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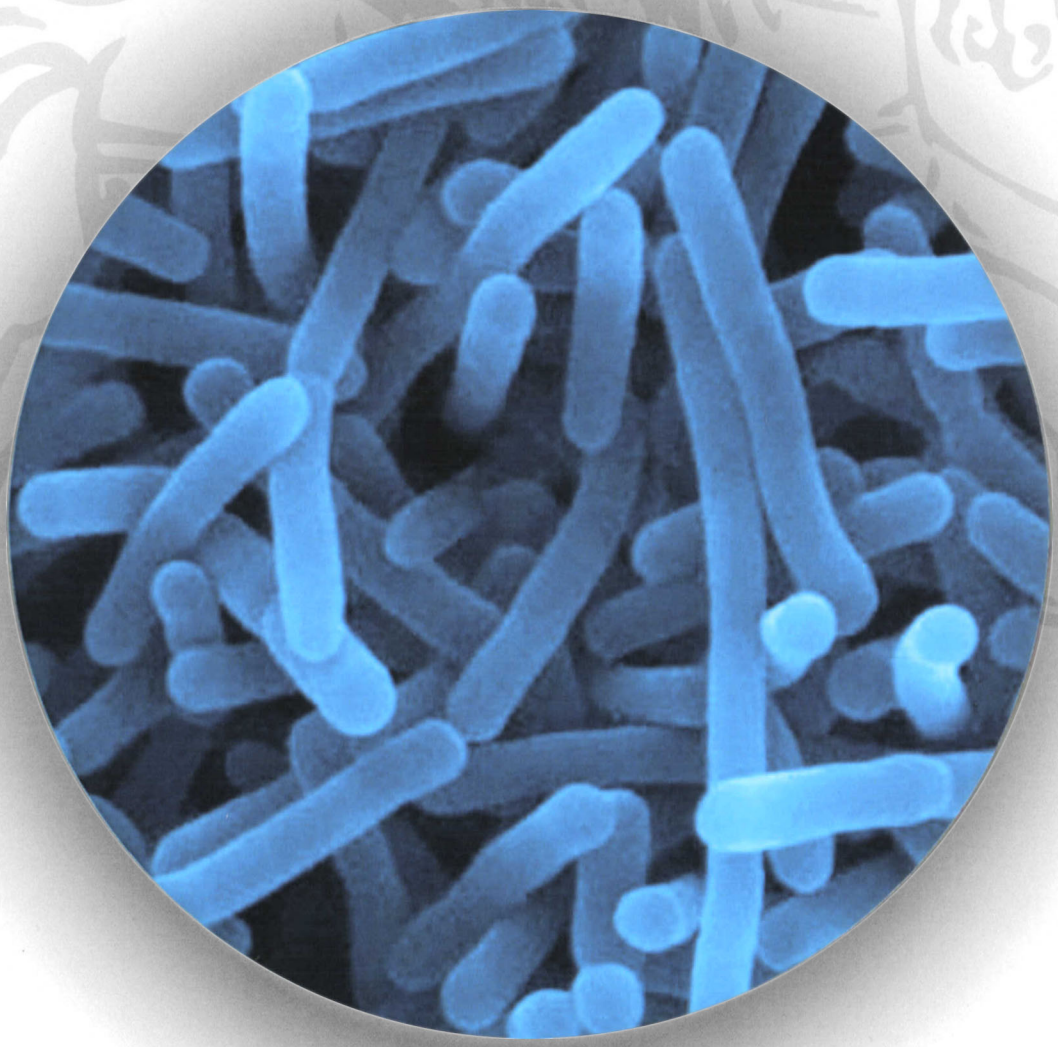

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The clinical and predictive value of C-reactive protein/albumin ratio in critically ill and mechanically ventilated adult patients

Klinička i prediktivna vrijednost omjera C-reaktivnog protein/albumin u kritičnih, mehanički ventiliranih bolesnika

Domagoj Loinjak, Damir Mihić, Lana Maričić, Marija Kadović, Livija Sušić, Ivana Tolj*

Summary

Introduction: CPR/albumin ratio represents a new biomarker that integrates two laboratory-tested acute phase reactants: a positive one (C-reactive protein) and a negative one (albumin), and which can be used as an indicator of the severity, progression and outcome of various illnesses, including critical illnesses. In this retrospective study, we investigated the impact of the CRP/albumin ratio on the clinical characteristics and outcome of the treatment of critically ill and mechanically ventilated adult patients.

Patients and methods: This retrospective study included 100 critically ill patients (65 % males and 35 % females; median age of 67) treated at the medical intensive care unit (ICU) which required the use of invasive mechanical ventilation. The primary diagnoses upon admission to the intensive care unit were: sepsis and septic shock (39 %), acute heart failure or worsening chronic heart failure (20 %), exacerbation of chronic obstructive pulmonary disease (16 %), pneumonia (11 %), acute kidney injury or the exacerbation of chronic kidney disease (7 %) and other conditions (7 %).

Results: Correlation analysis showed a significant moderate positive correlation between CRP/albumin ratio and the duration of mechanical ventilation measured in hours ($r = 0.48$, $p = 0.001$) and the time spent in the intensive care unit, measured in days ($r = 0.44$, $p = 0.001$). The median of the CRP/albumin ratio was 58.77 and the patients in the above-the-median group had a higher SOFA score. In terms of the outcomes, it has been determined that the surviving patients (56 %) had a significantly lower CRP/albumin ratio compared to those that had not survived (44 %), which correlates with their SOFA scores as well. In the group of survivors, the correlation between the ratio of CRP/albumin and the SOFA score is positive and statistically significant ($r = 0.29$, $p = 0.03$), in the group non-survivoris ($r= 0.45$, $p = 0.003$.)

Conclusion: Based on the results of our study, the CRP/albumin ratio has proved to be a good predictor of clinical characteristics and outcomes of critically ill and mechanically ventilated patients.

Key words: C-reactive protein, albumin, critically ill, outcome, mechanical ventilation

Sažetak

Uvod: Omjer CPR/albumin predstavlja novi biomarker koji integrira dva laboratorijski ispitana reaktanta akutne faze: pozitivni (C-reaktivni protein) i negativni (albumin), a koji se može koristiti kao pokazatelj težine, progresije i ishoda raznih bolesti, uključujući kritične bolesti. U ovoj retrospektivnoj

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studiji istraživali smo utjecaj omjera CRP/albumin na kliničke karakteristike i ishod liječenja kritično bolesnih, mehanički ventiliranih bolesnika.

Bolesnici i metode: Ova retrospektivna studija uključila je 100 kritično oboljelih bolesnika (65 % muškaraca i 25 % žena, prosječne dobi 67 godina) liječenih na Jedinici intenzivnog liječenja (JIL) koji su zahtijevali primjenu invazivne mehaničke ventilacije. Primarne dijagnoze po prijemu u jedinicu intenzivnog liječenja bile su: sepsa i septički šok (39 %), akutno zatajenje srca ili pogoršanje kroničnog zatajenja srca (20 %), egzacerbacija kronične opstruktivne plućne bolesti (16 %), upala pluća (11 %), akutno oštećenje bubrega ili egzacerbacija kronične bubrežne bolesti (7 %) i druga stanja (7 %).

Rezultati: Korelacijska analiza pokazala je značajnu umjerenu pozitivnu korelaciju između omjera CRP/albumin i trajanja mehaničke ventilacije mjerenog u satima (r = 0,48, p = 0,001) i vremena provedenog u Jedinici intenzivne njege, mjerenog u danima (r = 0,44, p = 0,001). Medijan omjera CRP/albumin bio je 58,77, a bolesnici u skupini iznad medijana imali su viši SOFA rezultat. Što se tiče ishoda, utvrđeno je da su preživjeli bolesnici (56 %) imali značajno niži omjer CRP/albumin u usporedbi s onima koji nisu preživjeli (44 %), što također korelira s njihovim SOFA rezultatima. U skupini preživjelih korelacija između omjera CRP/albumin i SOFA bodovnog zbroja je pozitivna i statistički značajna (r = 0,29, p = 0,03), a u skupini preminulih (r= 0,45, p = 0,003).

Zaključak: Na temelju rezultata naše studije, omjer CRP/albumin pokazao se kao dobar prediktor kliničkih karakteristika i ishoda kritično bolesnih, mehanički ventiliranih nekirurških bolesnika.

Ključne riječi: C-reaktivni protein, albumin, kritično bolesni, ishod, mehanička ventilacija

Introduction

The C-reactive protein/albumin ratio or CRP/alb ratio represents a new prognostic marker, the role of which has been examined and proved in different illnesses and conditions, and which is based on well-known, basic characteristics of the C-reactive protein and serum albumins. The C-reactive protein represents a marker of the systemic inflammatory response (positive acute phase reactant), which is mostly synthesized in the liver under the influence of interleukin 6 (IL-6), increased levels of which are linked to worse clinical outcomes of various illnesses, especially in critically ill patients. Serum albumins are proteins with multiple roles (maintaining osmotic pressure, the transport of hormones, metabolites and medicines) and their levels are used as a predictive marker both in chronically and in critically ill patients, since they belong to the group of so-called negative acute phase reactants because their levels are decreased in systemic inflammatory responses.[1-4] Except in inflammatory responses, decreased values of albumins may be a consequence of malnutrition, which occurs in chronic illnesses, and of increased catabolism, which occurs in acute illnesses.[5,6] Based on the foregoing, it would be logical to assume that CRP/alb ratio as an indicator of the severity of inflammatory and nutritional status will be more sensitive in predicting the severity, progression and outcome of an illness than the individual levels of the two proteins. The prognostic significance of the CRP/alb ratio has mostly been studied in malignant diseases, but its role is being increasingly studied in other illnesses as well, such as cardiovascular diseases, systemic diseases and immunological disorders, severe infections, etc. Its predictive significance in surgical patients is also being studied. The CRP/alb ratio has also been studied as a prognostic marker in critically ill patients; however, studies to date have focused on critically ill patients with predominantly surgical pathology (trauma, surgery) and on neurological patients.[7-15] In addition, the CRP/alb ratio may also be interesting in terms of predicting the duration of mechanical ventilation of critically ill patients, considering that one of the main factors associated with prolonged mechanical ventilation is the intensity of the systemic inflammatory response and the severity of malnutrition.[16] The primary aim of this study is to investigate the relationship between the CRP/alb ratio and clinical characteristics of the medical critically ill patients (the duration of mechanical ventilation, laboratory parameters and SOFA score). The secondary aim of the study is to examine the association of CRP/alb with the outcome of the treatment of critically medical ill patients.

Patients and methods

This retrospective study involved 100 patients treated at the Intensive Care Unit of the Clinical Hospital Centre in Osijek over a period of three months. The study included critically ill patients who required mechanical ventilation for longer than 72 hours due to respiratory insufficiency as a result of the underlying disease (sepsis and septic shock, acute heart failure or worsening chronic heart failure, the exacerbation of chronic obstructive pulmonary disease, pneumonia, acute kidney injury or the

exacerbation of chronic kidney disease). Patients were excluded from the study if they: 1) were younger than 18 years; 2) had been mechanically ventilated for less than 72 hours; 3) had an active malignant disease; 4) had an acute surgical illness and receieved immediate surgical intervention; 5) had an acute neurological event. Data on the patients, methods and the course of treatment, outcomes and laboratory test results were obtained by searching the hospital information system, upon prior approval of the competent Ethics Committee (number approval R2-208/2021). For the purposes of this study, besides demographic data (age, sex), other data were used as well, such as: primary diagnosis (the reason for admission to the intensive care unit), total time spent on mechanical ventilation (the duration of mechanical ventilation) expressed in hours, time spent in the Intensive Care Unit (in days), the outcome of treatment (survival or fatality), laboratory parameters (red blood cell count, white blood cell count, lymphocyte count, platelet count, C-reactive protein, urea, creatinine, sodium, potassium, albumin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, lactates, procalcitonin, pH values and arterial blood gas tests) and the SOFA score (Sequential Organ Failure Assessment). The CRP/alb ratio was calculated based on the standard formula:

$$\frac{\text{C reactive protein (mg/L)}}{\text{albumin (g/dL)}} \times 10$$

CRP and albumin values used in the calculation of the CRP/albumin ratio were those measured upon the arrival at the Intensive Care Unit or those measured within 24 hours after admission.

