRS). In addition to sepsis, the term severe sepsis is defined as sepsis associated with organic dysfunction, hypoperfusion and hypotension, and the term septic shock as a condition of sepsis with arterial hypotension insensitive to fluid replacement. The diagnosis of sepsis was based on the presence of a suspected infection and clinical or microbiological evidence of infection in the presence of at least two of the four systemic inflammatory response criteria (SIRS).. The following SIRS criteria were established: body temperature above 38 ° C or below 36 ° C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 beats per minute or carbon dioxide partial pressure below 4.3 kPa, and neutrophilia above 12000 / mm3 or neutropenia below 4000 / mm3 with 10% or more of non-segmented peripheral blood neutrophils.[1] Severe sepsis is sepsis with organic dysfunction, hypoperfusion or hypotension. Septic shock is sepsis-induced hypotension despite adequate fluid resuscitation in the presence of perfusion abnormalities. The first definition of sepsis was not specific enough to distinguish sepsis patients from those patients who had a normal inflammatory response to infection or an inflammatory condition not caused by infection.

To improve the diagnosis of sepsis, in 2001 the definition of sepsis was supplemented by an expanded list of clinical and laboratory indicators that made it easier for clinicians to diagnose sepsis[2]. According to this definition, septic patients are grouped according to the severity of the clinical condition. Sepsis is classified as a clinical syndrome ranging from septicemia to severe sepsis followed by the failure of vital organ function and septic shock as the most severe form of sepsis, in which deep hypotension is the dominant sign[2]. The new definition has not yet solved the problem of "specificity," but the incidence of sepsis and septic shock has increased significantly. The reason is the higher number of patients with many associated diseases, a higher proportion of those who are immunocompromised, but also the lack of specificity of the definition according to which the group of patients with sepsis includes those patients with uncomplicated infection or mild cold.[3,4] On the other hand, following these guidelines provides sufficient time for timely detection of sepsis and early inclusion of valid therapy, which is extremely important in preventing the progression of this condition to severe sepsis, and especially septic shock, which is accompanied by significantly higher mortality rates[5].

The third redefinition of sepsis was made in 2016.[6] Due to the already mentioned insufficient specificity of the existing (old) definition of sepsis, there was a need for a new definition that would be more specific than the previous one and allow easier recognition of sepsis in everyday clinical practice. It is based on the pathobiology and pathophysiology of the host's response to infection, which is described as "non-homeostatic." The most important changes are the elimination of the terms "SIRS" and "severe sepsis." Sepsis is now defined as a life-threatening organ failure caused by the host's inappropriate response to infection. Organ failure is now considered if there is a change in sequential, sepsis-related organ failure assessment (SOFA), where two points or more are associated with a hospital mortality rate greater than 10%. Septic shock is defined as a subtype of sepsis, and is manifested by circulatory, cellular, and metabolic instability associated with a higher risk of death than sepsis itself. The criteria for diagnosing septic shock are: hypotensions requiring vasopressor therapy to maintain mean arterial pressure >65 mmHg and serum lactate levels greater than 2 mmol/L after appropriate management of hypovolemia. This combination is associated with a hospital mortality rate of more than 40%. To avoid delays in the start of treatment for patients who are placed outside the ICU, a new simplified version of the SOFA scale has been designed - a fast SOFA scoring system called quick SOFA (qSOFA). It is recommended for rapid diagnosis in outpatients and emergency hospital admissions for patients with suspected infection and sepsis. The qSOFA scale assesses the patient's mental, cardiovascular and respiratory status. The criterion for hypotension is systolic pressure <100 mmHg, for tachypnea respiratory rate >22 breaths per minute and Glasgow coma scale (GCS) <15. They emphasize that qSOFA does not de-

fine sepsis but allows rapid identification of all patients at potential risk of sepsis because it is an indicator of an increased risk of clinical deterioration.[7] The key advantages of qSOFA are that it is easy to measure and does not require laboratory testing. It can be performed quickly and repeatedly.

Previous sepsis survival campaign recommendations

Despite significant advances in understanding pathophysiology and supportive treatment options, mortality from sepsis and septic shock remains very high. It is estimated that one in five patients diagnosed with sepsis dies. Mortality is also high in patients in whom transient improvement is achieved through intensive treatment, and the reason for this is most often complications associated with existing diseases or irreversible impairment of the function of one of the vital organs [3,8,9]. Sepsis and septic shock have been identified as important public health issues, prompting intensive care professionals to develop guidelines, the SSC, that could guide clinicians in treating septic patients. The campaign to introduce the guidelines was initiated at a meeting in Barcelona, based on all previous guidelines based on evidence and renewed research on more than 30,000 patients[10]. The main idea was to define global criteria for early detection of sepsis with recommendations for the implementation of certain therapeutic procedures in order to improve their effectiveness and reduce mortality by 25% over five years. The guidelines have undergone many changes over the years as part of the latest clinical research and new pathophysiological findings on sepsis. The first original guidelines were published in 2004[3], and have been updated and supplemented on several occasions to date in 2008, 2012, 2016 and 2018. The last renewal and amendment of the SSC was performed in 2021. Evidence based methodology was used in the renewal of the guidelines.

The first SSC guidelines from 2004 included two bundles called "Sepsis resuscitation bundle" and "Sepsis management bundle" for the care of patients who had to be completed as soon as possible within 6 hours and 24 hours, respectively. The 6-hour initial care package included serum lactate extraction, exclusion of blood culture samples, administration of broad-spectrum antibiotics within 3 hours of hospital admission, hypotension or serum lactates >4 mmol / L fluid replacement 20 ml / kg, and the introduction of vasopressor support at MAP <65 mmHg despite fluid replacement. It was recommended that central venous pressure >8 mmHg be maintained in persistent hypotension (septic shock) despite fluid and / or lactate replacement >4 mmol / L. The 24-hour beam included GUK glycemic control <8.3 mmol / L, peak pressure <30 cm H2O in patients on mechanical ventilation, steroid use in patients on continuous vasopressor therapy, and recombinant human activated protein C (rhAPC).

The second edition of the 2008 amended guidelines incorporated the previous two bundles for the management of sepsis and septic shock with minimal changes, but now with incorporated recommendations for clinicians. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system has been adopted, which is a link between clinical research and everyday practice and describes the levels of recommendations with the strength of evidence.[11]

The SSC campaign updated and revised the sepsis guidelines in 2012.[12] The update introduced several important changes to recommendations important for the treatment of severe sepsis and septic shock in emergency departments. The guidelines have been changed to a "3-hour bundle" and a "6-hour bundle" with similar elements but recommends that interventions be carried out in a shorter period of time. The 3-hour bundle requires: measurement of serum lactates, exclusion of blood culture samples prior to antibiotic administration, broad-spectrum antibiotic administration, and crystalloid replacement of 30 ml / kg for hypotension or serum lactates $\geq$ 4 mmol / L. within 3 hours of patient triage. The 6-hour bundle recommends the use of vasopressor support for hypotension that does not respond to initial fluid resuscitation or lactate $\geq$ 4 mmol / L. The guidelines advise measuring central venous pressure and oxygen saturation of venous blood. They also recommend re-measuring lactate if initial lactate levels are $\geq$ 4 mmol / L. The 24-hour bundle is no longer recommended.

Following the redefinition of sepsis in 2016,[4] a new updated edition of the SSC recommendations was published. According to the 2016 guidelines, sepsis and septic shock are emergencies and treatment should be started as early as possible, immediately after the

presentation of a patient with sepsis or septic shock criteria.[6] Thirty-two-strong recommendations, 39 weak recommendations, and 18 best practice statements were published. The 3-hour and 6-hour bundles were revised or remained the same but with the elimination of central venous pressure measurements and venous blood oxygen saturation. In the case of sepsis accompanied by severe hypotension, the guidelines require aggressive volume compensation (administration of 30 ml / kg intravenous crystalloid solution within the first three hours). Prior to initiating antimicrobial therapy, at least two blood samples should be taken for blood cultures, and empirical administration of one or more broad-spectrum antimicrobial drugs should be initiated to address all possible causes. If the patient's clinical condition indicates septic shock, antimicrobial drugs should be administered within one hour. If hemodynamic stabilization is not achieved with volume compensation, vasoactive support should be included. Noradrenaline is recommended as the first-choice vasopressor. If the expected therapeutic effect of noradrenaline is absent (a target mean arterial pressure of 65 mmHg or more), adrenaline or a combination of vasopressin and adrenaline or vasopressin alone may be added to reduce the noradrenaline dose. Dopamine has been used as a good substitute for norepinephrine according to the updated guidelines, but only in patients at low risk for tachyarrhythmias. The use of corticosteroids has been recommended in patients with septic shock whose volume resuscitation and vasopressor support have not achieved hemodynamic stability. Appropriate mechanical support should be used in patients with sepsis failure. Protective ventilation is recommended, so that the target inspiratory volume does not exceed 6 ml / kg. Also, using the SOFA identify patients with sepsis to more quickly, a new "qSOFA" scoring system is proposed for quick screening of patients outside the ICU who are at risk of developing sepsis.[7]

With the revision of the SSC guidelines in 2018, 3-hour and 6-hour bundles are combined into a revised Hour -1 bundle with the intention of starting the care for septic patient's immediately[12]. It takes more than an hour to complete all recommendations, but it is crucial to start all treatment recommendations immediately. Zero time is defined as the time of triage in the emergency department or from the time the sepsis criteria are recorded in the medical documents. The new 1-hour bundle includes 5 steps: measurement of serum lactates, and re-measurement in 2-4 hours if $\geq$ 2 mmol / L, exclude blood cultures before antibiotics, administration of broad-spectrum antibiotics, volume resuscitation 30 ml / kg in case of hypotension or if lactate $\geq$ 4 mmol / L and vasopressor administration in hypotension during or after volume replacement to maintain MAP $\geq$ 65 mmHg.

Latest SSC guidelines

The fourth updated SSC campaign guidelines were published in 2021.[13]. They include recommendations for recognition and early care, source diagnosis and treatment of infection, hemodynamic care, ventilation, and additional therapeutic treatment recommendations. A new strong recommendation in the guidelines is the use of programs and tools like qSOFA, National Early Warning Result (NEWS), and Modified Early Warning Result (MEWS)) to improve care, including recognition in the populations of acutely ill and high-risk patients. It is recommended that qSOFA not be used as the only method for recognizing sepsis and septic shock, without SIRS, NEWS or MEWS. MEWS is a simple physiological result that helps to improve quality and safety in patient care. Five physiological parameters are measured: respiratory rate, systolic blood pressure, heart rate, level of consciousness and body temperature. NEWS is a scoring system for physiological measurements that are routinely recorded next to the patient's bed. Its purpose is to identify acutely ill patients, including those with sepsis. It measures six physiological parameters and evaluates values from 0 to 3: respiratory frequency, oxygen saturation, systolic blood pressure, pulse rate, neurological level of consciousness and body temperature. The guidelines emphasize that a systematic screening process is key to early identification of patients with sepsis.

For patients with sepsis-induced hypoperfusion or septic shock, we suggest that at least 30 mL/kg of IV crystalloid fluid should be given within the first three hours of resuscitation. The recommendation has now been moved from a strong to a weak recommendation level (caution in patients with heart failure and kidney disease). It is also recommended to lower serum lactate levels (weak recommendation), and an additional new recommendation (weak) is to monitor capillary filling to assess tissue perfusion.

If septic shock is suspected, it is recommended to use antimicrobial drugs immediately or within one hour of recognition (weak recommendation), and if sepsis is suspected without shock, consider non-infectious causes but administer antimicrobials within three hours from the time recognition of sepsis (weak recommendation). It is recommended to exclude microbiological samples before initiating therapy. In patients with suspected sepsis / shock but without confirmation of infection, continuous reevaluation and research of alternative diagnoses is recommended, as well as discontinuation of empirical antibiotic therapy if there is a suspicion of a cause other than infection (best practice statement), because 1/3 of patients with suspected sepsis eventually have a non-infectious disease.