Based on the previous studies, the sample size was estimated a priori using G-power 3.1. Categorical data were presented as absolute and relative frequencies. Numeric data were described as the median and interquartile range. A correlation analysis was used for determining the correlation between the observed phenomena. The comparison of continuous variables was made by using the t-test, and the effect size of the observed phenomenon was measured by Cohen's d, which was calculated by subtracting the mean of one group from the other and dividing the result by the standard deviation. The calculated common standard deviation refers to the total sample of participants. The effect size was calculated only for statistically significant differences and was interpreted as trivial (<0.2), small (≥0.2), medium (≥0.5) and large (≥0.8). Statistical analysis was performed by using the MedCalc Statistical Software version 19.1.7 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020).

Results

This study included 100 patients, 65 (65%) males and 35 (35 %) females. The patients' median age was 67 and the interquartile range was 34 to 89 years of age. The presentation of clinical characteristics is provided in Table 1.

The correlation analysis showed a significant moderate positive correlation between the CRP/alb ratio and the duration of mechanical ventilation measured in hours ($r = 0.48$, $p = 0.001$), with patients whose CRP/alb ratio was higher spending longer time on mechanical ventilation. Furthermore, the correlation analysis showed a significant moderately positive correlation between the CRP/alb ratio and the time spent in the Intensive Care Unit, measured in days ($r = 0.44$, $p = 0.001$), with patients whose CRP/alb ratio was higher staying longer at the ICU.

Those patients' median CRP/alb ratio was 58.77 (the interquartile range was from 0.25 to 181.92), with 50 patients below and 50 above the median. Table 2 shows a comparison of patients below and above the median CRP/alb ratio in terms of their clinical presentation and laboratory test results. As evident from (Table 2), patients in groups below and above the median CRP/alb ratio exhibited statistically significant differences in seven elements of clinical presentation and laboratory test results. In this context, patients in the above-the-median group had a statistically significant longer stay in the Intensive Care Unit, longer mechanical ventilation, a higher SOFA score and their laboratory test results showed significantly higher levels of CRP, white blood cells and urea and significantly lower levels of albumin compared to the patients in the below-the-median group. The effect size for the identified statistically significant differences ranged from small (pertaining to white blood cells) to large (pertaining to the other elements of clinical presentation and laboratory test results).

In terms of the outcomes, it has been determined that the surviving patients (56 %) had a significantly lower CRP/albumin ratio compared to those that had not survived (44 %), which correlates with their SOFA scores as well. In this context, the effect sizes for both differences determined between these groups of patients were large. The effect of CRP/albumin ratio and the SOFA score on the outcome of treatment of these patients is presented in Table 3.

Table 1 Patients' clinical characteristics
Tablica 1. Kliničke karakteristike pacijenata

Demographic data ***Demografski padaci***	
Males *Muškarci*	65 (65 %)
Females *Žene*	35 (35 %)
Median age *Medijan dobi*	67
Primary diagnosis (reason for admission) ***Primarna dijagnoza po prijemu***	
Sepsis and septic shock *Sepsa i septički šok*	39 (39 %)
Acute heart failure or worsening chronic heart failure *Akutno srčano zatajenje / pogrošanje kroničnog srčanog zatajenja*	20 (20 %)
Exacerbation of chronic obstructive pulmonary disease *Pogoršanje kronične obstruktivne plućne bolesti*	16 (16 %)
Pneumonia *Pneumonija*	11 (11 %)
Acute kidney injury / exacerbation of chronic kidney disease *Akutno bubrežno zatajenje / pogoršanje kroničnog bubrežnog zatajenja*	7 (7 %)
Other conditions *Ostala stanja*	7 (7 %)
SOFA* score ***SOFA rezultat***	
Median SOFA score *Medijan SOFA bodovnog zbroja*	7.68 ± 3.25

* SOFA - Sequential Organ Failure Assessment)

Table 2 The comparison of elements of clinical presentation and laboratory test results in patient groups above and below the median CRP/albumin ratio
Tablica 2. Usporedba elemenata kliničke prezentacije i rezultata laboratorijskih pretraga u skupinama pacijenata iznad i ispod srednjeg omjera CRP/albumin

	Below the median (n = 50) ***Ispod medijana (n = 50)***		**Above the median (n = 59)** ***Iznad medijana (n = 50)***		**Group comparison** ***Usporedba skupina***	
	M	**SD**	**M**	**SD**	**P value*** ***P vrijednost***	**Effect size**** ***Veličina učinka***
Time spent at the ICU (in days) *Vrijeme u JIL-u (u danima)*	6.82	5.32	12.90	7.52	4.66 (*0.001*)	0.93
Mechanical ventilation (in hours) *Mehanička ventilacija (u satima)*	76.48	75.44	240.60	164.40	6.42 (*0.001*)	1.28
SOFA score *SOFA bodovni zbroj*	5.46	1.58	9.90	2.96	9.35 (*0.001*)	1.87
Red blood cells ($\times 10^{12}$/L) *Eritrociti ($\times 10^{12}$/L)*	4.38	0.78	4.19	0.90	1.13 (*0.25*)	–
White blood cells ($\times 10^{9}$/L) *Leukociti (x 10^{9}/L)*	11.74	5.88	14.89	8.69	2.12 (*0.04*)	0.42
Lymphocytes ($\times 10^{9}$/L) *Limfociti ($\times 10^{9}$/L)*	10.44	7.74	9.69	8.78	0.45 (*0.65*)	–

	Below the median (n = 50) ***Ispod medijana (n = 50)***		**Above the median (n = 59)** ***Iznad medijana (n = 50)***		**Group comparison** ***Usporedba skupina***	
	M	**SD**	**M**	**SD**	**P value*** ***P vrijednost***	**Effect size**** ***Veličina učinka***
Platelets (× 10^9/L) *Trombociti (× 10^9/L)*	229.24	106.55	246.28	102.55	0.81 (*0.42*)	–
RDW (%)*** *RDW (%)*	14.47	2.262	14.52	2.49	0.12 (*0.90*)	–
C-reactive protein (mg/L) *C-reaktivni protein (mg/L)*	76.79	54.92	258.64	140.34	8.53 (*0.001*)	1.70
Urea (mmol/L) *Ureja (mmol/L)*	10.90	6.97	15.10	11.69	2.19 (*0.03*)	0.43
Creatinine (µmol/L) *Kreatinin (µmol/L)*	132.30	112.69	187.96	177.77	1.87 (*0.06*)	–
Sodium (mmol/L) *Natrij (mmol/L)*	137.16	8.53	138.80	7.73	1.00 (*0.32*)	–
Potassium (mmol/L) *Kalij (mmol/L)*	4.17	0.64	4.22	0.75	0.34 (*0.73*)	–
Albumin (g/L) *Albumin (g/L)*	34.30	6.48	23.77	5.30	8.89 (*0.001*)	1.78
Aspartate aminotransferase (U/L) *Asparat aminotransferaza (U/L)*	236.40	887.41	235.04	743.99	0.01 (*0.99*)	–
Alanine aminotransferase (U/L) *Alanin aminotransferaza (U/L)*	188.64	642.63	149.16	444.57	0.66 (*0.72*)	–
Lactate dehydrogenase (U/L) *Laktat dehidorgenaza (U/L)*	545.28	817.10	690.46	1071.33	0.76 (*0.45*)	–
Lactates (mmol/L) *Laktati (mmol/L)*	10.10	58.17	2.55	2.69	0.92 (*0.36*)	–
Procalcitonin (mg/L) *Prokalcitonin (mg/L)*	2.60	9.46	11.04	31.18	1.83 (*0.07*)	–
pH *pH*	7.37	0.10	7.35	0.16	0.93 (*0.35*)	–
pO_2 (kPa) *pO_2 (kPa)*	8.56	3.38	8.56	3.38	0.41 (*0.68*)	–
pCO_2 (kPa) *pCO_2 (kPa)*	5.87	1.77	5.37	2.09	1.28 (*0.14*)	–

*t-test (*t-test*)

**Cohen's d (*Cohen's d*) Effect size was calculated only for statistically significant differences and was interpreted as trivial (<0.2), small (≥0.2), medium (≥0.5) and large (≥0.8).

Cohenov d (Cohen's d) Veličina učinka izračunata je samo za statistički značajne razlike i tumačena je kao trivijalna (<0,2), mala (≥0,2), srednja (≥0,5) i velika (≥0,8).

*** Red Cell Distribution Width *(Raspodjela eritrocita po volumenu)*

Table 3 The impact of CRP/albumin ratio and SOFA score on the outcome of treatment
Tablica 3. Utjecaj omjera CRP/albumin i SOFA bodovnog zbroja na ishod liječenja

	Survivals (n = 56) ***Preživjeli (n = 56)***		**Fatalities (n = 44)** ***Umrli (n = 44)***		**Group comparison** ***Usporedba skupina***	
	M	**SD**	**M**	**SD**	**P value*** ***P vrijednost***	**Effect size**** ***Veličina učinka***
CRP/albumin ratio *CRP/albumin omjer*	39.81	36.86	100.64	61.18	6.16 (*0.001*)	1.20
SOFA score *SOFA bodovni zbroj*	5.71	2.12	10.18	2.67	9.39 (*0.001*)	1.85

*t-test (*t-test*)
**Cohen's d (*Cohen's d*) Effect size was calculated only for statistically significant differences and was interpreted as trivial (<0.2), small (≥0.2), medium (≥0.5) and large (≥0.8).
Cohenov d (Cohen's d) Veličina učinka izračunata je samo za statistički značajne razlike i tumačena je kao trivijalna (<0,2), mala (≥0,2), srednja (≥0,5) i velika (≥0,8).

Discussion

Our study showed a significant moderately positive correlation between the CRP/alb ratio and longer mechanical ventilation measured in hours (patients with a higher ratio were mechanically ventilated for a longer period of time). This is consistent with the results of Bai M. et al, who studied the prognostic role of CRP/albumin ration in critically ill neurological patients[15] and of Ozciftci Y. P. et al, who looked at the role of CRP/albumin ration in the prognosis of critically ill patients who required urgent surgery.[17] In this context, a significant moderate positive correlation was found between CRP/alb ratio and the time spent in the intensive care unit (patients with a higher ratio spent more days in the intensive care unit), which is also consistent with the results of the mentioned papers. Both the duration of mechanical ventilation and the time spent in the intensive care unit also depend on the intensity of the inflammatory response, the metabolic response (catabolism) and the nutritional status, so it can be expected that patients with a stronger inflammatory response and increased catabolism, accompanied by a poorer nutritional status, will also have poorer outcomes (longer mechanical ventilation, longer treatment), and this is something that a higher CRP/albumin ratio indicates. Systemic inflammatory response and malnutrition have an indirect effect on the respiratory function, this ratio can be expected to serve as a good indicator in predicting the duration of mechanical ventilation in critically ill individuals.[16] Considering that previous papers dealing with the correlation between clinical indicators and outcomes of critically ill patients with their CRP/alb ratio were mostly based on critically ill surgical and neurocritically ill patients, our study focused on critically ill patients whose primary diagnoses were those within the scope of internal medicine, including patients suffering from infectious diseases, the severity and nature of which required invasive mechanical ventilation.Moreover, patients with a higher CRP/alb ratio exhibited a higher mortality rate in the Intensive Care Unit, and in this respect, the CRP/albumin ratio has a positive correlation with the SOFA score, as shown in Table 3 (the surviving patients' median CRP/alb ratio was 39.81 and their median SOFA score was 5.71, whereas the median CRP/alb ratio for the patients that did not survive was 100.64 and their median SOFA score was 10.18). This correlation between the SOFA score and the CRP/alb ratio on the one side and mortality on the other has been tested and proved in critically ill surgical patients.[13] By comparing the laboratory test parameters with the CRP/alb ratio, we found a positive correlation with the white blood cell count and urea levels.The white blood cell count is expectedly elevated in conditions involving inflammatory response, whereas elevated urea values can be interpreted by the influence of anti-inflammatory mediators such as NF-α and IL-6 as the promotors of protein catabolism and increased production of urea.[18] Based on our study, and by comparison with other papers dealing with surgical, traumatological and neurological patients, we see similar results, so it is safe to assume that CRP/alb ratio can serve as a good indicator of clinical outcomes of critically ill patients (duration of mechanical ventilation, time spent in the intensive care unit and outcome - survival or fatality). Our contribution is primarily based on investigating the role of the CRP/alb ratio in patients with primary

medical critical illness in order to contribute to the overall consideration of the predictive role of the CRP/alb ratio in medical critically ill patients. Nevertheless, when interpreting our results, just like the results of other similar papers, one should keep several limitations in mind. Firstly, this was a retrospective study with a limited number of patients included (patients that met the inclusion criteria and were treated in the specified period). Secondly, patients with very high CRP levels (and consequently very high CRP/albumin ratio) have a much more serious clinical condition, which could end fatally very quickly, which in turn has an impact on the duration of mechanical ventilation (patients who were worse off and died sooner were ultimately mechanically ventilated for a shorter period of time), which is why we included patients treated at the Intensive Care Unit over a minimum period of 72 hours. Thirdly, when interpreting the impact of CRP/alb ratio on these patients' outcomes, one has to consider the fact that outcome was defined as a fatality if the patient died while in the intensive care unit, and that survival in fact meant dismissal from the intensive care unit (mostly involving transfer to another ward), which can be a relatively short period of time.