For hemodynamic resuscitation, the use of balanced crystalloids instead of saline is recommended. The old guidelines recommended balanced crystalloids or saline. The use of albumin is recommended in patients who have received a large volume (moderate level), and the use of hydroxyethyl starch or gelatin is not recommended (strong recommendation). For septic shock on vasopressors, an initial target mean arterial pressure (MAP) of 65 mm Hg **over** higher MAP targets is recommended (strong recommendation). The new recommendation is to initiate vasopressor therapy peripherally to restore mean arterial pressure, rather than delaying onset until central venous access is provided (weak recommendation). Noradrenaline is still the vasopressor of first choice (high level of evidence). In the absence of the expected therapeutic effect of norepinephrine (target mean arterial pressure of 65 mmHg or more), vasopressin may be added to reduce the dose of norepinephrine (moderate level). As a third line alternative, adrenaline (weak recommendation) may be added. For shock with cardiac dysfunction and persistent hypoperfusion despite adequate volume status, the use of dobutamine in addition to norepinephrine is recommended (weak recommendation). The new guidelines suggest that levosimendan not be used. There is insufficient evidence to recommend a restrictive versus a liberal approach to fluid replacement during the first 24 hours of treatment in patients with sepsis / shock who continue to show signs of hypoperfusion and volume depletion.

New guidelines for sepsis-induced respiratory failure recommend the use of high flow nasal oxygen (HFNO) over noninvasive ventilation (NIV) (weak recommendation). Another new recommendation is that in severe acute respiratory distress syndrome caused by sepsis, the guidelines suggest the use of venous extracorporeal membrane oxygenation when conventional mechanical ventilation fails in experienced centers with infrastructure supporting its use.

The guidelines suggest that vitamin C should not be used to treat sepsis or septic shock (weak recommendation). The use of hemoperfusion with polymyxin B is not recommended (weak recommendation) and there is insufficient evidence for other blood purification techniques. It is recommended that corticosteroids be administered to patients in septic shock who require vasopressor therapy (weak recommendation) in a dose of hydrocortisone 200 mg / day, 50 mg every six hours or as a continuous infusion. In 2016, there was insufficient evidence for their use if hemodynamic stability was achieved by volume or vasopressor support. For suspected sepsis or septic shock, they suggest against using procalcitonin plus clinical evaluation to decide when to start antimicrobials, compared to clinical evaluation alone (weak recommendation). New guidelines for the first time place increased emphasis on improving care for sepsis patients after they are discharged from the intensive care unit. Recommendations for survivors of sepsis or septic shock include assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge.

Conclusion

The incidence of sepsis is still on the rise, although data from sepsis campaign efforts have shown some positive results. Further education and dissemination of knowledge that sepsis must be treated as a medical emergency is needed. The fact that the bundles for the care of septic patients have changed with their revision to shorter and shorter time determinants emphasizes the importance of emergency physicians as the first to recognize and begin emergency resuscitation and treatment for septic patients. Education, further clinical research, and adherence to recommendations and guidelines are important both in treatment and in further efforts to reduce mortality.

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Sažetak

DEFINICIJA SEPSE:"ŠTO JE NOVO U SMJERNICAMA ZA LIJEČENJE"

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Sepsa je po život opasna disfunkcija organa uzrokovana nereguliranim odgovorom domaćina na infekciju. Septički šok je najteži oblik sepse koji se očituje padom krvnog tlaka prilikom kojeg se smanjuje tlak perfuzije tkiva što uzrokuje hipoksiju tkiva koja je karakteristična za šok. Sepsa je još uvijek jedan od vodećih uzroka morbiditeta i mortaliteta u današnjem svijetu. Incidencija je u porastu još od prvog konsenzusa definicije iz 1991. Podizanje razine svijesti o sepsi, njenom značenju, prepoznavanju i potrebi što boljeg liječenja dovelo je i do usavršavanja definicije sepse te razvoja smjernica za liječenje. Prve smjernice su objavljene 2004.god., druge 2008., treće 2013., četvrte 2016. a zadnje revidirane smjernice 2021. godine. U ovom radu bit će opisana dosadašnja i nova definicija sepse i septičkog šoka, prikaz dosadašnjih smjernica za prepoznavanje i liječenje te najnovije preporuke. Pravovremena dijagnoza ključna je za ishod liječenja u bolesnika sa sepsom i septičkim šokom. Činjenica da su se snopovi postupaka za zbrinjavanje septičnih bolesnika svakom izmjenom mijenjali do sve kraćih vremenskih odrednica, naglašava ulogu I važnost liječnika hitne medicine kao onih koji prvi prepoznaju i započinju hitno zbrinjavanje septičnih bolesnika.

Ključne riječi: *sepsa, septički šok, liječenje, definicija, snopovi*

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Review

HIGH-DOSE INSULIN EUGLYCEMIC THERAPY

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SUMMARY – Calcium channel blockers and beta-blockers toxicity/poisoning are one of the most common causes of poisoning. More importantly, they are among the deadliest types of poisoning caused by cardiac drugs that emergency physicians can encounter. Common toxidrome caused by these medications includes the following symptoms: hypotension, bradycardia, hypoglycemia/hyperglycemia, hypothermia, arrhythmia, and seizures. Treatment is usually complex, It consists of administration of various medications, such as crystalloids, intravenous calcium, glucagon, vasopressors/inotropes, and especially high-dose insulin euglycemic therapy. In this paper, we will review the mechanism for this type of treatment, propose a potential protocol for its application and address possible adverse effects. High-dose insulin euglycemic therapy should be an integral part of the treatment protocol for calcium channel blockers and beta-blockers toxicity.

Key words: *calcium channel blockers, beta-blockers, toxicity, high-dose insulin euglycemic therapy*

Introduction

Cardiovascular drug poisoning is the second leading cause of death by drug poisoning, according to the U.S. Poisoning Network/National Poison Data System (NPDS). Among all cardiovascular drugs, most deaths were caused by beta-blockers and calcium channel blockers[1], a trend has been increasing for years. On the other hand, hyperinsulinemia-euglycemia therapy of cardiovascular drug toxicity has been unfairly neglected. In some scientific papers it has been mentioned as a last line of treatment, which should not be the case because treatment with high doses of insulin while maintaining euglycemia is an excellent way to treat the toxicity of cardiovascular drugs. There are not many articles or randomized studies on this topic in the literature, but it is known that the success rate of treatment of calcium blockers and beta-blockers toxicity with this protocol is between 84 and 100%. In this review, we will discuss the protocol, and its indications and safety, focusing on its use and effectiveness in an emergency department.

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Discussion

Symptoms of poisoning

The most common symptoms of poisoning with calcium channel blockers and beta-blockers are hypotension, bradycardia, and shock. The onset of symptoms depends on the formulation of the drug. In most cases of typical poisoning the symptoms will develop within eight hours, while drugs with a prolonged action period may take 24 hours. In cases of poisoning with unknown cardiovascular drugs and in which typical toxidromes occur, measuring blood sugar levels may be a key factor, since poisoning with calcium channel blockers usually results in hyperglycemia, while poisoning with beta-blockers results in hypoglycemia. Among other symptoms, it is important to mention the occurrence of nausea and vomiting, arrhythmias, as well as neurological symptoms, such as delirium, epileptic seizures, and coma.

The emergence of different symptoms caused by calcium channel blockers poisoning also depends on the characteristics of the drug itself. Thus, non-dihydropyridine blockers, such as verapamil, usually lead to deep myocardial suppression and less noticeable vasodilation. These patients are commonly presented with severe bradycardia. In contrast, patients with dihydro-

pyridine drug poisoning, such as amlodipine, usually present with more pronounced vasodilation and therefore predominantly with vasodilatory shock and reflex tachycardia, and only in high doses with bradycardia. Furthermore, there are differences in beta-blocker poisoning depending on the subgroup of the drug. Lipophilic drugs, such as propranolol, due to their characteristics, will lead to frequent CNS symptoms, such as delirium and epileptic seizures. Drugs that predominantly affect myocardial sodium channels (propranolol, carvedilol) may lead to the development of arrhythmias, especially with the widening of the QRS complex and development of monomorphic ventricular tachycardias, as well as the development of profound hypotension. Peripheral vasodilators (nebivolol) usually lead to profound hypotension due to their primary action.[2]

The treatment of poisoning

The treatment of poisoning caused by these drugs is complex and requires action using multiple mechanisms. Among the non-specific drugs that are used in the treatment, decontamination is worth mentioning. Activated charcoal can be applied if it one to two hours has passed since the ingestion of the drug. Irrigation of the entire intestine with polyethylene glycol should be considered when ingesting a large amount of a slow-releasing drug or amlodipine, which has a long action. Further treatment depends on the assessment of the patient's hemodynamic status, which can be made with ultrasound. This step is crucial because it is important to distinguish whether the cardiotoxic effect of the drug is predominant, which may manifest itself with reduced cardiac output, or whether the main problem is peripheral vasodilation. The recommended vasopressors are adrenaline and noradrenaline.[3] Adrenaline is the drug of choice because it can affect both hypotension and bradycardia. Noradrenaline is recommended in patients who predominantly present with symptoms of vasodilation, such as in cases of ingestion of dihydropyridine calcium channel blockers and beta-blockers with vasodilatory effect. Glucagon is also used in the first-line treatment. Glucagon acts by increasing intracellular levels of cAMP and has a positive inotropic and chronotropic effect, independent of beta-receptor activation, hence glucagon is superior in the treatment of beta-blockers poisoning, especially in patients presenting with reduced ejection fraction and bradycardia. On the other hand, glucagon has no effect on calcium channel blockers poisoning that have a dominant vasodilating effect. Application of intravenous calcium is indicated for calcium channel blockers poisoning as well as beta-blockers poisoning. Atropine may also be considered but is unlikely to affect bradycardia caused by poisoning with these drugs. As a second-line treatment, the use of methylene blue, ECMO, hemodialysis, and the application of lipid emulsions may be considered.

Hyperinsulinemia-euglycemia therapy

Part of the first-line treatment of calcium channel blockers and beta-blockers poisoning is certainly hyperinsulinemia-euglycemia therapy.[4] Hyperinsulinemia-euglycemia therapy (HIET) is primarily used in treating severe overdoses of calcium channel blockers, although it can also be used to treat beta-blockers poisonings that require inotropic support.

The mechanism of action is simple because this method of treatment supports the "metabolic hunger" of the heart, which is caused by the toxicity of calcium channel blockers or beta-blockers and which has a direct cardio-toxic effect. Poisoning with calcium channel blockers alone leads to several metabolic effects that must be emphasized:

- Hyperinsulinemia (insulin release is dependent on calcium uptake into the pancreatic beta cells via L-type calcium channels)
- Insulin resistance, which is caused by the toxicity of calcium channel blockers
- Calcium channel blockers act on the heart muscle cells by reducing the utilization of free fatty acids, increasing myocardial dependence on carbohydrates by reducing the intake of free fatty acids and glucose into muscle cells and by reducing the activity of mitochondria, which are essential for carbohydrate catabolism.

Insulin itself has several effects related to the repair of toxic effects:

- It increases the uptake of glucose and lactate into myocardial cells.
- It improves myocardial function without the need to increase oxygen demand.
- It increases pyruvate dehydrogenase activity, which improves lactate oxidation and the "cleansing" of cytosols from glycolysis byproducts that may affect calcium turnover and lead to diastolic dysfunction.

- It improves myocardial contraction due to greater glucose availability.
- It increases the activity of calcium-dependent ATPase in the sarcoplasmic reticulum.
- It increases the concentration of calcium in the cytoplasm.
- It improves calcium inflow into mitochondria.

In animal models of beta-blockers and calcium channel blockers poisonings, this treatment has led to better hemodynamic stability and survival compared to the treatment with vasopressors and glucagon.[5] In clinical studies, hyperinsulinemia-euglycemia therapy leads to a significant normalization of blood pressure and hemodynamic parameters in poisoning with various drugs from groups such as verapamil, diltiazem, amlodipine, propranolol, and other beta-blockers.[6,7,8]

Hyperinsulinemia-euglycemia therapy can be used together with catecholamines (as part of inotropic support) since they act favorably on each other. Insulin inotropy itself is not related to catecholamines and it is not affected by beta-blockade, thus an additive effect is expected. Furthermore, insulin itself has a beneficial effect on myocardial contraction, but without chronotropic effect, and in high doses it can lead to vasodilation.

The treatment of calcium channel blockers or beta-blockers toxicity with this method is particularly important in patients with predominantly myocardial disjunction (bradycardia and reduced ejection fraction) and the effect of this treatment is usually lower in patients with a clinical picture of vasodilatory shock.

Treatment protocol

The following treatment protocol is recommended. Begin the treatment with an insulin bolus at a dose of 1 unit/kg intravenously (IV). If the glucose level is lower than 11,1 mmol/L, administer 25g of glucose intravenously (IV). Next, start to administer insulin as a continuous infusion at a dose of 0.5-1 units/kg/h (in adults this does is usually between 35 and 100 units/h). It is recommended that insulin be administrated via an infusion pump to a separate intravenous route. If the response after 20 minutes is not adequate, the insulin dose should be increased by 0.5 units/kg/h every 15 minutes up to a maximum dose of a 4 units/kg/h (although there are scientific papers in which dosing went up to a maximum of a 14 units/kg/h). A favorable response is considered to be a hemodynamic stabilization of the patient. In addition, it is necessary to give glucose and maintain its range between 6 and 12 mmol/L. Start the infusion at 0.5 mg/kg/h (in any formulation - 5%, 10%, 25% glucose). Five percent glucose can lead to hyponatremia. Therefore it is necessary to monitor sodium levels every two hours. In addition, when administering 25% or 50% glucose, it is important to establish a central venous pathway to prevent the development of peripheral venous thrombophlebitis. At the beginning of the treatment, glycemia should be monitored every 15 to 30 minutes. The usual dose of glucose maintenance in patients treated with this protocol is 10 to 70 g of glucose per hour. After the hemodynamic stabilization of patients and improvement of organ perfusion, it is expected that the need for glucose to maintain normoglycemia will increase. After four hours of treatment with the maintenance of euglycemia, monitoring can be less frequent. It is recommended to monitor glucose every four hours. Potassium and acid-base status are initially monitored every 30 minutes, less frequently at a later stage of treatment. Patients should be hemodynamically monitored with blood pressure measurements every half hour and with frequent assessments of cardiac ejection fraction and myocardial contractility.[9]

Adverse effects

The adverse effects of this treatment are predictable and easy to treat. Even in extreme cases, when 1,000 units of insulin were accidentally given as loading doses in case of verapamil poisoning, there were no adverse events. Common side effects of this treatment are hypoglycemia (in 16% of cases), hypokalemia, hypomagnesemia, and hypophosphatemia. Hypoglycemia is paradoxically more common in cases of milder clinical toxicity presentations with hypotension. Glucose usually does not need to be given initially in patients with calcium channel blocker poisoning. Hypokalemia is a less common side effect and correction of hypokalemia should be avoided, as hypokalemia itself is the result of intracellular displacement of potassium from the extracellular space due to insulin rather than kaliopenia itself. Hypokalemia in this method of treatment also has positive effects, since it leads to improved myocardial contractibility due to increased calcium inflow into systole, and elevated intracellular potassium levels have a stabilizing effect on cardiac muscle cell membranes during excessive excitation (as in catecholamine treatment). Potassium levels should

be monitored every hour at the beginning of treatment and every two hours thereafter.[10] Regarding other electrolytes, it seems reasonable to monitor magnesium and phosphate levels every six hours, because during treatment, hypophosphatemia and hypomagnesemia may occur, primarily due to fluid loading. For all of these reasons and the need for constant monitoring, patients with beta-blockers or calcium channel blockers poisoning should be treated in the intensive care units.

Conclusion

Although there is a wealth of data in the literature on the safe treatment with hyperinsulinemia-euglycemia protocol, there are still many questions that can only be answered by randomized clinical trials, which are still lacking. However, since it is known in literature that the success of this treatment is very high, between 84 and 100%, this method of treatment is effective and safe in patients who have poisoning with calcium channel blockers or beta-blockers. The protocol can be started in parallel with other first-line treatment modalities. In cases where patients do not respond well to volume therapy, therapy with intravenous calcium or glucagon can be conducted. Hyperinsulinemia-euglycemia therapy is cheap, effective, and readily available. It has had excellent therapeutic responses with a small number of side effects that can be treated quickly and adequately.

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Sažetak

HIPERINZULINEMIJA-EUGLIKEMIJA LIJEČENJE

J. Hamzić, D. Raos i B. Radulović

Otrovanja sa blokatorima kalcijevih kanala i sa beta-blokatorima spadaju u jedne od češćih uzroka trovanja, ali još i važnije, jedne od najsmrtonosnijih trovanja sa kardiološkim lijekovima sa kojima se liječnici u hitnoj medicini mogu susresti. Tipičan toksidrom uključuje simptome poput hipotenzije, bradikardije, aritmije, hipoglikemije/hiperglikemije, hipotermije i epileptičkih napada. Liječenje je kompleksno, a samo specifično liječenje uključuje primjenu kalcija, volumena, vazopresora/intropa, glukagona, te osobiti naglasak stavlja na primjenu hiperinzulinemija-euglikemija liječenja. U ovom preglednom radu osvrnuti ću se na mehanizam ovog načina liječenja, protokol primjene te nuspojave koje se mogu javiti. Hiperinzulinemija-euglikemija liječenje trebao bi biti integralni dio protokola liječenja trovanja sa beta-blokatorima i blokatorima kalcijevih kanala.

Ključne riječi: *blokatori kalcijevih kanala, beta-blokatori, toksičnost, hiperinzulinemija-euglikemija, liječenje*

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Review

PERIPHERAL NERVE BLOCKS FOR HIP FRACTURES IN EMERGENCY MEDICINE

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SUMMARY – Hip fractures represent a major public health issue with increasing incidence as a population ages. The aim of this review is to describe peripheral nerve block techniques (the fascia iliaca compartment block and the pericapsular nerve group block) as pain management for hip fractures in emergency medicine, and to emphasize their benefits. Hip fractures are extremely painful injuries. The pain itself is unpleasant for patients and if left untreated it can lead to multiple complications during preoperative, operative and postoperative patient management. Pain management for elderly hip fracture patients is often challenging. Non-steroidal anti-inflammatory drugs are not recommended due to their side effects, the increased risk of gastrointestinal bleeding, renal function impairment and platelet aggregation inhibition. Paracetamol alone is often insufficient, and opioids have many potentially harmful side effects, such as delirium development. Peripheral nerve blocks for hip fractures are safe and effective, also in emergency medicine settings. The benefits for patients are greater pain relief, especially during movement, less opioid requirements and decreased incidence of delirium. Regional analgesia should be routinely used in hip fracture pain management.

Key words: *Hip Fractures; Pain Management; Nerve Block; Emergency Medicine*

Introduction

Hip fractures represent major public health issue with increasing incidence as a population ages.[1] The worldwide number of hip fractures in 1990 was 1.66 million and is estimated to increase to 6.26 million by 2050.[2] Approximately 75% of patients are women.[2-4] Hip fractures occur mostly in elderly patients after minor trauma, such as a fall from standing height.[2-4] One-year mortality among the elderly after a hip fracture is 30%, although novel studies suggest approximately 23%.[5]

Hip fractures are extremely painful injuries.[6] The pain itself is unpleasant for patients, and if left untreated it can lead to multiple complications during preoperative, operative and postoperative patient management.[7-9] The stress response represents physiological hormonal and endocrinal changes following trauma or injury, also known as the "fight or flight" response. The

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goal of stress response is to prevent further damage to tissue or the organism itself. But if prolonged, it consumes cell and tissue capacity to respond in a physiological way and causes pathophysiological disbalance. Inadequate pain management leads to prolonged stress response, which increases morbidity and mortality.[8-10]

Pain management in elderly hip fracture patients is often challenging.[11] Non-steroidal anti-inflammatory drugs are not recommended due to their side effects; increased risk of gastrointestinal bleeding, renal function impairment and platelet aggregation inhibition.[12] Paracetamol alone is often insufficient and opioids have many potentially harmful side effects[13,14] The role of regional analgesia, especially peripheral nerve blocks, is rising but they are still not used as often as they should.[11-5]

The aim of this review is to describe peripheral nerve block techniques for hip fractures in emergency medicine and to emphasize their benefits.

Peripheral Nerve Blocks

Fascia Iliaca Compartment Block

The fascia iliaca compartment block (FICB) was first described in 1989 by French investigator Dalens and his colleagues.[16] In FICB, a local anesthetic is injected beneath fascia iliaca to block simultaneously the femoral nerve, the obturator nerve, and the lateral cutaneous nerve of the thigh. At first it was performed as a "two-pops" technique with needle popping trough fascia lata and then fascia iliaca. The patient is in a supine position. The site of the injection is one centimeter distal from the medial two thirds and lateral third of a line between the anterior superior iliac spine and the ipsilateral pubic tubercule. It requires a large volume of local anesthetics, 30 to 40 ml, (0.25% levobupivacaine or 0.25% ropivacaine).[17] The advantage of FICB is a low learning curve and low complication rate, which is especially important for non-anesthesiologists, such as emergency medicine practitioners.[18-20] Today, FICB is performed with ultrasound guidance, which increases the success rate and decreases the rate of complications.[21]

Pericapsular Nerve Group Block

The pericapsular nerve group block (PENG) was first described in 2018 by Canadian investigator Girón-Arango and colleagues.[22] It requires a smaller volume of local anesthetic than FICB, 20 ml. PENG is performed with the patient in a supine position and injected with a local anesthetic between the psoas tendon anteriorly and the pubic ramus posteriorly. The authors used an ultrasound probe placed in a transverse plane over the anterior inferior iliac spine and then aligned with the pubic ramus by rotating the probe counterclockwise approximately 45 degrees. In this view the iliopubic eminence, the iliopsoas muscle and tendon, the femoral artery, and the pectineus muscle are clearly visible. The needle was then inserted in-plane. Some investigators have performed PENG without ultrasound guidance using nerve simulator[23] PENG is a relatively new technique and evidence is limited, but it appears that it could be even more effective than FICB, with a similar low learning curve.[24-25]

Methods

For purposes of this narrative review, we conducted s search of the MEDLINE and Cochrane databases in January 2022 to identify meta-analyses, systemic reviews and reviews published in last five years. The search key words were "hip fracture,*" "pain,, "peripheral nerve block,*" "analgesia," and "anesthesia" in various combinations. We identified 15 studies, 12 of them written according to the PRISMA statement and dealing with preoperative peripheral nerve blocks in hip fracture patients.

Results

Benefits of preoperative regional analgesia in hip fracture patients

Pain relief

Hip fracture patients experience severe pain, which becomes even stronger with movement. Patients must be moved from the site of trauma into an emergency medicine service vehicle, transported to emergency medicine department, transferred to an in-hospital stretcher, moved for radiological diagnostics, transported to a hospital bed, moved for personal hygiene, and finally transferred to an operating theater, where they are often positioned for regional anesthesia. As expected, preoperative regional analgesia provided significantly better pain relief to systemic analgesia alone, especially when dealing with pain on movement.[26-29].

Opioid requirements

Opioids have been used for a several centuries and remain potent analgesics when dealing with severe pain. Unfortunately, they have many well know side effects such as constipation, nausea and vomiting, etc. Among elderly, their role in developing delirium (an acute confused state) was controversial. Today, evidence supporting opioids as a factor in causing delirium is rising. So, it is of great importance to relieve pain in the elderly without opioids, or at least with a minimum dosage, if possible. Due to its effect on pain relief regional analgesia has been shown to decreases opioid requirements in hip fracture patients.[30-32]

Delirium – an acute confused state

Severe pain is one of the main risk factors for developing delirium among hip fracture patients. On the other hand, a second risk factor is opioid usage. Regional analgesia decreases the risk of developing delirium in hip fracture patients, particularly in the subgroup of patients with intermediate risk.[33-35]

Probable benefits

Preoperative regional analgesia probably shortens the time to mobilization after surgery, reduces the risk of pneumonia within 30 days from hip fracture, the hospital length of stay, and the cost of pain management for a single-shot block. With wider clinical use of peripheral nerve blocks, it will be possible to better evaluate these effects in observational studies.[36]

Safety

Data from multiple clinical studies demonstrate that FICB and PENG are safe and effective procedures[36]. However, as in every emergency medicine procedure, it is important to be aware of potential adverse events to reduce their incidence and effectively treat patients in jeopardy.

Potential adverse events in regional analgesia are structural damage of underlying tissue, such as nerves, major vessels or muscle tendons. Damage may occur due to needle placement or mechanical pressure of intra or perineural/peritendon injection.