Conclusion

Based on the results of our study, the value of the CRP/alb ratio proved to be a good predictor of clinically adverse events' outcomes, such as prolonged mechanical ventilation, prolonged stay in the Intensive Care Unit, and the unfavorable final outcome of treatment in critically ill and mechanically ventilated adult patients.

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Stavovi studenata sestrinstva o Covid-19 i cijepljenju protiv Covid-19 bolesti

Attitudes of nursing students about Covid-19 and vaccination against Covid-19 disease

Lucija Lesjak, Alan Medić, Margareta Mesić, Mira Klarin, Diana Nonković, Tatjana Nemeth Blažić*

Sažetak

Tijekom trajanja pandemije stavovi o cijepljenju protiv COVID-19 su se mijenjali, a ta je podjela bila izraženija što je tijek pandemije dulje trajao. Imali smo priliku čuti razna mišljenja i stavove o cijepljenju. Sudjelovali smo u mnogim raspravama koje su rezultirale iznošenjem i pozitivnih i negativnih stavova o cijepljenju protiv koronavirusa.

Cilj ovoga istraživanja bio je utvrditi postoje li razlike u stavovima o bolesti COVID-19 između studenata sestrinstva koji su cijepljeni i onih koji nisu, te procijeniti kakvo je povjerenje prema odlukama Nacionalnog stožera. Istraživanje je provedeno od 4. travnja do 4. svibnja 2022. godine.

Kako bi se odgovorilo na postavljena pitanja, u istraživanju je korišten modificirani mjerni instrument stvoren na temelju modela zdravstvenog vjerovanja *(eng. Health Beliefs model -HBM)* tvrtke Wang et al. (2021.).

U istraživanju je sudjelovao 271 ispitanik, studenti Preddiplomskog i Diplomskog studija sestrinstva u Republici Hrvatskoj iz Varaždina, Osijeka, Zagreba, Rijeke, Pule, Splita i Zadra, od čega je bilo 231 (85,2%) studentica i 40 (14,8%) studenata.

Rezultati istraživanja pokazuju da studenti koji su se cijepili, situaciju s COVID-om procjenjuju ozbiljnijom. Za njih je dobrobit cijepljenja veća, manje je zapreka za cijepljenje i manje odbijaju cijepljenje od studenata koji se nisu cijepili. Nadalje, studentice izražavaju više zabrinutosti i prepreka u odnosu na studente, ali razlike u pogledu razine obrazovanja nisu dobivene. Studenti koji su se cijepili drže da bi obitelj, prijatelji, struka, Vlada i mediji trebali zagovarati i preporučiti cijepljenje, u odnosu na studente koji se nisu cijepili.

Važno pitanje odnosilo se na ispitivanje povjerenja prema Nacionalnom stožeru. Ispitanici su pokazali relativno nisku razinu povjerenja, a oni studenti koji su cijepljeni imali su više povjerenja u zdravstvene stručnjake, medije i članove Vlade.

Drukčiji pristup osobama kod kojih postoji zabrinutost u pogledu učinkovitosti i sigurnosti cjepiva i mogućih nuspojava, trebalo bi biti jedna od aktivnosti usmjerenih prema toj populaciji, kako bi oni mogli donijeti odluke na temelju objektivno stečenog znanja i informacija koje donosi znanost.

Ključne riječi: cijepljenje, COVID-19, stavovi, studenti, sestrinstvo

Summary

During the duration of the pandemic, attitudes regarding vaccination against COVID-19 changed, and

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this division was more pronounced the longer the course of the pandemic lasted. We had the opportunity to hear various opinions and attitudes about vaccination. Likewise, we participated in many discussions that resulted in the presentation of both positive and negative views on vaccination against the corona virus.

The aim of this research was to determine whether there are differences in attitudes about the disease COVID-19 between nursing students who have been vaccinated and those who have not, and to assess the level of trust in the decisions of the National Headquarters. The research was conducted between April 4 and May 4, 2022.

In order to answer the questions, the study used a modified measurement instrument created on the basis of the Health Beliefs Model (HBM) by Wang et al. (2021).

Two hundred seventy-one respondents of undergraduate and graduate Nursing students in the Republic of Croatia from Varaždin, Osijek, Zagreb, Rijeka, Pula, Split and Zadar took part in the research, of which 231 (85.2%) were female students and 40 (14.8%) male students.

The results of the research show that students who have been vaccinated assess the situation with COVID as more serious, for them the benefit of vaccination is greater, there are fewer obstacles to vaccination and they refuse vaccination less than students who have not been vaccinated. Furthermore, female students express more concerns and obstacles compared to male students, but differences regarding the level of education were not obtained. Students who have been vaccinated believe that family, friends, the profession, the Government and the media should advocate and recommend vaccination in comparison to students who have not been vaccinated.

An important question is related to the examination of trust towards the National Headquarters. Respondents showed a relatively low level of trust, and those students who were vaccinated had more trust in health experts, the media and members of the Government.

A different approach to people who have concerns about the effectiveness and safety of vaccines and possible side effects should be one of the activities aimed at this population so that they can make decisions based on objectively acquired knowledge and information provided by science.

Key words: vaccination, COVID-19, attitudes, students, nursing

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Uvod

Svijet se krajem 2019. i tijekom 2020. godine suočio s pandemijom virusne bolesti COVID-19 uzrokovane SARS-CoV-2 virusom. Korona virusi pripadaju obitelji Coronaviridae, koji uzrokuju respiratorne infekcije kod sisavaca, a od njih mogu obolijevati šišmiši, deve ili neke ptičje vrste.[1,2] Kod ljudi, infekcije koronavirusom mogu biti asimptomatske ili popraćene vrućicom, kašljem, kratkim dahom i gastrointestinalnim smetnjama.[3,4] U određenim slučajevima, pogotovo u osoba starije životne dobi, u imunokompromitiranih osoba ili pak u osoba kod kojih su prisutni komorbiditeti, infekcije mogu dovesti do teške upale pluća, a posljedično i do smrti.[2]

Cijepljenje je postupak unošenja cjepiva u organizam, a ono potiče aktivnu imunost stvaranjem vlastitih protutijela protiv uzročnika određenih bolesti. Svjetska zdravstvena organizacija ističe da je imunizacija najučinkovitija mjera prevencije o uspjehu u zdravstvu i razvoju, koja svake godine spašava milijune života.[5] Cijepljenje što većeg broja osoba važno je za učinkovito suzbijanje i sprječavanje pandemije, za smanjivanje rizika od nastajanja novih varijanti i budućih izbijanja epidemija, te za promicanje zdravlja i sigurnost svakog pojedinca.[6]

Razvoj cjepiva protiv SARS-CoV-2 virusa igra značajnu ulogu u povijesti zdravstva. Prema SZO, pandemija COVID-19 bolesti bila je proglašena u ožujku 2020. godine, a u prosincu iste godine već se započelo s cijepljenjem.[7] Unatoč tome što je prepoznata kao jedna od najuspješnijih javnozdravstvenih mjera, jedan dio populacije cijepljenje smatra nesigurnim i/ili nepotrebnim.[8] Društvene podjele postale su sve očitije između cijepljenih i necijepljenih pojedinaca. Separacija mišljenja cijepljenih i necijepljenih, uzajamno osuđivanje njihovih odluka, donosi nelagodu i osjećaj srama, osobito u skupinama necijepljenih koji su manjina.[9]

Tijekom pandemije kao što je COVID-19 – unutar zajednice javljali su se strah i tjeskoba. U takvim vremenima, oslanjanje na znanost i znanstvene spoznaje ključan je element u provedbi mjera za sprječavanje ili usporavanje daljnjeg širenja bolesti. Rezultati znanstvenih istraživanja, a posebno ispravno tumačenje tih rezultata, postaju ključne sastavnice javnog zdravstva u pogledu osvješćivanja javnosti o potrebitosti određenog medicinskog tretmana. Na taj način, objektivno definiranim i znanstveno potkrijepljenim mjerama smanjuje se pojavnost nepovjerenja u javnosti u pogledu potrebitosti primjene različitih medicinskih tretmana, pa tako i cijepljenja. Osim stručno i znanstveno utemeljenih preporuka, važna je i komunikacija s

javnošću oko tih preporuka, te drugačija komunikacijska strategija. Imunizacija jest krucijalna komponenta primarne zdravstvene zaštite i neosporno je ljudsko pravo na zaštitu zdravlja. Ona podupire globalnu zdravstvenu sigurnost i potrebno je sredstvo u borbi protiv otpornosti na antimikrobne lijekove. Isto tako, jedno je od najboljih ulaganja u zdravlje.[10] Pojava novog koronavirusa predstavljala je ozbiljnu prijetnju svjetskom javnom zdravstvu i izazvala veliku i dugotrajnu pandemiju u naivnoj ljudskoj populaciji.[11]

U Republici Hrvatskoj su u trenutku pisanja ovoga rada odobrena sljedeća cjepiva: Comirnaty, Spikevax (ranijeg naziva COVID-19 Vaccine Moderna), Jcovden (ranijeg naziva COVID-19 Vaccine Janssen), Vaxzevria (ranijeg naziva COVID-19 Vaccine AstraZeneca) te Nuvaxovid.[12]

Studenti su značajna skupina stanovništva koja svojim djelovanjem i primjerom može utjecati na razvoj društvenih trendova, a studenti sestrinstva kao studenti zdravstvenog usmjerenja i sadašnji ili budući zdravstveni radnici imaju dodatno obrazovanje iz područja imunizacije, te svojim djelovanjem i primjerom mogu pozitivno djelovati na druge zdravstvene djelatnike, kao i na svoje buduće bolesnike.[13]

Cilj ovoga istraživanja bio je utvrditi postoje li razlike u stavovimao o COVID-19 bolesti između studenata sestrinstva koji su se cijepili i onih koji to nisu učinili, te procijeniti kakvo je povjerenje prema odlukama Nacionalnog stožera.