And there is also a potential for developing local anesthetic system toxicity (LAST). The effects of LAST can be divided into two major groups: central nervous system toxicity (CNS) toxicity and cardiovascular system toxicity (CVS) toxicity. Early manifestations of CNS toxicity could be perioral paresthesia, confusion, audio-visual disturbances, dysgeusia, agitation, or reduced level of consciousness leading to seizures, loss of consciousness, coma, and respiratory arrest. CVS toxicity can display dysrhythmias, conduction deficits, hypotension, and eventually cardiac arrest. In case of LAST, local anesthetics injections must be stopped immediately. An antidot for local anesthetics is lipid emulsion and it must be available in emergency medicine settings during regional analgesia treatment. And of course, patients must be treated according to the emergency medicine ABCDE approach with the use of appropriate medications, if needed, (oxygen, saline infusion, benzodiazepines for seizures and adrenalin boluses less than 1 mcg/kg). However, the incidence of LAST is very low (0.04 to 1.8/1000 peripheral nerve blocks).[37,38]

Discussion

As shown above, the benefits of peripheral nerve blocks in pain management for hip fracture patients are evident. Current NICE guidelines recommend paracetamol every six hours, additional opioids if needed and regional analgesia if the pain has not abated.[3] The guidelines of the Association of Anesthetics and the American Academy of Orthopedic Surgeons guidelines recommend peripheral nerve blocks as a first line treatment in preoperative pain management for hip fractures. Surgery should be performed on the day of, or the day after, admission.[40,41] Peripheral nerve blocks are safe and effective in emergency medical settings, including out of hospital use.[42-47]

Evidence strongly supporting regional analgesia as a first line treatment of choice in preoperative pain management in hip fractures is paramount, but these procedures are still not widely accepted in clinical practice. The probable reasons are overcrowded emergency medical services and emergency medical departments, a shortage of trained personnel, the availability of equipment and behavioral barriers to provide reliable pain assessment, especially in elderly patients. The solution may be the introduction of educational programs and also defining pain management algorithms/care pathways for hip fracture patients. Also, it would be beneficiary to have more physicians and nurses working in emergency medicine.[48-52]

The limitations of this narrative review are the use of only two databases, and also that all of the included articles were written in English.

In conclusion, peripheral nerve blocks for hip fractures are safe and effective also in emergency medicine settings. The benefits for patients are greater pain relief, especially during movement, less opioid requirements and a decreased incidence of delirium. Regional analgesia should be routinely used in hip fracture pain management.

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Sažetak

BLOKOVI PERIFERNIH ŽIVACA U BOLESNIKA S PRIJELOMOM KUKA

A. Simić, V. Nesek Adam, D. Rošić, N. Kočet, M. Svetec, A. Herceg, A. Keranović i *Ž. Rašić*

Prijelom kuka predstavlja značajan javno zdravstveni problem čija će incidencija rasti sa starenjem populacije. Cilj ovog preglednog članka je opisati blokove perifernih živaca u liječenju boli kod bolesnika s prijelomom kuka, (bloka ilijakalne fascije i bloka perikapsularnih živaca), te naglasiti prednosti njihove primjene. Prijelom kuka je izrazito bolna ozljeda. Bol sama po sebi je neugodna za bolesnika, a ukoliko je neodgovarajuće liječena može dovesti do višestrukih komplikacija tijekom prijeoperacijskog, operacijskog i poslijeoperacijskog zbrinjavanja bolesnika. Unatoč postojanju brojnih analgetika, liječenje boli u starijih bolesnika s prijelomom kuka često je zahtjevno. Nesteroidni protuupalni lijekovi se ne preporučuju radi svojih neželjenih učinaka, paracetamol je često nedovoljan, a opioidi također mogu imati brojne neželjene učinke, uključujući razvoj akutnog smetenog stanja. Primjena blokova perifernih živaca je sigurna i učinkovita, također u uvjetima hitne medicine. Koristi za bolesnike su bolje ublažavanje boli, osobito prilikom pomicanja, smanjena potreba za primjenom opioida i smanjena incidencija akutnog smetenog stanja. Primjena blokova perifenih živaca u liječenju boli kod bolesnika s prijelomom kuka trebala bi postati svakodnevnica u kliničkoj praksi.

Ključne riječi: *prijelom kuka; liječenje boli; blok živca; hitna medicina*

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Case Report

BLUNT TRAUMA INTERCOSTAL LUNG HERNIATION AND DELAYED EXTRA PLEURAL HEMATOMA

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SUMMARY – Blunt chest trauma is an important cause of morbidity and mortality in traumatized emergency patients. We report the case of a 74-year-old man who suffered a glenohumeral joint dislocation, trans trochanteric femur fracture, multiple rib fractures, diaphragmatic rupture with chest herniation of the spleen and stomach associated with herniation of the lung through an anterior chest wall defect after blunt trauma. Although immediate surgical repair was performed, he developed a delayed complication of multiple rib fracture in the form of large extrapleural hematoma that had to be surgically removed. Due to massive pulmonary contusion and prolonged pulmonary collapse, we used surfactant to facilitate alveolar opening after evacuation of the hematoma.

Key words: *Chest trauma, lung herniation, extrapleural hematoma, diaphragmatic rupture, surfactant*

Introduction

Traumatic lung herniation is an extremely rare, potentially life-threatening condition, caused by the rapid increase in intrathoracic pressures coupled with defects in the chest wall. It is defined as **a** protrusion of lung tissue from the thoracic cavity through an abnormal opening in the chest wall, diaphragm or mediastinum.[1] Because of its extreme rarity traumatic lung herniation has been reported mainly as case reports in the literature and its incidence and prevalence are unknown.[2] Although there is no consensus on the management of lung herniation, surgical repair is generally recommended. We report a patient suffering from multiple injuries including intercostal lung herniation that was surgically repaired and delayed complications in the form of large organized extrapleural hematoma.

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Case report

A 74-year-old man suffered blunt chest trauma and presented to our emergency room complaining only about severe left shoulder pain. There was no history of loss of consciousness. During primary survey, the patient was in stable hemodynamic and respiratory condition. Oxygen saturation was maintained at a level of 96% on oxygen supplement. Blood pressure was 120/70 mmHg and pulse rate was 115 beats per minute. The Glasgow Coma score was 15. Examination revealed flail chest and subcutaneous emphysema with decreased breath sound on the left side. Further evaluation revealed clinical suspicion of a left femur fracture and a dislocated left shoulder. A whole-body computed tomography (CT) scan was notable for ventral intercostal left lung herniation (Figure 1.A), a rupture of the left hemi-diaphragm associated with herniation of the stomach and spleen into the chest (Figure 1B.), left-side fractures of the 1st to 3rd and 4th to 11th rib that were significantly displaced (Figure 2.), right-side fracture of the 3rd to 6th rib, left-side hemothorax and

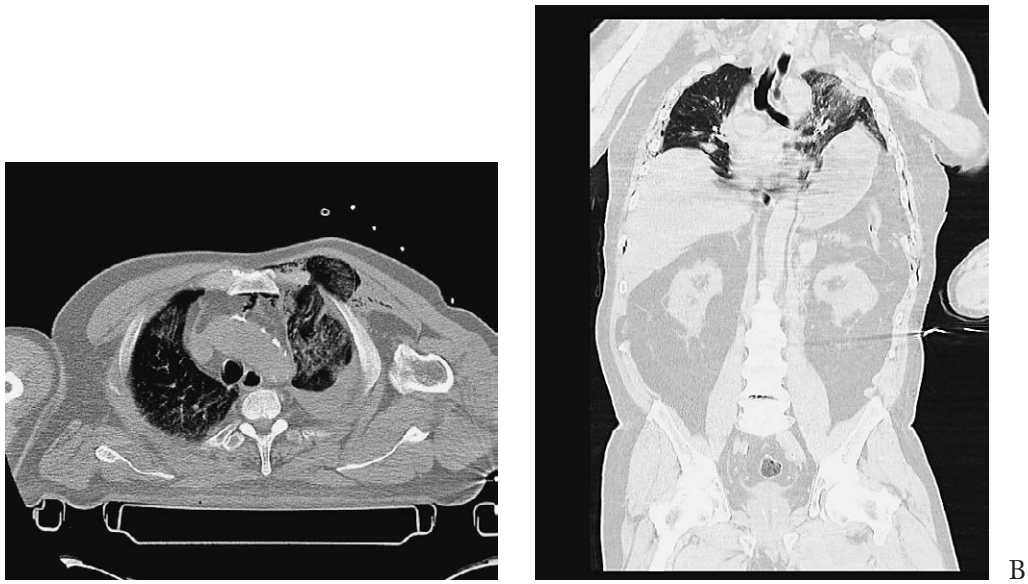
A  B

Figure 1 A. Ventral intercostal left lung herniation and Figure 1 B. Herniation of the stomach and spleen into the chest

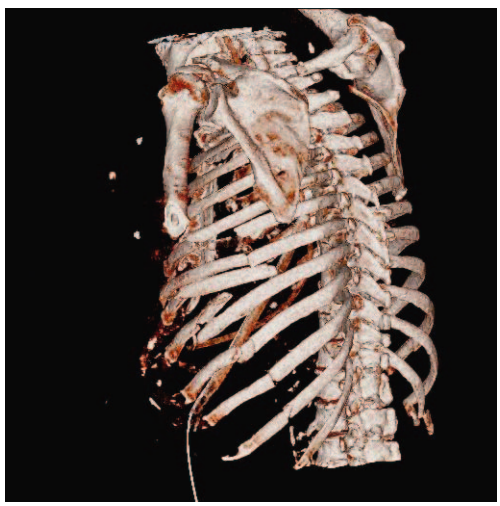


Figure 2. 3D reconstruction of left- side rib fractures that are significantly displaced

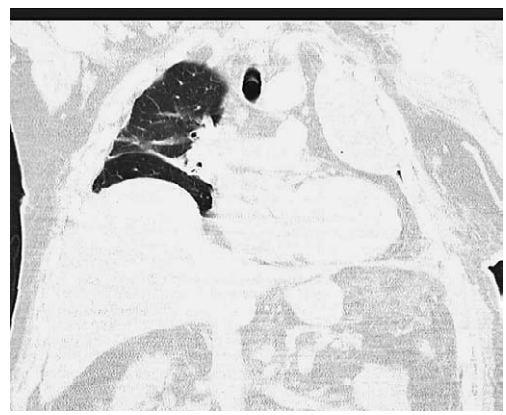


Figure 3. Complete left lung collapse due to extrapleural hematoma

pneumothorax, insignificant right - side pneumothorax, dislocation of left glenohumeral joint, and trans trochanteric fracture of the left femur. The decision was made for an emergency thoracotomy to repair the lung herniation. A left thoracotomy in right decubitus position was performed. The abdominal organs were reduced to their normal anatomic position and a diaphragmatic defect was repaired. Further hemostats sutures to the thoracic wall and lung sutures due to left lung laceration were done. The left lung was repositioned, and its full re-expansion was achieved. After surgery, the patient was admitted to ICU, sedated and mechanically ventilated due to unstable left chest wall with thoracic drainage on the left side.

The patient was ventilated on the bilevel positive airway pressure modalities. Therapeutic bronchoalveolar lavage with flexible fiberoptic bronchoscopy (FOB) was done routinely or when clinically indicated. After subcutaneous emphysema was resolved, transesophageal echocardiogram was performed and showed no cardiac injury. On day 10 a surgical tracheostomy was performed under general anesthesia to facilitate respi-

ratory wean with simultaneous osteosynthesis of left femur. On day 16 the patient was successfully weaned from mechanical ventilation.

After a short period of clinical and functional improvement, the patient's respiratory condition worsened. Because of a complete left lung collapse observed on the CT scan (Figure 3,) re-thoracotomy was performed on the day 23. Intra-operatively, the patient was found to have a large extrapleural hematoma. Surgery included dissection of the pleural adhesions, evacuation of the large hematoma and decortication with the aim of obtaining the largest possible pulmonary expansion. Shortly after re-admission to ICU, a bronchoalveolar lavage (BAL) was performed by FOB and 240 mg of surfactant (Curosurf, Chiesi Pharmaceuticals) diluted with 20 mL of 0.9% NaCl was inserted into the distal layers of the left lung. The patient was successfully weaned from the ventilator on post-operative day 1. Intense respiratory therapy was performed and showed remarkable improvement in respiratory condition. On the day 29, the tracheostomy tube was removed. A pulmonary function test revealed moderately restrictive and obstructive pulmonary ventilation impairment and further radiographic examination revealed almost complete re-expansion with only a very small atelectatic area remaining in the lung.

Discussion

Progressive worsening of left lung on the chest X-ray after the first surgical intervention was noticed, but initially it had no negative respiratory contribution. We thought it was atelectasis, but since it did not resolve on repeated bronchoscopy procedures, we suspected that the cause was of extra pleural origin. The CT revealed a large extrapleural hematoma. The presence of extra pleural fat sign on the CT scans is a typical radiological finding of extrapleural hematoma.[3] In blunt trauma, rib fractures can result in small vascular tears of intercostal vessels with slow blood accumulation in extrapleural space forming extrapleural hematoma. The incidence of this finding is 7.1%[4]. It is often misdiagnosed as hemothorax.[5] If the chest drain is in the correct position and not occluded, the blood would be evacuated, but in this case the drain was occluded by massive adhesions. As the parietal pleura was sutured, the patient did not develop pleural hemothorax, but extra pleural hematoma.

Direct and indirect lung injuries can also result in the dysfunction of lung surfactant and atelectasis may impede the function of surfactant.[6] Such decreased function results in reduced alveolar stability and causes alveolar collapse. Due to large contusion of the left lung and prolonged atelectasis, we decided to use the surfactant after surgical evacuation of extrapleural hematoma because of surfactants stabilizing effect on the alveoli, which may improve the recruitment of non-ventilated alveoli or prevent end-expiratory collapse. Furthermore, due to the direct mechanical trauma to the lung parenchyma from herniation, a state of alveolar leakage of proteins may have led to some degree of surfactant dysfunction that exacerbated the lung injury and alveolar collapse.[7] It is described that BAL facilitates removal of breakdown products and blood components, the recruitment of contused lung regions and the maintenance of surfactant pool size.[8] BAL and surfactant probably blocked the inflammatory cascade (biotrauma). In conclusion, further studies about surfactant administration as treatment option for pulmonary contusion are warranted.

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The authors have no conflict of interest.

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Sažetak

INTERKOSTALNA HERNACIJA PLUĆA NAKON TUPE TRAUME I ODGOĐENI IZVAN PLEURALNI HEMATOM

T. Klancir, V. Nesek Adam, S. Berić, M. Matolić, E. Grizelj Stojčić i *A. Smiljanić*

Trauma prsnog koša uzrokovana udarcem tupim predmetom značajan je uzrok mortaliteta i morbiditeta bolesnika u hitnoj medicinskoj službi. Prikazujemo slučaj sedamdesetčetverogodišnjeg bolesnika koji je kao posljedicu udarca teškim predmetom doživio dislokaciju ramenog zgloba, transtrohanternu frakturu bedrene kosti, obostranu serijsku frakturu rebara, rupturu dijafragme s hernijacijom slezene i želuca u prsište uz pridruženu interkostalnu ventralnu hernijaciju pluća kroz ozlijeđeno prsište. Unatoč hitnom kirurškom zbrinjavanju, kao kasna posljedica serijskog prijeloma rebara razvio se veliki izvan pleuralni hematom koji je bilo potrebno kirurški evakuirati. Zbog velike kontuzije pluća i dugotrajnog kolapsa alveola, nakon odstranjena hematoma primijenili smo surfaktant kako bi potpomogli otvaranje i održavanje alveola otvorenima.

Ključne riječi: *trauma prsnog koša, plućna hernijacija, hematom prsnog koša, ruptura dijafragme, surfaktant*

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Case Report

DRUG-INDUCED HYPERSENSITIVITY SYNDROME CAUSED BY LAMOTRIGINE, A CASE REPORT

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SUMMARY – Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome (DIHS), is an under-recognized and potentially life-threatening hypersensitivity reaction associated with a variety of medications, many of them anti-epileptics. Patients with DRESS syndrome typically present with rash, swelling, fever, and systemic manifestations. We report a case of a patient admitted to out hospital after the administration of an anticonvulsive drug lamotrigine. She was presented with high fever, rash, face oedema and elevated liver enzymes. At admission, all previous medications were discontinued, systemic corticosteroid therapy was administered, and the patient was monitored for signs of clinical recovery. This case report suggests that in patients presenting with skin rash and systemic abnormalities after a recent change in medications, physicians should consider DRESS syndrome as a possible diagnosis and switch to a more aggressive therapy if removal of the offending agent does not result in clinical improvement. Early diagnosis can reduce the risk of complications and the mortality rate.

Key words: *drug-induced hypersensitivity, drug reaction, lamotrigine*

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome (DIHS), is an under-recognized and potentially life-threatening hypersensitivity reaction associated with a variety of medications, many of them anti-epileptics. Patients with DRESS syndrome typically present with rash, swelling, fever, and systemic manifestations such as a severe transaminitis.[1]

Isolated elevation of liver transaminases is the most common laboratory manifestation of hepatitis in DRESS syndrome. In severe cases it can progress to

Table 1. Drug groups associated with DRESS/DIHS

Drug groups:
Anticonvulsants
Antidepressants
Sulfonamides/sulfones
Anti-infammatories
Anti-infectives
Angiotensin-converting enzyme inhibitors
Beta-blockers
Specific Examples:
phenytoin, carbamazepine, phenobarbital, lamotrigine, valproate
despiramine, amitriptyline, fluoxetine
dapsone, sulfasalazine, trimethoprim-sulfamethoxazole
piroxicam, naproxen, diclofenac, sulindac, ibuprofen
abacavir, nevirapine, linezolid, doxycycline, nitrofurantoin
captopril, enalapril
atenolol, celiprolol

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fulminant liver failure, occurring in as many as 10% of cases and accounting for the principle cause of mortality in patients affected by DRESS syndrome.[1]

These patients are typically found to have started one of a few select medications in the past two to eight weeks with aromatic anti-epileptics being the most commonly implicated.[2,3]

Drug group's associates with DRESS/DIHS are shown in the table (Table 1.).

Although its true incidence is unknown, DRESS syndrome has been estimated to occur in approximately one out of 1,000 to 10,000 new users of anti-epileptic medications.[4,5]

Case report

A 52-year-old woman was presented at the Emergency Department (ED) of the Clinical Hospital Sveti Duh with a high fever (40°C), maculopapular rash prominent on most parts of the chest, back, extremities, and face oedema and erythema (Fig. 1,2).

Two days prior she was administered for first time an anticonvulsive drug (lamotrigine) during the modification of chronic psychiatric therapy at the University Psychiatric Hospital Vrapče. She was referred to the Clinical Hospital Sveti Duh for further evaluation.

There was no involvement of the oral mucosa, palms, or soles. The patients past medical history included hypertension, diabetes type II and depression. There were no previously known allergies to drugs. Physical examination showed that heart rhythm is normal. No murmurs, gallops, or rubs were auscultated. There were no signs of respiratory distress. Lung sounds were clear in all lobes bilaterally without rales, rhonchi, or wheezes. The abdomen was soft, symmetric, and non-tender and without distention. No masses, hepatomegaly, or splenomegaly were noted. No focal deficits were appreciated on neurological examination. The initial laboratory results revealed elevated liver enzymes and leukocytosis, but no eosinophilia. The chest X-ray showed normal size and shape of the chest wall and the main structures in the chest. Covid19 infection was excluded after negative reverse-transcription of a polymerase chain reaction (PCR) test for severe acute respiratory syndrome coronavirus (SARS COV2). The diagnostic panel for hepatitis serology showed past HBV infection. Other diagnostic

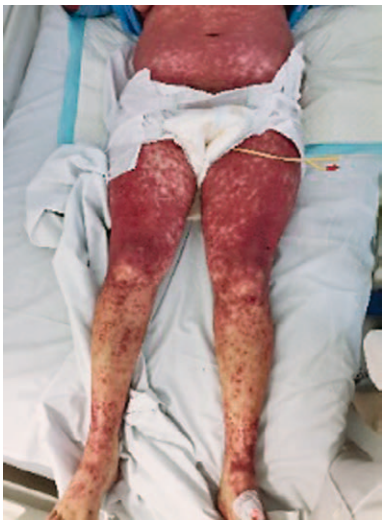

Figure 1. Maculopapular rash

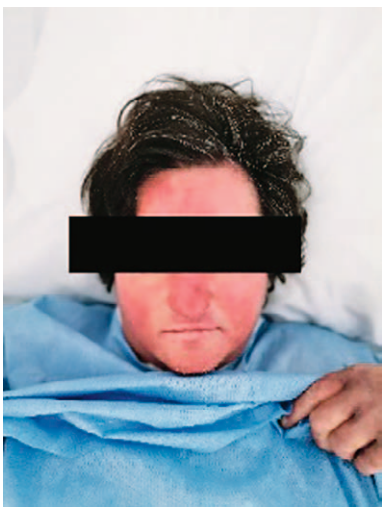

Figure 2. Face erythema and swelling

tests that excluded the possible causes of the symptoms were also carried out - anti-nuclear antibodies (ANA), blood cultures, serology for chlamydia and/or mycoplasma.

She was admitted to the Clinical Hospital Sveti Duh with a presumptive diagnosis of a drug-induced hypersensitivity. At admission, systemic corticosteroid therapy was started, all previous medications were discontinued and the patient was monitored for signs of clinical recovery.

Although no formal diagnostic criteria for DRESS syndrome have been widely accepted, the Kardaun *et al.* of the Severe Cutaneous Adverse Reactions (RegiS-

Table 2. Scoring system by RegiSCAR

Criteria	No	Yes	Unknown
Fever greater than 38.5°C	-1	0	-1
Enlarged lymph nodes	0	1	0
Atypical lymphocytosis	0	1	0
Eosinophilia 10-19,9% >20%	0	 1 2	0
Skin rash > 50% of the skin surface morphology suggestive of DRESS biopsy suggestive of DRESS	 0 -1 -1	 1 1 0	 0 0 0
Organ involvement 1 2 or more	0	 1 2	0
Resolution greater than 15 days	-1	0	
Evaluation of other causes (ANA, blood cultures, serology for hepatitis A virus, hepatitis B virus, hepatitis C virus, and chlamydia and/or mycoplasma)	0	1	0

DRESS= Drug reaction with eosinophilia and systemic symptoms, ANA= Anti-nuclear antibodies

CAR) study group published a scoring system in 2007 that has been widely used to evaluate potential cases of DRESS syndrome (Table 2.)[6]

The criteria for this system include: first, fever greater than 38.5°C; second, enlarged lymph nodes; third, eosinophilia; fourth, atypical lymphocytosis; fifth, skin involvement; sixth, organ involvement; seventh, resolution greater than 15 days; and eighth, evaluation of other causes (ANA, blood cultures, serology for hepatitis A virus, hepatitis B virus, hepatitis C virus, and chlamydia and/or mycoplasma). Using this scoring system, a final score of less than two indicates no case, a final score of between two and three indicates a possible case, and a final score of between four and five indicates a probable case, and a final score of greater than five indicates a definite case.

The patient in this case report had a score of five points (one each for fever greater than 38.5°C, skin rash suggestive of DRESS, affecting >50 % of the skin surface, liver involvement, and evaluation of other potential causes), indicating a 'probable case' of DRESS per the RegiSCAR scoring guidelines.

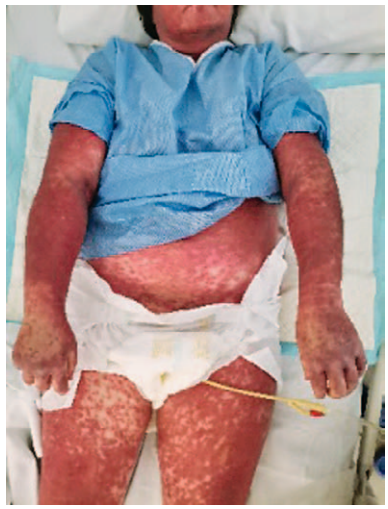

Figure 3. Confluent configuration of the rash

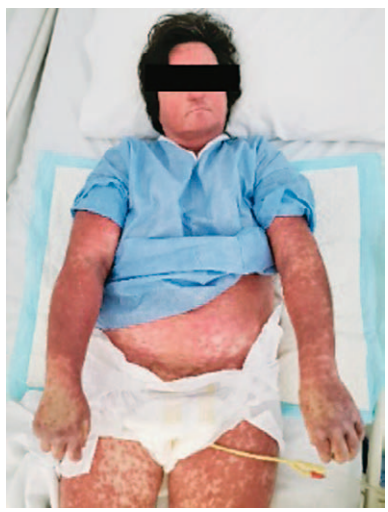

Figure 4. Confluent configuration of the rash

Within five days of admission and corticosteroid treatment, the laboratory results showed a slight progression of elevated liver enzymes. Other laboratory results were without significant change. Confluent configuration of the rash was noticed (Fig. 3,4).

On 10th day of the admission, the clinical improvement was obvious. There was no face erythema or swelling, and the skin rash had begun to resolve (Fig. 5, 6 and 7). The levels of transaminases began to improve, and she was discharged home, with metilprednizolon still in the therapy until a follow-up with an immunologist within four weeks.