Ispitanici i metode

U istraživanju je sudjelovao 271 student Preddiplomskog i Diplomskog studija sestrinstva na području Republike Hrvatske na sveučilištima i visokim učilištima. Od ukupnog broja ispitanika , njih 40 (14,8%) pohađa prvu godinu Preddiplomskog studija sestrinstva, 94 (34,7%) ispitanika je druge godina Preddiplomskog studija sestrinstva, 117 (43,2%) je treća godina Preddiplomskog studija, 18 (6,6%) ispitanika je prva godina Diplomskog studija sestrinstva, a dvoje (0,7%) ispitanika su s druge godine Diplomskog studija sestrinstva. Prema procjeni upisane kvote redovnih studenta sestrinstva sveučilišta i veleučilišta kojima pripadaju naši ispitanici, ukupan procijenjeni uzorak je oko 1200 studenata/ica, što naš uzorak čini reprezentativnim s 22% udjela od ukupnoga broja.

Od 271 ispitanika, 231 (85,2%) je ženskog, a 40 (14,8%) muškog spola. Najviše ispitanika je u dobnoj skupini od 18-24 godine, njih 182 (67,2%), 56 (20,9%) ih je u dobi od 25-34 godine, te 33 (12,1%) ispitanika u dobi od 35 godina i više. Raspon godina je 19-52 godine, prosjek godina je 24,9 godina., a medijan dobi 24.

U istraživanju je sudjelovao 271 student Preddiplomskog i Diplomskog studija sestrinstva na području Republike Hrvatske na sljedećim sveučilištima i visokim učilištima: 34 (12,5%) ispitanika pohađa Studij sestrinstvo na Sveučilištu Sjever (Varaždin), 66 (24,4%) ispitanika na Veleučilištu u Bjelovaru, jedan (0,4%) na Sveučilištu Josipa Jurja Strossmayera (Osijek), 44 (16,2%) na Zdravstvenom veleučilištu (Zagreb), 51 (18,8%) na Sveučilištu u Rijeci, 11 (4,1%) na Sveučilištu Jurja Dobrile (Pula), 39 (14,4%) na Sveučilištu u Zadru, dvoje (0,7%) na Sveučilištu u Splitu, a 23 (8,5%) ispitanika pohađa studij Sestrinstvo na Sveučilištu u Dubrovniku. Od 271 ispitanika, 231 (85,2%) je ženskoga, a 40 (14,8%) muškoga spola, te je 182 (67,2%) ispitanika u dobi od 18-24 godine, 56 (20,9%) u dobi od 25-34 godine i 33 (12,1%) ispitanika u dobi od 35 godina i više. Od ukupnog broja ispitanih studenata, njih 73 (26,9%) nije se cijepilo protiv COVID-19.

Istraživanje je odobrilo Etičko povjerenstvo Sveučilišta u Zadru KLASA: 114-06/22-01/14, URBROJ: 15-22-01 od 17.ožujka 2022.

Istraživanje se provodilo u razdoblju od 4. travnja do 4. svibnja 2022. godine putem internetske platforme Google Forms, a u potpunosti je bilo anonimno i dobrovoljno (prigodni uzorak). Uzorak ispitanika je prigodni, tj. ispitani su svi dostupni pojedinci kojima je distribuirana on-line anketa koju su dobrovoljno ispunjavali.

Mjerni instrument sastojao se od dva dijela. Prvi dio odnosio se na socio-demografske značajke ispitanika istraživanja, a drugi dio na stavove o zarazi COVID-19 i stavu prema cijepljenju (modificirana verzija upitnika). Također, mjerili smo razinu anksioznosti kod sudionika istraživanja, kao potencijalnu posljedicu razgovora o bolesti.

Faktorskom analizom pitanja nakon Warimax rotacije ekstrahirano je 6 logičnih faktora. Prvi se odnosi na „percipiranu osjetljivost na zarazu COVID-19“i sadrži 4 tvrdnje. Karakteristična tvrdnja (kriterij je najveće faktorsko zasićenje) glasi: „Svjestan/na sam da se mogu zaraziti COVID-om 19“. Pouzdanost ove subskale iznosi Cronbach Alpha=064 (eig. vrijednost = 2,26). Sadržaj tvrdnji odražava razinu svjesnosti o opasnosti koju ova bolest nosi. Drugi faktor odnosi se na „percepciju ozbiljnosti bolesti“i uključuje 4 tvrdnje od kojih je karakteristična „Biti ću teško bolestan/na ukoliko se zarazim COVID-om 19“. Pouzdanost ove subskale iznosi Cronbach alpha=0,71 (eig. vrijednost= 2,03). Rezultat na ovoj skali interpretira se kao doživljaj straha i procjena ozbiljnosti bolesti COVID-19. Treća subskala odnosi

se na „procjenu dobrobiti cijepljenja protiv COVID-19 bolesti“ i čini je 5 tvrdnji. Pouzdanost ove subskale iznosi Cronbach alpha=0,87 (eig. vrijednost=3,60). Karakteristična tvrdnja na ovoj subskali glasi „Trebao/-la bih se cijepiti protiv bolesti COVID-19, ako bih trebao/-la ići u područje s visokim brojem pozitivnih slučajeva“, a rezultat na subskali interpretira se razina dobrobiti koje cijepljenje nosi. Četvrta subskala odnosi se na „prepreke vezane za cijepljenje“ i sadrži 5 tvrdnji. Pouzdanost ove subskale iznosi Cronbach Alpha=0,87 (eig. vrijednost=3,43). Karakteristična tvrdnja glasi „Brinu me neželjene nuspojave cjepiva protiv COVID-19 bolesti“, a ukupni rezultat se interpretira kao briga i zabrinutost povezana uz cijepljenje. Peta subskala sadrži 4 tvrdnje koje se odnose na „odbijanje cijepljenja, te preporuke, odnosno očekivanje aktivnosti vezanih za cijepljenje“. Karakteristična tvrdnja glasi „Odbio/la bih primiti drugu/treću dozu cjepiva ukoliko bi mi se javila povišena ili visoka tjelesna temperatura nakon prve/druge doze“. Pouzdanost ove subskale iznosi Cronbach alpha=0,83 (eig. vrijednost=3,18), a rezultat na skali se interpretira kao odbijanje cijepljenja zbog različitih mogućih nuspojava. Šesta subskala odnosi se na faktor preporuke, a opisuje preporuke za cijepljenje od strane roditelja, medija, stručnjaka i članova Stožera. Pouzdanost ove subskale iznosi Cronbach alpha=0,89 (eig. vrijednost=3,50), a karakteristična tvrdnja glasi „Prijatelji/kolegi bi mi trebali preporučiti da se cijepim protiv COVID-19 bolesti“. Statistička obrada dobivenih podataka učinjena je uz pomoć statističkog programa Statistika za Windows-e verzija 14.0.0.15 (TIBCO – Date Science Workbench).

Rezultati

Prvi korak u obradi rezultata bila je deskriptivna statistika koja je prikazana u *Tablici 1*.

Tablica 1. Rezultati deskriptivne statistike za sve mjerene varijable
Table 1 Results of descriptive statistics for all measured variables

Varijable *Variables*	Medijan *Median*	Minimalno/ *Minimal*	Maksimalni/ *Maximum*	Stanardna Devijacija *Standard deviation*	Cronbach alpha/ *Cronbach alpha*
Osjetljivost na zarazu *Susceptibility to infection*	17,29	10	20	2,11	0,64
Percepcija ozbiljnosti bolesti *Perception of the severity of the disease*	7,76	4	15	2,56	0,71
Procjena dobrobiti cijepljenja *Evaluation of the benefits of vaccination*	15,90	6	28	5,66	0,87
Prepreke vezane za cijepljenje *Obstacles related to vaccination*	17,41	5	25	4,27	0,87
Odbijanje cijepljenja *Vaccination refusal*	8,75	4	29	3,71	0,83
Preporuke *Recommendations*	12,96	5	25	5,19	0,89

Na temelju Cronbach Alpha koeficijenata pouzdanosti prikazanih u prethodnoj tablici može se zaključiti da primijenjene mjerne ljestvice posjeduju visoku razinu pouzdanosti, odnosno potvrđuju se kao valjani instrumenti za mjerenje stavova i mišljenja ispitanika (*Tablica 1).* Prvi istraživački problem bio je utvrditi postoje li razlike u mjerenim varijablama između ispitanika koji su cijepljeni i sudionika koji nisu cijepljeni. U tu svrhu učinjeno je šest jednosmjernih analiza varijanci (*Tablica 2).* Rezultati upućuju na zaključak da ne postoji statistički značajna razlika u osjetljivosti na zarazu, odnosno svjesnosti da je COVID-19 opasna bolest. Cijepljeni i necijepljeni studenti jednako su svjesni opasnosti koju donosi ova bolest.

Na svim drugim varijablama, međutim, razlika u procjenama je statistički značajna. Studenti koji su se cijepili, situaciju s COVID-om procjenjuju ozbiljnijom, za njih je dobrobit cijepljenja veća, manje je zapreka za cijepljenje i manje odbijaju cijepljenje od studenata koji se nisu cijepili.

Tablica 2.Rezultati analize varijance za sve mjerene varijable s obzirom na to jesu li studenti cijepljeni (N=198) ili nisu cijepljeni (N=73)
Table 2 Results of variance analysis for all measured variables, considering whether students were vaccinated (N=198), or not (N=73)

	Cijepljeni/*Vaccinated* (N=198)		Necijepljeni/*Non-vaccinated* (N=73)			
	Medijan *Median*	Standardna devijacija *Standard deviation*	Medijan *Median*	Standardna devijacija *Standard deviation*	$F_{(1,269)}$	p
Osjetljivost na zarazu *Susceptibility to infection*	17,36	2,01	17,09	2,37	0,86	0,35
Percepcija ozbiljnosti bolesti *Perception of the severity of the disease*	8,09	2,56	6,85	2,36	13,09	0,000
Percepcija dobrobiti cijepljenja *Evaluation of the benefits of vaccination*	17,91	4,84	10,45	3,84	140,66	0,000
Prepreke vezane za cijepljenje *Obstacles related to vaccination*	16,51	4,22	19,88	3,32	37,83	0,000
Odbijanje cijepljenja *Vaccination refusal*	7,80	3,34	11,43	3,41	59,33	0,000
Preporuke *Recommendations*	14,48	4,91	8,85	3,42	81,44	0,000

Također, studenti koji su se cijepili smatraju da bi obitelj, prijatelji, struka, Vlada i mediji trebali zagovarati i preporučiti cijepljenje, u odnosu na studente koji se nisu cijepili.

Sljedeće istraživačko pitanje odnosilo se na ispitivanje razlike u mjerenim varijablama između mlađih i starijih studenata. Tom prilikom mlađi studenti su oni koji su na prvoj i drugoj godini Preddiplomskog studija, a stariji su oni koji su na trećoj godini Preddiplomskog studija sestrinstva. Jednosmjerna analiza varijance ukazuje za zaključak da nema statistički značajne razlike u svim mjerenim varijablama između dvije skupine studenata. Drugim riječima, razina obrazovanja i stečeno znanje nisu doprinijeli razlici u stavovima i vjerovanjima povezanim s COVID-19 bolešću.

Rezultati nadalje upućuju na razliku s obzirom na spol i to na skali prepreka i zabrinutosti povezanih s cijepljenjem. Studentice (M=17,77) izražavaju više zabrinutosti, brige i prepreka povezanih s cijepljenjem u odnosu na studente (M=15,35), t-test za nezavisne uzorke iznosi t-test$_{(269)}$=3,37; p=0,001. S obzirom na mali uzorak muških studenata, potreban je oprez u generaliziranju ovih rezultata.

Značajno pitanje na koje smo pokušali odgovoriti ovim istraživanjem odnosilo se na povjerenje koje studenti imaju prema Stožeru. Ono je relativno nisko. Distribucija dobivenih rezultata pomaknuta je prema nižim vrijednostima. Na skali od 10 stupnjeva studenti su u prosjeku zadovoljni M=3,95 s SD=2,51. Pri tome je evidentno da studenti koji su se cijepili imaju veće povjerenje prema Stožeru (M=4,40; SD=2,60), u odnosnu na studente koji nisu cijepljeni (M=2,75; SD=1,78). Rezultat t-testa za nezavisne uzorke statistički je značajan i iznosi t-test$_{(269)}$=4,98; p=0,000.