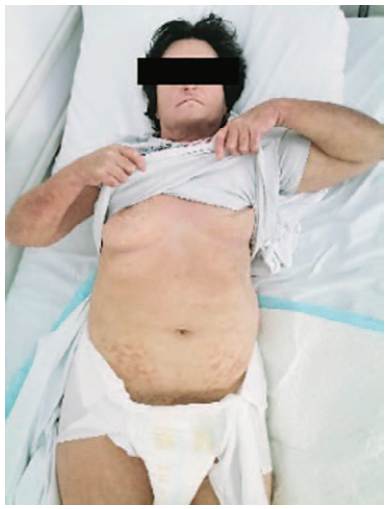

Figure 5. Rash resolution

Figure 6. Resolution of the face oedema and erythema

Discussion

As with most severe allergic reactions, DRESS syndrome involves a rash, diffuse swelling, and eosinophilia.[2,6,7] The hallmark of DRESS syndrome, however, is the presence of systemic manifestations, such as inflammation of the liver, kidneys, heart, or other organs.[8] Prompt recognition of the adverse drug reaction and discontinuation of the offending medications are imperative steps in limiting the progression of DRESS syndrome. Systemic corticosteroids have become a mainstay of therapy in severe cases and often produce a marked improvement in clinical symptoms and laboratory measures within just a few days of the initiation

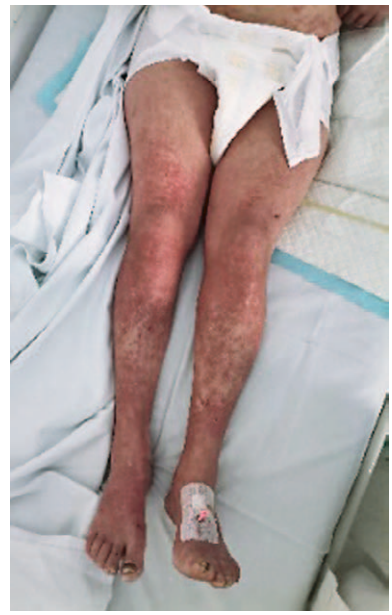

Figure 7. Rash resolution

of the treatment.[9] If symptoms continue to progress despite the use of corticosteroids, other options include intravenous immunoglobulin (IVIG) and/or plasmapheresis.[10] The mortality rate in patients affected by DRESS syndrome is about 10%, with the principle cause of mortality being fulminant liver failure.[1]

Conclusion

In patients presenting with skin rash and systemic abnormalities after a recent change in medications, physicians should consider DRESS syndrome as a possible diagnosis and switch to more aggressive therapy if removal of the offending agent does not result in clinical improvement. Early diagnosis can reduce the risk of complications and the mortality rate.

Consent

Verbal informed consent was obtained from the patient for the publication of this case report and the accompanying images.

The authors state that this manuscript has not been published previously and is not currently being assessed for publication by any journal other than the Acta Clinica Croatica. The authors disclose that they did not receive any financial support for the study. No proprietary interest is involved in the study.

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Sažetak

SINDROM PREOSJETLJIVOSTI UZROKOVAN LAMOTRIGINOM; PRIKAZ SLUČAJA

D. Vrhovski, M. Ikić Matijašević i *V. Nesek Adam*

Reakcija na lijek s eozinofilijom i sistemskim simptomima (DRESS, engl. Drug Reaction with Eosinophilia and Systemic Symptoms), ili sindrom preosjetljvosti uzrokovan lijekom (DIHS, engl.Drug-inducec Hypersensitivity Syndrome), je često neprepoznato i potencijalno životno ugrožavajuća reakcija preosjetljivosti povezana s uzimanjem raznih lijekova, najčešće antiepilepticima. Pacijenti s DRESS/DIHS se najčešće prezentiraju osipom, febrilitetom i zahvaćanjem unutarnjih organa. U ovom prikazu slučaja predstavljena je pacijentica koja je nakon uzimanja lamotrigina razvila osip, visoki febrilitet, edem lica te hepatitis. Po primitku u bolnicu, isključena je sva dotadašnja terapija te započeto sistemsko liječene kortikosteroidima. Ovaj rad sugerira razmatranje dijagnoze DRESS/DIH kod pacijenata s naglom pojavom osipa te sistemskim simptomima, a nakon uvođenja novog lijeka u terapiju te se preporuča agresivniji pristup u terapiji osim prestanka uzimanja uzročnog lijeka. Rano prepoznavanje može smanjiti rizik komplikacija i mortalitet.

Ključne riječi: *preosjetljivost uzrokovana lijekom, reakcija na lijek, lamotrigin*

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Case Report

METHEMOGLOBINEMIA – A CASE REPORT AND LITERATURE REVIEW

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SUMMARY – The objective of this case report is to present a patient with acquired methemoglobinemia due to poisoning of an unknown cause. A 55-year-old man was brought to the Emergency Department, University Hospital Center Zagreb, with an unwell appearance, cyanotic, restless, and presented with a quantitative consciousness disorder. An initial assessment showed decreased oxygen saturation (SpO2 85 [%]), while point-of-care arterial blood gas (ABG) analysis assessed normal partial pressure of oxygen (pO2). Severe lactic acidosis with a compensatory drop in partial pressure of carbon dioxide (pCO2) and high rates of methemoglobin were found. Supportive oxygen therapy and crystalloid solutions were administered, which resulted in rapid clinical recovery within 40 minutes of the initial assessment. Clinical recovery was accompanied by normalized ABG test results taken serially. Typical antidotes, methylene blue and vitamin C, were not administered due to rapid clinical improvement. Methemoglobinemia can be congenital (hereditary) or acquired (toxic). Both conditions are rarely seen in emergency departments, nevertheless, they should be approached properly since methemoglobinemia can be a severe, and fatal, condition. Methemoglobinemia symptoms are the results of inadequate oxygen transport. The diagnosis was confirmed by co-oximetry, while three clinical entities suspected methemoglobinemia: refractory hypoxia, "cyanosis-saturation gap" and dark brown blood. This paper reports our patient's clinical presentation, discusses the causes and mechanisms of possible poisoning, and reviews recent guidelines for methemoglobinemia management.

Key words: *lactic acidosis, methemoglobinemia, poisoning*

Introduction

Methaemoglobinaemia is not the first among differential diagnoses that crosses a clinician's mind when assessing a cyanotic and hypoxemic patient. In this case report, we will present a patient with acquired methemoglobinemia, explain the pathophysiology of methemoglobinemia and the diagnostic process, together with specific and supportive treatment for such patients.

Case report

A 55-year-old man was brought to the emergency department of the University Hospital Center Zagreb. He was delirious, with an altered state of consciousness (Glasgow Coma Scale =11) and presented with pronounced grey skin and a disheveled appearance. According to the physician from the Emergency Medical Service (EMS), the patient was found in this condition at a tram station, and passers-by called an ambulance. While being transported, he lost consciousness at times, urinated, and had diarrhea on several occasions. During the initial assessment in the emergency room, it was not possible to obtain a medical history data from the patient due to his altered mental status. The patient maintained normal blood pressure (RR 134/88 mmHg) and heart rate (c/p 88/min) but was tachypneic, hypoxic (SpO2 90 [%]), and hypothermic (T 34.5 [°C]). The examination was difficult due to the patient's extreme restlessness and uncooperativeness. Except for cold and pale-grey skin, no specific pathological signs were observed. Human fixa-

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Table 1. Initial ABG on room air – results.

pH 7.04	pCO2 3.1 kPa	pO2 12.2 kPa	SaO2 85%	BE ecf -23 mmol/L	HCO_3^- 5.2 mmol/L
Na^+ 147mmol/L	K^+ 4.0 mmol/L	Lac >20 mmol/L			

Figure 1. Dark brown blood color of a patient with methaemoglobinaemia.

tion, intramuscular haloperidol injection (1 ampoule in total), and IV diazepam infusion (1 ampoule in 500mL saline) were administered, and a urinary catheter was inserted. Upon obtaining an arterial blood specimen, a dark brown blood color was noticed (Figure 1). An arterial blood gas (ABG) analysis at room air (see Table 1) showed marked acidemia (pH 7.04), normal partial pressure of oxygen (pO2 12.2 [kPa]), reduced oxygen saturation (SpO2 85 [%]), reduced partial pressure of carbon dioxide (pCO2 3.1 [kPa]) and bicarbonate ion (HCO3- 5.2 [mmol/L]), excess bases (BE ecf -23.0 [mmol/L]) and markedly elevated lactates (Lac> 20 [mmol/L]. Oxygen was delivered via an oxygen mask with a flow of 15 L/min. In addition, 75 mL of bicarbonate ion in 500 mL of 5% glucose solution and 1000 mL of heated crystalloid solution (PlasmaLyte) were administered. Reassessment of vital signs indicated hypotension (RR 88/61 mmHg), tachycardia (c/p 115/min) and reduced oxygen saturation (SpO2 90 [%]), despite the maximal oxygen flows via a non-rebreather mask. The ECG showed atrial fibrillation, 150 beats/min, normal electrical axis and diffuse ST-segment displacement. Mild macrocytic anemia and leukocytosis (Lkc=17.6 [$x10^9$/L]), hypokalemia (K=3.0 [mmol/L]), mildly elevated creatine kinase (CK=225 [U/L] and the presence of ethanol in the blood (ALC=0.6 [g/L]) were found, while other parameters were within the limit of physiological intervals, including cardioselective enzymes. A toxicology screen determined only the presence of nicotine and lidocaine (due to urinary catheter placement), but not all psychoactive substances were included in the analysis. The ABG test was repeated (Table 2) 40 minutes after the initial monitoring. Severe acidosis with increased anion gap (pH 7.14) was still present, now with elevated partial oxygen pressure (pO2 36.6 [kPa]), normal oxygen saturation (SpO2 99.8 [%]) and normal partial pressure of carbon dioxide (pCO2 4.1 [kPa]). Lactate values were still increased (Lac 16.7 [mmol/L]), as well as excess bases (BE ecf -18.4 [mmol/L]) and bicarbonate ion (HCO3- 9.8 [mmol/L]), but with a normalization tendency compared to the initial values. An elevated percentage of methemoglobin (MetHb 36.4 [%]) was observed. During the observation of our patient in the emergency unit, pH and lactate values normalized (pH 7.42, Lac 1.3 [mmol/L]), and his mental status improved. In an interview with the patient, we found out that he drank 0.5L of water from a hydrant at the main station, after which he fell ill. We cannot claim with certainty that water from a hydrant was the definite cause of poisoning. We later discovered that he was homeless with no regular income and did not suffer from chronic diseases and did not take chronic drug therapy. The patient was admitted to the post-intensive care unit at the Department of Internal Medicine, University Hospital Center Zagreb. Serial monitoring of the patient's acid-base status was continued. A decrease in the percentage of methemoglobin, normal-

Table 2. ABG test results on a non-rebreather mask with a 15L/min flow.

pH 7.14	pCO2 4.1 kPa	pO2 36.6 kPa	SaO2 99.8%	BE ecf -18.4 mmol/L	HCO_3^- 9.8 mmol/L
Na^+ 145 mmol/L	K^+ 3.6 mmol/L	Lac 16.7 mmol/L	**MetHb 36.4%**		

ization of vital signs and adequate response to the given therapy were recorded. The paroxysm of atrial fibrillation spontaneously converted to a sinus rhythm that was later maintained permanently. During hospitalization, the patient was briefly sub febrile on several occasions. The patient had no signs of infection, no increase in inflammatory parameters was observed, so there was no indication for antibiotic therapy. Due to the favorable clinical course with the use of oxygen therapy and intravenous replacement of crystalloid solutions, there was no need to use antidotes - methylene blue and vitamin C. The social service was contacted. The patient recovered fully and was discharged from the hospital five days after admission.

Discussion

Methaemoglobinaemia is a rare disorder characterized by the oxidation of divalent iron to the trivalent form (from ferrous to ferric form) in the hemoglobin molecule. Oxygen can bind to hemoglobin only in divalent (ferrous) form, and as a result of binding, oxygen is temporarily oxidized to ferric form. Various substances, which will be listed later, can cause hemoglobin to remain permanently in a ferric form and thus no longer be able to bind oxygen. Therefore, the symptoms of methemoglobinemia are a direct consequence of inadequate oxygen transport. The specific mechanism is an allosteric change in the hemoglobin molecule. In addition, due to further changes in the oxygen–hemoglobin dissociation curve (a change in oxygen dissociation to the left), there is reduced peripheral oxygen release[1], hypoxia, and functional anemia[2] with no decrease in hemoglobin level. Methaemoglobinaemia can occur as a result of a congenital defect or as an acquired disorder. Acquired disorders are more common and occur as a result of exposure to substances that directly or indirectly oxidize hemoglobin. Congenital causes of methemoglobinemia arise from an autosomal recessive variant of the CYB5R3 gene or an autosomal dominant variation of genes encoding a globin molecule known as HbM disease. Hereditary methemoglobinemia, as a consequence of mutations in the CYB5R3 gene, leads to NADH-cytochrome-reductase deficiency, with up to 80 different variants of this disorder known today.[3,4] Autosomal dominant disease involving various genes encoding alpha-globin, beta-globin, and gamma-globin leads to the formation of M-hemoglobin, in which structural abnormalities of globin lead to auto-oxidation of iron, and thus to the occurrence of methemoglobinemia. Patients suffering from this disease are cyanotic but usually asymptomatic[5]. Acquired methemoglobinemia results from drug intake or exposure to toxins lead to accelerated oxidation of hemoglobin from ferrous to ferric form.[6] Table 3 lists the most common drugs that can lead to the development of methemoglobinemia.

Table 3. Drugs and substances that can result in the development of methemoglobinemia

Drug group	Representatives (common causes are bold)
Local anesthetics	**Benzocaine** (often used in endoscopic procedures) Prilocaine, tetracaine, lidocaine
Nitrates	**Nitroglycerin** **Inhaled nitric oxide** Nitroprusside, oral nitrates, amyl-nitrate
Antibiotics	**Dapsone** Rifampicin, sulfonamides, antimalarials
Other drugs	**Rasburicase** (especially in G6PD deficiency) Oncological drugs: cyclophosphamide Metoclopramide Various drugs in which some oxidizing substance is used in the making
Environmental causes	Fertilizers, herbicides Plastic (various types) Paints and rubber

The clinical presentation of methemoglobinemia is various and depends on the percentage of methemoglobin, a patient's usual hemoglobin level, and cardio-

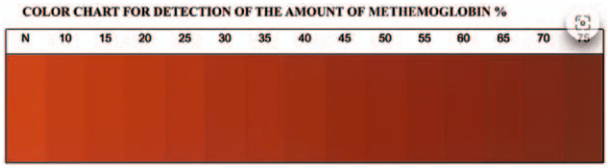

Figure 2. Brown blood color shade scale for a rough assessment of methaemoglobinaemia.

Source: Shihana F, Dissanayake D, Buckley N, Dawson A. A Simple Quantitative Bedside Test to Determine Methemoglobin. Annals of emergency medicine. 2009. 55. 184-9. 10.1016/j.annemergmed.2009.07.022.
Available from: https://www.researchgate.net/figure/Color-chart-for-the-measurement-of-methemoglobin-The-color-chart-was-prepared-according_fig2_26884296 [accessed 26 Feb, 2022]

vascular reserve. The normal percentage of methemoglobin is below 25%. Patients with levels between 3 and 15% are usually asymptomatic, and cyanosis is rare. Patients with methemoglobin levels between 20-30% are always symptomatic, with mild symptoms such as fatigue, tachypnea, dyspnea, tachycardia, anxiety, dizziness, qualitative disturbance of consciousness, nausea, and vomiting. At levels above 40%, life-threatening and serious symptoms occur, such as epileptic seizures, coma, arrhythmias, elevated lactate levels, and death. The final diagnosis is made using co-oximetry, but clinical suspicion itself can be made based on the following three entities:[7]

- Refractory hypoxia: methemoglobinemia can typically be suspected in a patient with oxygen saturation between 82-86%, who is at high oxygen flows (FiO2 100%), and no other explanation for hypoxia
- "Cyanosis-saturation gap": methemoglobinemia leads to the development of central cyanosis (attention to the color of the tongue). Oxygen saturation of 80-90% usually does not lead to cyanosis, so patients with 80-90% saturation who present with central cyanosis are clinically suspicious of methemoglobinemia
- Brown blood color: methemoglobinemia causes a change of blood color to chocolate-like. Also, if we put a patient's blood on white gauze, the blood will remain brown when dry, unlike deoxygenated blood, which will absorb oxygen in the air and turn red again

As noted, the diagnosis of methemoglobinemia was made based on co-oximetry. Unlike standard pulse oximeters that measure light absorption at two wavelengths, co-oximetry measures light absorption at four wavelengths: 600nm (carboxyhemoglobin), 631nm (methemoglobin), 660nm (deoxyhemoglobin), and 940 nm. Based on this analysis, multiple disorders can be diagnosed - both carboxyhaemoglobinaemia and methemoglobinemia.[8] In addition to this formal test, simple tests can be used for rough assessment, which, based on the color of the blood on a white paper, provide an estimate of the level of methemoglobinemia.[9] Figure 2 shows the blood color shades scale of brown, which could be helpful in everyday clinical work.[9] Finally, calculation of the so-called "saturation gap" (the difference between the measured saturation and that measured with a pulse oximeter), could also be useful. A difference of more than 5% may raise a suspicion of methemoglobinemia.

Treatment of methemoglobinemia is primarily based on supportive care and discontinuation of the drug or substance use that leads to this condition. Definitive treatment involves the reduction of methemoglobin to a non-oxidized state using methylene blue, which is the drug of choice for the treatment of methemoglobinemia. Methylene blue, along with nicotinamide-adenine dinucleotide phosphate (NADPH), is a co-factor of the enzyme NADPH-methemoglobin reductase. It works by accepting an electron from NADPH and in this form reduces trivalent iron from ferric form to ferrous form.[10] The use of methylene blue is indicated in symptomatic methemoglobinemia regardless of methemoglobin level, and in cases where the methemoglobin level is above 30%. The drug is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and caution is required in patients at risk of developing serotonin syndrome. Methylene blue is a monoamine oxidase (MAO) inhibitor and can lead to the development of serotonin syndrome in interaction with other drugs. The drug dose is 1-2 mg/kg IV over five minutes, while the clinical effect is visible within a few minutes. Cyanosis resolves within one hour after application. When applying the drug, there may be a "drop" in oxygen saturation, because methylene blue turns the blood blue, and it falsely reduces the saturation value measured via pulse oximetry. The drug can be administered again after 60 minutes if the patient is still cyanotic, although a dose failure of 2 mg/kg raises suspicion of G6PD deficiency. Rebound-methaemoglobinaemia

may recur within 12 hours after drug administration, after which continuous infusion of methylene blue may be considered1,[11] In patients with G6PD deficiency, treatment is more complex. It is important to note that this deficit occurs in African Americans but also presents in people from the Mediterranean region.[12] These patients lack NADPH, due to G6PD deficiency, and therefore methylene blue either has no effect at all, or has some effect, but the further application of already low NADPH levels will lead to lower glutathione levels, leading to hemolysis. In these patients, treatment with high doses of vitamin C (1.5-3g IV every six hours) may be attempted. In addition, riboflavin (vitamin B2), which acts as an electron acceptor, can be added to the therapy. The use of methylene blue may also be considered, but with caution. If all of the treatment modalities listed fail, complete erythrocyte transfusion and hyperbaric chamber transplantation may be considered. Methylene blue can be redosed if needed. Caution should be exercised when the drug level comes close to 7ml/kg as there is a risk of drug toxicity.[13] At toxic or subtoxic doses, methylene blue may worsen methemoglobinemia and hemolysis, which occurs because of the bioaccumulation of methylene blue, leading to a reversal of the reductive action. Side effects of methylene blue are as follows: systemic and/or pulmonary hypertension (via a reaction that prevents nitric oxide-mediated vasodilation), motor restlessness, dyspnea, nausea, vomiting, sweating, and anaphylaxis.

Conclusion

Methaemoglobinaemia is a rare disorder characterized by elevated levels of methemoglobin, a hemoglobin molecule that contains an oxidized form of iron that cannot bind oxygen and results in an inadequate oxygen supply to tissues. There are two forms of the disease - genetic and acquired methemoglobinemia. Genetic methemoglobinemia is a chronic disease that leads to numerous morbidities, and patients are mostly characterized by cyanosis without associated other symptoms. Acquired methemoglobinemia, on the other hand, is an acute condition that is most often the result of poisoning by certain drugs and compounds, which can be fatal. The severity of symptoms depends on the percentage of methemoglobin in the blood, and clinical presentation varies from fatigue, anxiety, dizziness, and cyanosis, to qualitative disorders of consciousness, epileptic seizures, arrhythmia, and coma. Unexplained symptoms of refractory hypoxia, cyanosis-saturation gap, and chocolate-colored blood may raise suspicion of methemoglobinemia, but the definitive diagnosis is made using co-oximetry and detecting methemoglobin levels in the blood. Treatment of methemoglobinemia is based on supportive care and discontinuation of the drug or substance that led to this condition. Despite being a rare condition, acquired methemoglobinemia can be a life-threatening condition and emergency services should be provided with antidotes - methylene blue and vitamin C.

Informed consent

Informed consent for publication of this paper was given by the patient verbally.

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Sažetak

METHEMOGLOBINEMIJA – PRIKAZ SLUČAJ I PREGLED LITERATURE

Ida Ivek, Tomislav Knotek, Toni Ivičić, Barbara Rubinić, Paola Bajlo i *Jasmin Hamzić*

Svrha ovog rada je prikaz slučaja pacijenta sa stečenom methemoglobinemijom uslijed trovanja nepoznatog uzroka. 55-godišnji muškarac zapuštenog izgleda dovežen je u Objedinjeni hitni bolnički prijem (OHBP) Kliničkog bolničkog centra (KBC) Zagreb cijanotičan, nemiran i kvalitativno promijenjenog stanja svijesti. U inicijalnoj obradi nađena je snižena saturacija kisikom (SaO2 85[%]), dok je plinska analiza arterijske krvi ukazivala na zadovoljavajuće vrijednosti parcijalnog tlaka kisika. Nađena je teška laktacidoza s kompenzatorno sniženim parcijalnim tlakom ugljikovog dioksida, a zamijećen je i visok postotak methemoglobina. Na primijenjenu suportivnu oksigenoterapiju te terapiju kristaloidnim otopinama, pacijentovo se kliničko stanje rapidno oporavlja unutar četrdesetak minuta, što se prati i normalizacijom serijski evaluiranog acidobaznog statusa. S obzirom na povoljan klinički tijek, nije bilo potrebe za primjenom antidota – metilenskog modrila i vitamina C. Postoje urođena (genetska) i stečena (toksična) methemoglobinemija. Oba stanja se rijetko viđaju na hitnom prijemu, a stečena methemoglobinemija može biti životno ugrožavajuće stanje. Simptomi methemoglobinemije izravna su posljedica neadekvatnog transporta kisika. Dijagnoza se postavlja na temelju ko-oksimetrije, ali sama klinička sumnja može se postaviti na temelju sljedeća tri entiteta: refraktorne hipoksije, „cyanosis-saturation gap“ i smeđe boje krvi. U ovom radu osvrnut ćemo se na klinički tijek našeg pacijenta, dotaći se potencijalnih mehanizama trovanja i uzroka toksične methemoglobinemije te prikazati recentne preporuke za zbrinjavanje ovakvih slučaja.

Ključne riječi: *laktacidoza, methemoglobinemija, trovanje*

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Case Report

CAN'T INTUBATE, CAN'T OXYGENATE: A RARE CASE OF A DIFFICULT AIRWAY DUE TO NONHEREDITARY ANGIOEDEMA

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SUMMARY – Angioedema is a form of allergic mediated by histamine and non-allergic mediated by bradykinin and can be lethal if not recognized and treated promptly. This case demonstrates the proper diagnosis of and intervention in rapid onset severe angioedema.

A 68-year-old male came to the emergency department with a complaint of dyspnea that started two hours before. He had type II diabetes, chronic kidney disease and several different antihypertensive medications, including an ACE inhibitor for hypertension. During physical examination, the patient was hypertensive, tachycardic, tachypnoic, and edematous. During his stay in the ED he was treated with a combination of corticosteroids, antihistamines and epinephrine, but the patient's edema and dyspnea worsened and his oxygen saturation started to deteriorate with a progression of skin edema. Intubation was not possible due to the large edema of the tongue, so a tracheotomy was done. An ampule of icatibant was administered and rapid regression of the edema, along with the stabilization of the patient's vital signs, followed after five minutes. The patient was discharged home after five days with a recommendation of discontinuing the ACE inhibitor.

While non-hereditary angioedema is not a rare condition, emergency physicians should be adequately educated about it.