Promatrajući prosječne vrijednosti na procjeni anksioznosti, možemo zaključiti da obje skupine studenata ne osjećaju anksioznost prilikom razgovora o COVID-19 bolesti (M cijepljeni=1,76; M necijepljeni=2,00),

Presudni momenti koji su motivirali studente da se cijepe svakako je vjerovanje u učinkovitost cjepiva i strah od posljedica COVID-19 zaraze.

S druge strane nepovjerenje u sigurnost cjepiva i sumnja u opasnost od zaraze, motivi su koji su značajni i koji utječu na odluku o cijepljenju, odnosno necijepljenju.

Rasprava

Širenjem COVID-19, mnogi gradovi diljem svijeta donijeli su preventivne mjere kao što su karantene ili lockdown, s ciljem smanjenja smrtnosti,

ali i smanjenja broja oboljelih od COVID-19.[14] Studente kao dio populacije, s obzirom na njihove akademske i životne potrebe, karakterizira visoka stopa mobilnosti, aktivne i vrlo česte društvene i profesionalne aktivnosti, što ih stavlja u zonu povećanog rizika od zaraze i većeg rizika od transmisije bolesti. Upravo je to i bio jedan od značajnijih razloga uključivanja studenata sestrinstva u ovo istraživanje. U našem istraživanju, od ukupnoga broja ispitanih studenata, njih 73 (26,9%) nije se cijepilo protiv COVID-19, dok je njih 198 (73,0%) primilo cjepivo, što ukazuje na visok postotak cijepljenih studenata u odnosu na studiju koju su proveli Wang i sur. na cjelokupnoj studentskoj populaciji, u kojoj je 64,0% studenata pokazalo namjeru da se cijepe.[13] Razlog ovoj razlici je vjerojatno taj što su u naše istraživanje ipak uključeni studenti zdravstvenih studija, pa je za očekivat i da vladaju boljim informacijama vezanim uz COVID-19.

U istraživanju Daniel i sur. prvi i najvažniji razlog za dobivanje ili odbijanje cjepiva je sigurnost COVID-19 cjepiva.[15] Naše istraživanje pokazalo je da studenti koji su se cijepili vide manje zapreka za cijepljenje i manje odbijaju cijepljenje, tj. manje ih brinu neželjene nuspojave cjepiva. Isto istraživanje pokazalo je da je doživljeni rizik ozbiljnosti bolesti drugi najvažniji prediktor za cijepljenje protiv COVID-19 bolesti, što su istaknuli i naši cijepljeni studenti.[16], po čemu se značajnije razlikuju u odnosu na necijepljene studente. Rezultati Goodwina i sur., gdje autori navode da je pritisak okoline za cijepljenje bio značajno viši u Izraelu i Japanu, u odnosu na Mađarsku, te je u prve navedene dvije zemlje bio i značajno povezan s prihvaćanjem cjepiva. Isto istraživanje ukazuje na to da na prihvaćanje ili spremnost na cijepljenje osobe važan utjecaj imaju prijatelji, obitelji i drugi[17], što je u skladu i s rezultatima ovoga istraživanja. Preporuke za cijepljenje od strane prijatelja, medija i stručnjaka značajni su čimbenici koji utječu na odluke za cijepljenje, kako su naveli studenti koji su se cijepili.

Drugo istraživanje otkrilo je da demografski čimbenici, te osobno i obiteljsko iskustvo s COVID-19 imaju malu povezanost sa željom za cijepljenjem.[18]U našem istraživanju studenti koji su se cijepili smatraju da bi obitelj, prijatelji, struka, Vlada i mediji trebali zagovarati i preporučiti cijepljenje, u odnosu na stavove studenata koji se nisu cijepili. Upravo u radu Goodwina i sur., povjerenje u Vladu, u sve se tri zemlje pojavilo kao značajan čimbenik spremnosti za cijepljenje.[17]To je najizraženije bilo u Mađarskoj, gdje je cijepljenje i izbor cjepiva bio značajno pod utjecajem politike.[18] Isto tako, uloga medija predstavlja značajan čimbenik o utjecaju na spremnost za cijepljenje, pri čemu lažne vijesti o virusu, koje najvjerojatnije dolaze iz društvenih medija, imaju negativnu povezanost sa zdravstveno-odgovornim ponašanjem vezano za COVID-19, uključujući i spremnost na cijepljenje.[18] Kao što je objavljeno i u drugim istraživanjima, pogrešna vjerovanja, odnosno zablude, značajno su negativno povezane s povjerenjem u Vladu, a u našem slučaju u Nacionalni stožer koji je upravljao pandemijom u Hrvatskoj. Da postoji razlika u stavovima između osoba koje su se cijepile i onih koje se nisu cijepili, već smo ranije spomenuli, no takva razlika je pronađena i u drugim istraživanjima, pri čemu je ona izrazito vidljiva u istraživanju Bennett i sur., gdje se cijepljeni ispitanici snažno zalažu za tvrdnju da je COVID-19 veliki javnozdravstveni problem, da su cjepiva sigurna i efikasna, te da je na njihovu odluku da se cijepe utjecala općedruštvena dobrobit, dok necijepljeni nisu imali takve stavove.[16] Kada je riječ o necijepljenim ispitanicima, na većinu pitanja koja se odnose na sigurnost i javnozdravstvene aspekte cjepiva odgovaraju neutralno, dok se snažno ne slažu s tvrdnjama vezanim uz efikasnost cjepiva i ostalim preventivnim javnozdravstvenim mjerama.Istraživanje Rosenfelda i Toiyame govore o moralnoj pozadini odlučivanja o cijepljenju ili necijepljenu i dolaze do spoznaje da je vlastita sigurnost od COVID-19 cjepiva bila najsnažniji prediktor hoće li se netko cijepiti ili ne.[15] Upravo u vidu ovih tvrdnji idu i rezultati ovog našeg istraživanja, gdje su presudni čimbenici o odluci o cijepljenju bili percepcija dobrobiti cjepiva i strah od posljedica COVID-19 zaraze, dok oprečno suprotni razlozi leže u činjenici nepovjerenja u cjepivo i nepoznavanju efikasnosti istog.

Kada je riječ o povjerenju/nepovjerenju prema Stožeru, kako se može vidjeti iz samih rezultata, ono je nisko. Najčešći razlog nepovjerenja (kod studenata koji nemaju povjerenje u Stožer) je nedosljednost, potom slijedi neučinkovitost, te neiskrenost, dok je na posljednjem mjestu nestručnost. Studenti koji imaju povjerenja u Stožer, kao razloge povjerenja redom navode: dosljednost koja značajno odskače prema učestalosti odgovora, te učinkovitost i stručnost koje su na drugom mjestu. Iskrenost kao razlog povjerenja kod studenata koji imaju povjerenje u Stožer, ističe samo 5 studenata. Dobivena razlika u povjerenju prema Stožeru statistički je značajna kada analiziramo dvije skupine ispitanika, cijepljene i necijepljene, pri čemu je ona viša u cijepljenih studenata, i to za 1,65 stupnjeva. Kako se iz samih odgovora može vidjeti, razlozi koji proizlaze su više iz spektra dimenzija ličnosti (tzv. kognitivnih dimenzija), nego iz spektra stručnosti, na što ukazuje i tvrdnja koja se odnosi na „nestručnost“ koja je na

posljednjem mjestu kod necijepljene grupe ispitanika. Zašto je to tako, vjerojatno proizlazi iz percepcije ispitanika o osobama koji su članovi Stožera, a često su pripadnici političke stranke na vlasti. Značajan utjecaj imaju i medijske informacije koje su ispitanici mogli slušali, a koje nisu uvijek bile uniformne i jednake za sve, te su bile nedosljedne s nedovoljno jasnim dokazima koji bi ih mogli potvrditi.

Do razlika između cijepljenih i necijepljenih može doći i zbog toga jer naglašavanje promjena mišljenja vezanih za cijepljenje može dovesti do moralnog osuđivanja, a to još više pojačava negativne stavove kod necijepljenih.[17]

Zanimljivo je i pitanje postoji li razlika u procjeni osjetljivosti na zarazu od COVID-19, prilikom razgovora o bolesti između cijepljenih i necijepljenih studenata. Rezultati upućuju na zaključak da razlika nije statistički značajna, što bi značilo da razgovor o bolesti jednako uznemiruje osobe koje jesu i osobe koje nisu cijepljene, ili da ih jednako ne uznemiruje. Iako je zabilježena tendencija nešto veće anksioznosti i nelagode kod necijepljenih studenata, u trenucima razgovora ta razlika nije statistički značajna. Ovakvi rezultati mogu upućivati na dvije hipoteze. Prva je da su cijepljeni ispitanici uistinu uvjereni da ih cjepivo štiti i nemaju strah od bolesti, a druga je da kod necijepljenih strah od cjepiva nadilazi strah od bolesti. U budućnosti svakako treba pokušati djelovati na onaj dio necijepljene populacije koji navodi da bi se u budućnosti cijepio. Prema istraživanju Lopes L i sur. navode da je većina necijepljenih upravo tog mišljenja, dok jedan dio njih (19%) navodi da nikada u budućnosti neće promijeniti mišljenje.[19] Mišljenja smo da na tu populaciju i ne možemo djelovati u smislu promjena stavova vezanih uz cijepljenje.

Svjesni smo određenih ograničenja ovoga istraživanja koja najviše proizlaze iz činjenice samog uzorka ispitanika. Naime, u ovom istraživanju analizirani su samo stavovi studenata/studentica sestrinstva, što je smanjilo veličinu uzorka u odnosu na sve zdravstvene djelatnike. Također smo svjesni da je na rezultate mogao utjecati i način anketiranja (on-line) tj. da bi anketiranje provedeno fizički za vrijeme nastave dalo pouzdanije rezultate i veći broj ispitanika. Ono što je moguće dobiti ovim istraživanjem je doprinos u određenoj budućoj analizi pozadinskih mehanizama koji čine osnovu odluke o cijepljenju ili necijepljenu - ne samo kod studenata, već generalno u cijeloj populaciji stanovništva ili pak u određenim, izabranim populacijama.

Daljnja istraživanja trebala bi istraživati osnovne razlike između cijepljenih i necijepljenih, više specifičnosti i s naglaskom na pitanja što bi najviše utjecalo na promjenu vašega mišljenja?

Da bismo utjecali na stavove i mišljenja potrebno je djelovati na više razina. Zdravstvenim djelatnicima, kao i općoj populaciji, nije dovoljno samo pričati o dobrobiti cijepljenja, već treba slati poruke o ozbiljnosti bolesti, objašnjavati, odnosno smanjivati zapreke za cijepljenje, te navoditi i moguće negativne pojavnosti cijepljenja. Jedan od mogućih načina je suočiti ih s rezultatima znanstvenih istraživanja koja se bave učinkovitošću određenog cjepiva, na taj ih način i educirati, ukazivati im na dobrobiti cijepljenja, te im dozvoliti da sukladno svojoj savjesti, a temeljem iznesenih argumenata, samostalno i bez prisile odluče o tome žele li se cijepiti ili ne. Tek cjelokupnim usklađivanjem svih ovih razina djelovanja možemo razviti svijest o tome treba li se svaki pojedinac cijepiti ili ne. Smatramo da bi kampanje koje promiču cijepljenje trebale imati fokus na efikasnosti cjepiva, ozbiljnosti bolesti, konfrontacij s dezinformacija i nastojati naglasiti pouzdanost ključnih aktera kao što su nacionalne zdravstvene službe. Javnozdravstvene institucije trebale bi tražiti osobe koje su udaljene od medija, a to su najčešće zdravstveni radnici (među njima, najmasovniji akteri su upravo medicinske sestre) koji mogu jako dobro razbiti mitove koji prate cijepljenje.