Key words: *angioedema, bradykinin, icatibant–B2 bradykinin receptor antagonist*

Introduction

Hereditary angioedema (HAE) is a rare hereditary disease, an autosomal dominant disorder.[1] It is a form of non-allergic angioedema mediated by bradykinin and can be lethal if not recognized and treated on time. It is defined by a deficiency of functional C1 esteraze infibitor (C1-INH), due to either C1-INH consumption (type 1) or inactivation (type 2).[1] Type 1 is most common, occurring in 85% of patients. It is characterized by decreased production of C1-INH, which results in reduced functional activity to 5-40% of normal value. Type 2 occurs in 15% of cases and C1-INH is dysfunctional in normal or elevated levels.[1] In addition to hereditary causes, a form of nonhereditary acquired angioedema (AAE) mediated by bradykinin is known.[2] Both HAE and AAE can be life-threatening. AAE is angioedema with normal CI-INH (previously called type 3, or non-type 1, non-type 2 HAE) and a normal complement C4 levels. Specific genetic mutations have been linked to factor XII, plasminogen gene and angiopoietin-1 in AAE. Patients with unknown mutations are classified as unknown.[1] A useful test to differentiate AAE from HAE is C1q protein, which is normal in HAE and low in AAE. The management of HAE includes on-demand therapy options like plasma and recombinant C1-INH for intravenous infusion, an ecallantide-an inhibitor of kallikrein administered subcutaneously, and icatibant-a bradykinin β_2 receptor antagonist administered subcutaneously.[1]

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Effective agents for long-term prophylaxis are C1-INH enzyme replacement and a monoclonal antibody against kallikrein (lanadelumab, administered subcutaneously).[1] It is typical in angioedema mediated by bradykinin has shown that the classic therapy (antihistamines, corticosteroids and adrenaline) is completely without effect. Clinical features are often associated with elevated bradykinin levels, which lead to increased vascular permeability and the development of angioedema.[3,4] There is increasing data in the literature on the effectiveness of HAE treatment (not only type I and II, but also AAE) related to angioedema caused by drugs for the treatment of hypertension from the ACEI group, such as in the case of our patient.[3,5,6] The number of patients who are taking ACEI therapy to treat hypertension is on the rise. Therefore, it is no surprise that that the number of different side effects has doubled in the last decade from 24% to 49%, which is explained by more regular reporting of side effects by doctors and higher awareness of possible side effects in patients.[2,3,4] Regardless of the form and etiology, timely intervention is crucial. This case demonstrates the proper diagnosis and prompt intervention in a scenario of rapid onset angioedema of unknown etiology, presumed to be nonhereditary, induced by angiotensin-converting enzyme inhibitors (ACEI).

Case report

A 68-year-old adipose (BMI 38kg/m^2) male came to the emergency department (ED) with a chief complaint of dyspnea that started approximately two hours before. He had a long history of arterial hypertension (8 years), type II diabetes (5 years), chronic kidney disease stage G3b/A3 (2 years) and two separate episodes of dyspnea with facial and oral edema and hoarseness, successfully treated before two and five years with a combination of corticosteroids, antihistamines and epinephrine. He had four different antihypertensive medications in his therapy, including an ACEI -ramipril 5 mg for 8 years. The time of first ACEI intake was 2,920 days. During the physical examination, the patient was hypertensive (blood pressure 180/95mmHg), tachycardic (100/min), tachypnoic, and edematous. No murmurs, gallops, or rubs were auscultated. Abdomen was soft, symmetric, adipose and non-tender without distention. No masses, hepatomegaly, or splenomegaly were noted. No focal deficits were appreciated on neurological examination. The initial laboratory results revealed elevated liver enzymes (AST 58 U/L, ALT 63 U/L) glucose (12.5 mmol/L) and creatinine (198umol/L). The chest X-ray showed normal size and shape of the chest wall and the main structures in the chest. He was admitted to the ORL Department with a presumptive diagnosis of

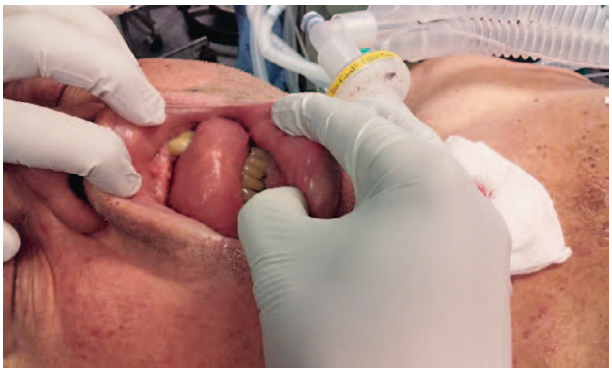

Figure 1. Swollen and enlarged tongue occupying oral cavity.

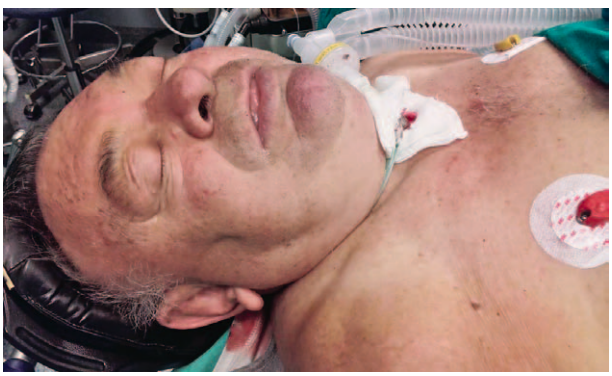

Figure 2. Whole-body edema.

Figure 3. On the second day of admission, there was no face and body swelling.

an angioedema. At admission, systemic corticosteroid therapy in high doses (500mg infusion) was started, all previous medications were discontinued and the patient was monitored during the night for signs of clinical recovery. The patient's edema and dyspnea worsened over eight hours and his oxygen saturation started to rapidly deteriorate. Intubation was not possible due to edema of the tongue, so a tracheotomy was performed to secure an airway (Figure 1). Rapid progression of the oedema development and additional therapy was indicated (Figure 2). An ampule of icatibant (B2 bradykinin receptor antagonist) was administered subcutaneously and rapid regression of the edema followed, along with the stabilization of the patient's vital signs. On the second day of the admission, clinical improvement was obvious and there was no face and body swelling (Figure 3). The levels of transaminases began to improve, so the patient was discharged after five days with a recommendation to discontinue the ACEI and other drugs from the Renin-Angiotensin-Aldosterone System (RAAS). The time from the onset of symptoms to settling down of the edema was 34.0 hours. Additional follow-up with an immunologist was included. HAE types I and II were excluded with C1q inhibitor levels within normal range (34.5 mg / dL, normal to 39) and with normal complement level C4 (0.4 g /L).

Discussion

The unpredictability of HAE is manifested primarily in the emergency department (ER) where patients first appear with various symptoms, including swelling of different parts of the body, allergic nonspecific symptoms, swelling of the tongue and abdomen. Regardless of present-day diagnostic possibilities, if this rare but potentially life-threatening hereditary disease is not considered an option, and most of its symptoms are not timely and adequately recognized, the patient is not referred for further treatment.[1] Acquired angioedema can occur with various lymphoproliferative diseases, as well as with the use of therapeutic drugs for hypertension, especially from the group of ACE inhibitors, as in our case.[1,3]

According to a 2015 study by Bas et al., patients who had induced angioedema while taking ACEI, if treated with bradykinin inhibitor icatibant, had a three-times faster recovery and felt five times better than with a standard glucocorticosteroid and antihistamine therapy.[5] According to Nosbaum et al., there were 76 patients (60.5% men; middle-aged, 64.4 ± 13.7 years) with angioedema provoked by ACEI treatment registered in France from 2008 to 2013.[6] All of them had normal levels of C1 inhibitors, and other possible causes of angioedema were ruled out. Angioedema (AE) was located on the tongue (49.3%), larynx (22.7%), abdomen (5.6%), and extremities (4.0%). The average time of ACEI intake was 589 days (1 to 5,400).[6] Of the 76 patients, 20 (26.3%) received icatibant. Since 58.3% of the patients were treated in the ICU, the efficiency of icatibant was obvious and there were no deaths. The average time from the onset of symptoms to the settling of the edema was (36.0±12.0 hours), which is longer than in the Bas et al. study and can be explained by more intensive symptomology of patients in the Nosbaum et al. study.[5,6]

The patient in question had previously manifested on two occasions Quincke's edema, which led to his hospitalization at ORL, where he was administered a supportive classic corticosteroid therapy in high doses of 500 mg (iv), after which his symptoms ceased. However, when the patient was hospitalized for the third time there was no clinical response to corticosteroid therapy and due to worsening clinical condition and progressive edema with inability to intubate, he was tracheotomized and administered with icatibant, to which he promptly responded and withdrawal of the edema occurred, as in other studies.[5,6] Mild cases of ACEI-AE may respond to antihistamine or corticosteroid therapy, but moderate to severe cases do not. Withdrawal of ACEI is the key to managing this condition.[6,7]

Medical experts in the ER have to be educated on the appropriate management of angioedema.[7-9] Angioedema may be primarily manifested by recurrent episodes of Quincke's edema (as in our patient), but also by edema of subcutaneous tissue, edema of the mucous membranes of the upper respiratory tract and the gastrointestinal tract, with great variability in occurrence, usually without urticaria, rash or itching.[10,11]

In our first study in Croatia we analyzed the frequency and treatment of bradykinin-induced angioedema as a cause for emergency treatment. Bradykinin-induced AE was the leading cause in the investigated group (31.5%).[11] Angioedema resulting from bradykinin-induced AE (AAE and HAE) was the

main reason for emergency arrivals of patients.[11] Our previously study confirmed a poor response to glucocorticoid, antihistamine and epinephrine treatment in severe AE, and the need for new therapeutic options to improve the resolution of AE. Advances in the treatment of HAE and case reports of patients with ACEI-AE treated with C1-INH concentrate or bradykinin receptor antagonist show that they may be a safe and efficacious therapeutic option.[11]

In conclusion, emergency physicians should be adequately educated on when to suspect nonhereditary angioedema, and how to manage the rapid onset of airway obstruction it causes it in the most severe cases. Emergency departments should also be equipped with the medications used in its management.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

The authors state that this manuscript has not been published previously and is not currently being assessed for publication by any journal other than the Acta Clinica Croatica. The authors disclose that they did not receive any financial support for the study. No proprietary interest is involved in the study.

Consent

Informed consent was obtained from the patient for the publication of this case report and the accompanying images.

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Sažetak

RIJEDAK SLUČAJ OTEŽANOG DIŠNOG PUTA ZBOG STEČENOG ANGIOEDEMA - BEZ MOGUĆNOSTI INTUBACIJE I OKSIGENACIJE

Đ. Delalić, V. Borčić i *I. Prkačin*

Angioedem može biti posredovan histaminom te se radi o alergijskom, no može biti posredovan bradikininom te se radi o nealergijskom angioedemu. Ukoliko se ne prepozna ili liječi pravovremeno može biti smrtonosan. U ovome radu prikazujemo slučaj pravovremene dijagnoze i intervencije nealergijskog angioedema 68-godišnjeg muškarca koji je došao u hitnu službu sa simptomima dispneje koja je započela dva sata ranije. Od pridruženih bolesti liječio se zbog šećerne bolesti, kroničnе bubrežne bolesti i hipertenzije zbog čega je godinama uzimao lijek iz skupine ACE-inhibitora. Na fizičkom pregledu pacijent je bio hipertenzivan, tahikardan, tahidispnoičan i edematozan ne samo u podoručju lica i tijela. Tijekom boravka u Hitnoj službi liječen je kombinacijom kortikosteroida, antihistamina i epinefrina, no edem i dispneja su progredirali kroz nekoliko sati, a zasićenost kisikom počela se pogoršavati. Intubacija nije bila moguća zbog izrazitog otoka jezika, stoga se pristupilo traheotomiji radi očuvanja dišnog puta. Obzirom na i dalje oticanje jezika i tijela postavljena je sumnja na bradikinski angioedem te je primijenjena ampula icatibanta nakon čega se prati promptna regresija edema jezika i tijela, sa stabiliziranjem vitalnih znakova pacijenta. Pacijent je otpušten kući peti dan s preporukom isključenja ACE inhibitora. Liječnici u hitnim službama trebaju biti upoznati s mogućnostima dodatnog liječenja nealergijskog angioedema.

Ključne riječi: *angioedema, bradikinin, icatibant–antagonist B2 bradikininskog receptora*

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