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Indikacije i liječenje udarnim valom u fizikalnoj medicini i rehabilitaciji – novije spoznaje

Indications and treatment with shock wave in physical medicine and rehabilitation - recent knowledge

Filip Begić, Valentina Delimar, Nadica Laktašić Žerjavić, Porin Perić*

Sažetak

Izvantjelesna terapija udarnim valom ima brojne fiziološke učinke, poput smanjenja bola i poticanja cijeljenja tkiva, zbog čega danas ima široku primjenu u mišićno-koštanoj patologiji. Postoje dva osnovna oblika udarnog vala, fokusirani i radijalni, a razlikuju se po tome što fokusirani udarni val najveću energiju postiže u žarištu na željenoj dubini, dok se kod radijalnog udarnog vala najveća energija stvara na mjestu ulaska u tretiranu regiju tijela, te slabi daljnjim prodiranjem u tkivo. Sam mehanizam djelovanja udarnog vala nije do kraja razjašnjen, a pretpostavlja se da mehanička stimulacija dovodi do stanične migracije, proliferacije, diferencijacije ili apoptoze stanica, s tim da visoka razina energije može djelovati i razorno, umjesto da posluži kao mehanički stimulus, zbog čega je nužna prilagodba energije, ovisno o tretiranom području. Modulacija bola objašnjava se „gate control“ teorijom i hiperstimulacijskom analgezijom. Osim ustaljenih indikacija poput epikondilitisa, tendinopatija, plantarnog fascitisa, kalcificirajućeg tendinitisa, udarni val danas nalazi sve širu primjenu, te se upotrebljava i u terapiji spasticiteta, poremećenog cijeljenja kosti, kronične križobolje, smrznutog ramena, osteoartritisa koljena, sindroma trkačke potkoljenice, škljocavog prsta, sindroma bolnoga trohantera, te kod sindroma miofascijalne boli. Međutim, potrebno je provesti dodatna istraživanja kako bi se utvrdila stvarna vrijednost i mjesto udarnog vala u liječenju navedenih bolesti i stanja.

Ključne riječi: Udarni val, rehabilitacija, fizikalna medicina

Summary

Extracorporeal shockwave therapy has numerous physical effects, such as pain reduction and tissue healing induction, which gives its way for therapeutic implementation in various musculoskeletal conditions. There are two main forms of shockwaves, focused and radial, the main difference being that focused shockwaves achieve the highest energy at certain tissue depth, while radial shockwaves have the highest energy at the entry point into the tissue. The underlying mechanism is still not fully elucidated, but it is presumed that mechanical stimuli cause cellular migration, proliferation, differentiation and apoptosis. Given in mind that this high energy can be disruptive instead being a mechanical stimulus, which calls for individual energy adjustment depending on the structure treated. Pain modulation is explained according to the gate control theory and hyperstimulation analgesia. Besides standard indications such as epicondylitis, tendinopathies, plantar fasciitis and calcific tendinitis, shockwave therapy is nowadays used more broadly, such as for treating spasticity, disrupted bone healing, chronic low back pain, frozen shoulder, knee

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osteoarthritis, medial tibial stress syndrome, trigger finger, greater trochanteric pain syndrome and myofascial pain syndrome. However, further research is needed to determine the exact value and place of extracorporeal shockwave therapy in treating these conditions.

Key words: extracorporeal shockwave therapy, rehabilitation, physical medicine

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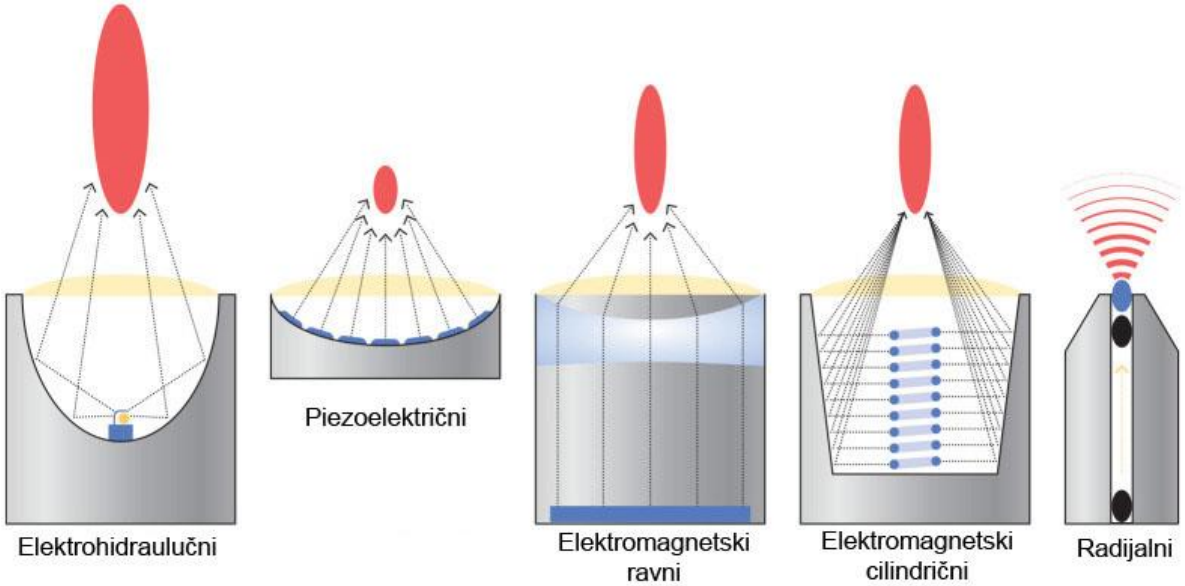
Uvod

Izvantjelesna terapija udarnim valom (engl. *Extracorporeal Schock Wave Therapy*, ESWT) je neivanzivni postupak koji se 1980-ih prvotno počeo koristiti u urologiji za razbijanje bubrežnih kamenaca.[1] Obzirom na to da su primijećeni pozitivni učinci na okolno tkivo, u smislu bržeg cijeljenja, provedena su daljnja istraživanja kojima je otkriveno da fiziološki učinci udarnog vala mogu djelovati na mišićno-koštani sustav u vidu smanjenja bola i poticanja cijeljenja tkiva, te danas ESWT ima široku primjenu u mišićno-koštanoj patologiji.[2] Cilj ovoga preglednog rada je prikazati mehanizam djelovanja, te nove spoznaje o indikacijama za liječenje ESWT-om.

Mehanizam djelovanja i oblici udarnog vala

Udarni val je oblik energije koji ima biološki učinak opisan na razini stanice, tkiva i organa.[2] Gustoću energije (engl. energy flux density, EFD) određuje protok energije kroz područje okomito na smjer širenja vala i izražava se u milidžulima (mJ). EFD ESWT-a tako može biti niska (<0.08 mJ/mm^2), srednja (<0.28 mJ/mm^2) ili visoka (<0.60 mJ/mm^2).[3] Fizikalni učinak ESWT-a vezan je upravo uz EFD, odnosno proizveden maksimalni pozitivni tlak, što se može smatrati ESWT dozom.[2] Postoje dva tipa udarnog vala: fokusirani i radijalni. Kod fokusiranog udarnog vala puls tlaka velike amplitude generira se izvan tijela i njegova energija se koncentrira na ciljno područje u tijelu. Valovi imaju incijalno visoki pozitivni tlak (do 80 MPa) s brzim usponom vala (30-120 ns), nakon čega slijedi negativni val nižeg tlaka (5-10 MPa).[4] Trajanje impulsa je kratko, oko 5 µs.[5] Generatori fokusiranog udarnog vala mogu biti elektrohidraulični, elektromagnetski i piezoelektrični, o čemu ovisi dubina prodiranja (Slika 1.). Elektrohidraulični generator prodire do dubine od 7 do 60 mm, elektromagnetni od 2,5 do 30 mm, a piezoelektrični od 2,4 do 17 mm.



Slika 1. Različite vrste generiranja udarnih valova proizvode različiti uređaji za ESWT (Izvor: EFORT Open Rev 2020;5:584-592)
Figure 1 - Different types of shock wave generation are produced by different ESWT devices (Source: EFORT Open Rev 2020;5:584-592)

Energija vala se oslobađa se na mjestima dodira dvaju tkiva različite akustičke impendancije, što dovodi do kompresivnog i smičnog opterećenja, te dolazi do tzv. fenomena kavitacije – stvaranja mikroskopskih mjehurića plina koji kolabiraju u intersticijskoj tkivnoj tekućini, što stvara lokalizirani stres, odnosno mehaničku stimulaciju.[6] Najveća energija postiže se u žarištu na željenoj dubini, dok su

koža i potkožno tkivo pošteđeni iritacije visokom energijom.[7] Kod radijalnog udarnog vala najveća energija se generira na mjestu ulaska u tretiranu regiju tijela, a slabi daljnjim prodiranjem u tkivo. EFD radijalnog ESWT-a iznosi 0,01-0,23 mJ/mm^2, tlak koji aplikator generira na tkivo iznosi 1-4 bara, a dubina prodiranja je 0-35 mm. Radijalni udarni val se koristi uglavnom zbog trofičkih sposobnosti, izazivanja hiperemije tkiva, te jačanja vaskularnog protoka.[8] Dio autora drži kako se radijalni ESWT ne može opisati kao pravi izvantjelesni udarni val s obzirom na to da nema određene fizikalne karakteristike, te se predlaže drugačija nomenklatura, poput radijalne terapije valom pod tlakom (engl. radial pressure wave therapy).[2] Unatoč brojnim provedenim istraživanjima i pozitivnim iskustvima vezano za tretiranje različite mišićno-koštane patologije, točan mehanizam djelovanja ESWT-a nije do kraja razjašnjen. Stanična mehanotransdukcija (mehanoterapija) govori kako mehanička stimulacija može dovesti do stanične migracije, proliferacije, diferencijacije ili apoptoze. Visoka razina energije može rezultirati disruptivnim, smičnim stresom, umjesto da posluži kao mehanički stimulus. Stoga je nužna indivudalna prilagodba energije, ovisno o tretiranom području. Modulacija bola, pak, može uzrokovati stanične promjene, što se objašnjava principima hiperstimulacijske analgezije.[2] Postoji više pretpostavljenih mehanizma djelovanja ESWT-a na staničnoj razini. Smatra se da dolazi do povećane sinteze kolagena uslijed pojačane proliferacije fibroblasta. Do stanične proliferacije i cijeljenja rane dolazi uslijed povećanja razine tenocita, pojačanog otpuštanja ATP-a i smanjenja ekstra celularne aktivacije kinaze, jačanja osteogeneze, te remodelacije tetiva posredovanog djelovanjem interleukina (IL) 6 i IL-8. Smanjenje bola objašnjava se „gate control“ teorijom (podraživanjem aferentnih osjetnih vlakana perifernih živaca mehaničkim stimulusom zatvaraju se vrata za nociceptivni bolni signal), modificiranjem otpuštanja supstance P, te smanjenjem CGRP-a (engl. calcitonin gene-related peptide). Poticanje neovaskularizacije objašnjava se indukcijom TGFβ1 (engl. transforming growth factor β1) i faktora rasta sličnog inzulinu 1. Također je zabilježen utjecaj na smanjenje kalcifikata mekih tkiva i smanjenje upale.[9,10,11] Pretpostavljeni mehanizmi djelovanja na razini tetiva su: smanjenje edema i infiltracije upalnih stanica, regeneracija tkiva konverzijom mehaničkog stimulusa u biokemijski signal, stimulacija tenocita i proliferacija kolagena povećanjem proizvodnje TGFβ1 i faktora rasta sličnog inzulinu 1, proliferacija protuupalnih citokina, povećana proliferacija i migracija tenocita, smanjena ekspresija metaloproteinaza, smanjena razina upalnih IL.[10,12] Na razini kosti djelovanje se objašnjava poboljšanjem angiogeneze i neovaskularizacije kosti, osteogenezom i remodelacijom kosti uslijed otpuštanja faktora rasta (koštani morfogentetski protein 2, vaskularni endotelni faktor rasta) i promocijom periostalnog stvaranja kosti (smanjena je aktivnost osteoklasta, a povećana aktivnost osteoblasta).[13] Na razini zgloba (koljena) se radi o smanjenju upale i edema, poboljšanja arhitekture subhondralne kosti i povećanja aktivnosti hondrocita.[14] Djelovanje na spasticitet objašnjava se učinkom na razini mišića i neuromuskularne spojnice smanjenjem rigidnosti vezivnog tkiva i stimulacijom sinteze dušikovog oksida (formiranje neuromuskularne spojnice i neovaskularizacija).[15] Istraživanja na životinjama pokazala su da ESWT može povećati koštano-cementnu površinu, pojačati osteogeni odgovor i poboljšati zarastanje prijeloma.[16] Valchanova je još 1991. godine pokazao povoljan utjecaj ESWT-a za nesrasle prijelome.[17] Prva izvješća o uspješnom liječenju bolesnika sa zakašnjelim koštanim cijeljenjem ili nesraslim prijelomima objavljena su 1991. g., te su pokazala da je primjenom ESWT-a došlo do poticanja cijeljenja prijeloma u 85% slučajeva.[2] Wang i sur. pokazali su da udarni valovi uzrokuju značajnu neovaskularizaciju u tretiranome tkivu, a bez provociranja pogoršanja stanja. Cijeljenje kosti stimulirano je regulacijom ekspresije različitih pro-angiogenih i pro-osteogenih čimbenika rasta, te je utvrđeno da dolazi do porasta neovaskularnih, angiogenih i osteogenih biljega rasta poput vaskularnog endotelnog faktora rasta (VEGF), endotelne dušik oksid sintaze (eNOS), jezgrin antigen proliferirajućih stanica (PCNA), te koštanog morfogenetskog proteina 2 (BMP 2).[18,19]

Indikacije za primjenu udarnog vala

Primjena ESWT-a je do sada najviše istražena u liječenju kroničnih tendinopatija i plantarnog fascitisa.[2] ESWT je generalno sigurna procedura koju bolesnici dobro toleriraju, a moguće lokalne nuspojave obuhvaćaju bol na mjestu primjene, eritem kože, nastanak hematoma ili površinske otekline, iritacija živaca, dok su od sistemnih moguće glavobolja ili migrena.[2] Ozbiljnije komplikacije su rijetko zabilježene u literaturi, primjerice Costa i sur. prijavili su dva slučaja rupture Ahilove tetive unutar 2 tjedna od primjene ESWT-a kod žena starijih od 60 godina.[20] Za bolove nakon tretmana ne savjetuje se uporaba nesteroidnih protuupalnih lijekova u prvoj fazi zbog mogućeg utjecaja na mehanizme cijeljenja.[9] Općenito, nakon tretmana bolesnicima se preporučuje dozirana fizička aktivnost, ovisno o tome koja

patologija i područje je bilo tretirano, upravo zbog rizika rupture tetiva.[2] Kontraindikacije za primjenu ESWT-a prema International Society for Medical Shockwave Therapy (ISMST) mogu se podijeliti na apsolutne – aktivna infekcija, maligni tumor (fokusirani ESWT), trudnoća; relativne –fokus terapije moždano tkivo ili živci, plućno tkivo ili pleura, epifizealna ploča rasta, značajna koagulopatija. Čimbenici na koje je potrebno posebno obratiti pozornost su prisutnost pacemakera ili drugih implantata, aktualna terapija nesteroidnim protuupalnim lijekovima, uporaba antikoagulansa, nedavne injekcije glukokortikoida.[11]

Lateralni epikondilitis

Lateralni epikondilitis je bolni sindrom koji se javlja u području lakta, a nastaje kao posljedica uzastopnih mikrotrauma uslijed ponavljanih kretnji. U općoj populaciji incidencija mu iznosi 1-3%, a u profesionalnih tenisača čak 5-10%, zbog čega se još naziva i teniskim laktom. Osim u sportaša, često se može susresti kao profesionalna bolest zidara, postolara, kuhara, kirurga i stomatologa.[21] Glavni simptomi su smanjena snaga stiska šake i snaga podlaktice, te bolovi u području lakta, koji su najintenzivniji prilikom palpacije lateralnog epikondila. Lateralni epikondilitis predstavlja izazov u liječenju, jer su recidivi česti, a liječenje može trajati i nekoliko mjeseci (prosjek trajanja tipične epizode je 6-24 mjeseca).[22] Liječenje je važno započeti što ranije. Konzervativno liječenje obuhvaća mirovanje i poštedu od radnih i sportskih aktivnosti, uz primjenu oralnih nesteroidnih protuupalnih lijekova. Nakon što se postigne osnovni cilj - kontrola bola, kreće se s vježbama za jačanje muskulature i povećanje opsega pokreta. ESWT se kod lateralnog epikondilitisa koristi primarno zbog svog analgetskog učinka. Prema metaanalizi Yao i sur. (13 radova i 1035 bolesnika, od čega je 501 bolesnik podvrgnut ESWT-u, a 534 drugim metodama), ESWT je učinkovito ublažio bol i smanjio funkcionalno oštećenje, te djelovao povoljno na snagu stiska šake, uz ukupno bolji sigurnosni profil u odnosu na druge metode poput lokalne infiltracije glukokortikoida.[23] Devrimsel i sur. usporedili su učinak terapije laserom i ESWT-om u bolesnika s lateralnim epikondilitisom. Iako su se obje metode pokazale učinkovitima, ESWT je bio učinkovitiji u smanjenju bola i poboljšanju funkcije.[24] Također, Turgay i sur. usporedili su učinak fokusiranog ESWT-a s laserom male izlazne snage (engl. low level laser therapy, LLLT), te pokazali da je, iako su oba načina liječenja bila učinkovita, ESWT bio učinkovitiji u ublažavanju bola i funkcionalnom oporavku.[25] Vulpiani i sur. pokazali su da je ESWT bio učinkovitiji od krioultrazvuka, uz bolje kliničke rezultate nakon 6 i 12 mjeseci praćenja.[26] Ozturan i sur. procijenili su kratkoročne, srednjoročne i dugoročne učinke lokalne infiltracije kortikosteroida, autologne krvi i terapiju fokusiranim ESWT-om u liječenju lateralnog epikondilitisa. I dok je kortikosteroidna terapija imala bolje učinke četiri tjedna nakon terapije, autologna injekcija krvi i terapija fokusiranim ESWT-om dale su bolje dugoročne rezultate, posebno uzimajući u obzir visoku stopu recidiva kod primjene lokalne infiltracije glukokortikoida. Nakon 52 tjedna uspješnost glukokortikoidne infiltracije je bila 50%, dok je učinkovitost ESWT-a bila 89%.[27] Međutim, postoje istraživanja koja nisu izvijestila o dobrom učinku fokusiranog ESWT-a ili je taj učinak bio manji i usporediv s placebom. Primjerice, Guler i sur. proveli su randomizirano, placebom kontrolirano, dvostruko slijepo, prospektivno istraživanje na 40 bolesnika, od kojih je 20 primilo ESWT, a 20 placebo ESWT, te nisu utvrdili postojanje razlike u snazi stiska šake između skupina nakon primijenjene terapije.[28] Lee i sur. su kod 22 bolesnika s novodijagnosticiranim lateralni ili medijalni epikondilitisom usporedili učinak ESWT-a (12 bolesnika) i infiltracije glukokortikoida (10 bolesnika). Utvrdili su da ESWT nije bio učinkovitiji u odnosu na infilitraciju glukokortikoida neposredno nakon terapije, niti nakon vremena praćenja od 8 tjedana.[29]

Plantarni fascitis

Plantarni fascitis karakterizira bol na prednjem dijelu pete koja nastaje zbog natezanja plantarne fascije, što se često javlja kod osoba sa spuštenim stopalima ili kod prevelikog mehaničkog opterećenja. Češće se javlja u sportaša, osobito trkača.[21] Konzervativno liječenje provodi se ortopedskim ulošcima, lokalnom infiltracijom anestetika s glukokortikoidom, te različitim modalitetima fizikalne terapije. Kod otprilike 10-20% bolesnika s plantarnim fascitisom konzervativnim se liječenjem ne postižu zadovoljavajući rezultati.[30] ESWT se u liječenju plantarnog fascitisa zbog neinvazivnosti i praktičnosti primjene počeo koristiti kao alternativna opcija liječenja, kako bi se odgodio operativni zahvat. U meta-analizi Al-Siyabi i sur. (7 istraživanja s ukupno 369 bolesnika) je uspoređen učinak ESWT-a i terapije ultrazvukom u bolesnika s plantarnim fascitisom. Rezultati ukazuju na to da je ESWT superiorna opcija u liječenju bolesnika s plantarnim fasciitisom, zbog toga što smanjuje intenzitet bola tijekom aktivnosti.[31] Meta-analiza Suna i sur. je

također pokazala bolju učinkovitost fokusiranog ESWT-a.[32] Malliaropoulos i sur. proveli su istraživanje individualiziranog protokola radijalnog ESWT-a, te procjene stope uspješnosti i stope recidiva tijekom razdoblja od jedne godine nakon liječenja. Bol se procjenjivala pomoću vizualne analogne skale (VAS) nakon 1-mjesečnog, 3-mjesečnog i 1-godišnjeg praćenja. Stope uspjeha procijenjene su kao postotak bolesnika koji imaju više od 60% smanjenja VAS bola na svakom praćenju. Stope uspjeha procijenjene su na 19% (1 mjesec), 70% (3 mjeseca) i 98% (1 godina). Jednogodišnja stopa recidiva bila je 8%. Autori su zaključili da individualizirani radijalni ESWT protokol predstavlja prikladan tretman plantarnog fasciitisa.[33] Li i sur. proveli su meta-analizu kojoj je cilj bio procijeniti učinak osam različitih terapija plantarnoga fascitisa - nesteroidnih protuupalnih lijekova, lokalne infiltracije glukokortikoide, autologne pune krvi, plazme bogate trombocitima, fokusiranog ESWT-a, ultrazvučne terapije, botulinum toksina A i tzv. „dry needlinga“. Procijenili su učinak na smanjenje bola prema VAS skali u četiri vremenske točke nakon terapije (1, 2, 4 i 6 mjeseci nakon terapije), te utvrdili da je ESWT imao najbolju ukupnu učinkovitost od svih oblika terapije.[34] Pozitivne rezultate dobili su i Dizon i sur. u svojoj meta-analizi, gdje je pokazana učinkovitost fokusiranog ESWT-a umjerenog i visokog intenziteta u vidu smanjenja bola i poboljšanja funkcije.[35] Okur i sur. su proveli prospektivno randomizirano kontrolirano istraživanje u kojem su usporedili učinak ESWT-a s individualnim ortopedskim ulošcima za stopala u liječenju plantarnog fascitisa, te zaključili da su oba modaliteta liječenja jednako kratkoročno i srednjeročno učinkovita u smanjenju bolova, poboljšanju funkcije i očuvanja zdravlja stopala.[36]

Kalcificirajući tendinitis rotatorne manšete

Kalcificirajući tendinitis rotatorne manšete (engl. rotator cuff calcific tendinitis, RCCT) je poremećaj koji se očituje nakupljanjem kalcijeva hidroksiapatita u području hvatišta tetiva za kost uz spontanu resorpciju kalcifikata i cijeljenje tetive. Ovo stanje se češće javlja u žena i u dijabetičara. Depozit kalcija je najčešće lokaliziran unutar tetive mišića supraspinatusa i nije u dodiru s kosti. Glavni simptomi su bol u ramenu za vrijeme formiranja kalcifikata, zbog čega posljedično dolazi do smanjene pokretljivosti ramena.[21] ESWT izaziva hiperemiju tkiva i neoangiogenezu, te utječe na smanjenje veličine i razgradnju kalcifikata.[7] Li i sur. proveli su placebom kontrolirano istraživanje u kojem su na 84 bolesnika s RCCT ispitali učinak ESWT-a, te utvrdili da ESWT može smanjiti intenzitet bola u ramenu i poboljšati funkciju ramena.[37] Fatima i sur. su također pokazali da je ESWT doveo do smanjenja bola, poboljšanja funkcionalnosti i kvalitete života ispitanika, te smanjenja veličine kalcificiranih naslaga.[38] Carlisi i sur. ispitali su učinak fokusiranog ESWT-a i ekscentričnih vježbi u terapiji RCCT-a. Utvrdili su da je fokusirani ESWT učinkovit u smanjenju bola u ramenu i poboljšanju funkcije bolesnika, te da dodavanje ekscentričnih vježbi ne pridonosi povoljnim učincima ESWT-a.[39] Frassanito i sur. su u svom istraživanju koristili ESWT u kombinaciji s kinesiotapingom (KT), te su zaključili da primjena KT, uz ESWT, ubrzava oporavak ispitanika u odnosu na primjenu samo ESWT-a.[40] Lee i sur. usporedili su učinak ESWT-a sintraartikularnom infiltracijom glukokortikoida pod kontrolom ultrazvuka. Utvrdili su da je ESWT siguran i učinkovit za liječenje tendinitisa ramena, a da intraartikularna aplikacija glukokortikoida nije učinkovitija od samog ESWT-a. S obzirom na potencijalne komplikacije i nuspojave koje nosi intraartikularna aplikacija glukokortikoida, ESWT se smatra boljom i sigurnijom terapijom.[41] Malliaropoulos i sur. proveli su retrospektivnu kohortnu analizu na 67 bolesnika (79 ramena) s RCCT-om o učinku radijalnog ESWT-a. Rezultati su pokazali visoke stope uspjeha i niske stope recidiva godinu dana nakon primjene ESWT terapije.[42] Abo Al-Khair i sur. usporedili su učinak fokusiranog, radijalnog ESWT-a, te kombinirane terapije ESWT-om. Bolesnici su podijeljeni u tri skupine, obzirom na primljenu terapiju: fESWT, rESWT ili kombinirani ESWT. U svim skupinama došlo je do značajnog smanjenja veličine kalcifikata, bola u ramenu i poboljšanja aktivnog opsega pokreta tjedan dana nakon završetka liječenja i nakon tri mjeseca praćenja, s time da je najbolje rezultate imala kombinirana fokusirana i radijalna ESWT terapija.[43] Avancini-Dobrović i sur. usporedili su učinkovitost radijalnog i fokusiranog ESWT-a na 60 bolesnika s RCCT-om, podijeljenih u dvije skupine od po 30 ispitanika. Svaki bolesnik primio je 3 do 5 tretmana u razmaku od barem tjedan dana. Terapija je dovela do vrlo dobre i brze regresije bola kod obje vrste ESWT-a, no valja naglasiti da je kod fokusiranog bila izraženija supresija bola i nakon 6 mjeseci. Nakon tretmana nisu bile zabilježene nepoželjne komplikacije niti nuspojave. Zbog smanjenja bola došlo je do povećanja opsega pokreta i poboljšanja funkcije ramenoga obruča. Radiološkom obradom nakon 6 mjeseci dokazano je značajno smanjenje veličine kalcifikata ramena nakon obje vrste terapije. Kod jednog dijela bolesnika liječenih fokusiranim ESWT-om došlo je do potpune regresije kalcifikata.

Također, prednost fokusiranoga ESWT-a nad radijalnim očitovala se i u smanjenju gustoće kalcifikata, dok je kod primjene radijalnog ESWT-a došlo do povećanja gustoće. Zaključno, autori su utvrdili da je u liječenju RCCT-a dokazana učinkovitost obiju vrsta ESWT-a sa statistički značajno boljim rezultatima fokusiranog ESWT-a.[44]

Ahilova tendinopatija i skakačko koljeno

Ahilova tendinopatija kliničko je stanje koje karakterizira bol i oteklina u Ahilovoj tetivi i oko nje, a često se javlja kod sportaša, te osoba srednje životne dobi s prekomjernom tjelesnom težinom. U posljednja tri desetljeća učestalost Ahilove tendinopatije porasla je kao rezultat većeg sudjelovanja u rekreativnom i natjecateljskom sportu.[45] "Skakačko koljeno", koje se naziva i patelarna tendinopatija, bolno je stanje koljena uglavnom vezano uz prekomjernu aktivnost, te se obično javlja u sportskim aktivnostima koje zahtijevaju učestale skokove poput košarke, odbojke, skoka u vis i u dalj, te trčanja i skijanja. Razdori su obično uzrokovani učestalim naprezanjem na tetivi kvadricepsa ili patelarnom ligamentu.[46] Istraživanja su pokazala da ESWT potiče neovaskularizaciju, diferencijaciju mezenhimalnih matičnih stanica i lokalno oslobađanje angiogenih faktora rasta u kostima i tetivama. Neovaskularizacija može igrati ulogu u poboljšanju krvne opskrbe i cijeljenju tetiva. Pretpostavlja se da udarni valovi ublažavaju bol u tendinopatiji mehanizmom hiperstimulacijske analgezije. ESWT smanjuje ekspresiju visoke razine upalnih medijatora, te stoga ESWT proizvodi regenerativni učinak i učinak obnavljanja tkiva u mišićnokoštanom tkivu.[47] Prema pregledu literature Gerdesmeyera i sur. pokazana je učinkovitost ESWT-a u kroničnoj Ahilovoj tendinopatiji. Randomizirana, placebom kontrolirana ispitivanja potvrdila su izvrsne rezultate u pogledu funkcije i bola, te se smatra da je terapija ESWT-om najučinkovitija terapijska opcija kod kronične Ahilove tendinopatije.[48] Feeney i sur. su u svom pregledu literature došli do sličnih zaključaka o ESWT-u kao sigurnom i učinkovitom načinu liječenja Ahilove tendinopatije. ESWT se pokazao djelotvornim u smanjenju bola i poboljšanju funkcije kod osoba s tendinopatijom Ahilove tetive, a ukazao je i na to da kombinacija ESWT-a s ekscentričnim vježbama i vježbama istezanja može biti čak i učinkovitija od samog ESWT-a.[49] U svojoj meta-analizi Fan i sur. pokazali su da ESWT može dovesti do smanjenja bola i boljeg funkcionalnog ishoda za bolesnike s Ahilovom tendinopatijom od drugih nekirurških tretmana.[50] Leal i sur. su pregledom literature utvrdili pozitivne učinke ESWT-a i kod patelarne tendinopatije. Prema njihovim saznanjima liječenje udarnim valom za kronične tendinopatije patele koje nisu reagirale na konzervativne mjere i fizikalnu terapiju, je učinkovit i siguran postupak. Također smatraju da se ESWT mora promatrati kao dio protokola liječenja, a ne kao izolirani tretman, te da se najbolji rezultati dobivaju kada se ESWT koristi u kombinaciji s ekscentričnim vježbama i standardiziranim protokolima fizikalne terapije.[51] Wheeler je proveo istraživanje gdje je za patelarnu tendinopatiju koristio radijalni ESWT, te je učinak ove terapije usporedio s autolognim injekcijama krvi. U konačnici, ova prospektivna kohortna studija pokazala je poboljšanje u bolesnika s kroničnom tendinopatijom patele nakon liječenja autolognim injekcijama krvi i radijalnim ESWT-om, u smislu smanjenja bola i poboljšanja funkcije, u vremenu praćenja od šest tjedana i tri mjeseca po primjeni terapije.[52] Mani-Babu i sur. proveli su meta-analizu koja je sveukupno obuhvatila 13 studija. Utvrdili su da je ESWT učinkovitiji od alternativnih neoperativnih tretmana, uključujući nesteroidne protuupalne lijekove, fizikalnu terapiju i program vježbanja, te da je dugoročno jednako učinkovit poput operativnog zahvata tenotomije patele za patelarnu tendinopatiju. Također, utvrdili su da je ESWT učinkovitiji od terapije ekscentričnim vježbama za Ahilovu tendinopatiju, te da postoje umjereni dokazi da kombinacija ESWT-a i ekscentričnog opterećenja kod Ahilove tendinopatije može proizvesti bolje rezultate nego samo ekscentrično opterećenje. Terapija ESWT-om učinkovita je intervencija i treba je razmotriti za patelarnu i Ahilovu tendinopatiju, posebno kod neuspjeha drugih neoperativni tretmana.[53]

Spasticitet

Spastičnost se odnosi na abnormalni porast tonusa mišića uzrokovan ozljedom gornjeg motoneurona.[54] Česta je posljedica moždanog udara, ozljeda kralježnične moždine, cerebralne paralize i multiple skleroze. Prema podacima Svjetske zdravstvene organizacije iz 2019. godine, moždani udar bio je drugi najčešći uzrok smrti u svih ljudi u svijetu.[55] Trenutno postoji više načina liječenja spastičnosti nakon moždanog udara, a neke od metoda su fizikalna terapija, farmakološka terapija antispazmoliticima i kemijska blokada živaca, te uporaba botulinum toksina.[56] Napretkom ESWT tehnologije uvidjela se mogućnost primjene i u području neurološke rehabilitacije. Tako su Taheri i sur. proveli istraživanje s ciljem procjene učinka fokusiranog ESWT-a na spastičnost u bolesnika nakon

preboljelog moždanog udara. Ispitanike su podijelili u dvije skupine, obje su primile peroralne antispazmolitike i vježbe istezanja, dok je ispitivana skupina primila i jedan fokusirani ESWT tretman tjedno kroz razdoblje od tri tjedna. Nakon jednog, tri i dvanaest tjedana, rezultati su uspoređeni temeljem Modificirane Ashworthove ljestvice (MAS), rezultata klonusa, pasivnog opsega pokreta (engl. range of motion, ROM) zgloba, razine bola, mjerenja hodne pruge od 3 m i funkcionalnog rezultata donjih ekstremiteta (LEFS). Nakon jedne sesije ESWT tretmana, MAS, bol, ROM i LEFS značajno su se poboljšali u usporedbi s početnim vrijednostima. Nakon tri tjedna ESWT tretmana, MAS, bol i hodna pruga od 3 m značajno su se poboljšali u usporedbi s prvim tjednom. U 12. tjednu MAS, bol, ROM, hodna pruga od 3 m i LEFS značajno su se poboljšali u usporedbi s kontrolnom skupinom. Autori su zaključili kako bi fokusirani ESWT mogao biti izuzetno koristan dodatni modalitet liječenja u kombinaciji s oralnim antispazmoliticima i vježbama istezanja za poboljšanje spastičnosti kod bolesnika nakon preboljelog moždanog udara.[57] Hsu i sur. proveli su meta-analizu koja je istraživala učinkovitost *botulinum toxin* injekcija (BoNT) u odnosu na ESWT u liječenju spastičnosti nakon moždanog udara, koristeći dokaze iz randomiziranih kliničkih studija. Rezultati su pokazali da su BoNT injekcije, fokusirani ESWT i radijalni ESWT bili učinkoviti u ublažavanju spasticiteta tijekom najmanje 12 tjedana u usporedbi s kontrolnim tretmanima. Radijalni ESWT je vjerojatno imao najbolji antispastični učinak među ispitivanim tretmanima.[58] Prema meta-analizi Jia i sur., fokusirani ESWT je pokazao dugoročne učinke na ublažavanje spastičnosti, istodobno smanjujući bol, poboljšanje ROM-a i motoričke funkcije kod bolesnika nakon preboljelog moždanog udara.[59] Brojni noviji podaci iz literature također potvrđuju korisnost ESWT-a u terapiji spasticiteta.[60-62] Opara i sur. stoga su u siječnju 2021. godine učinili pregled literature koji je obuhvatio razdoblje od siječnja 2000. godine do prosinca 2020. godine i uključio ukupno 22 istraživanja, odnosno 468 bolesnika nakon preboljelog moždanog udara. Pokazali su da fokusirani ESWT učinkovito snižava tonus mišića kod ljudi sa spastičnim udom kao posljedicom moždanog udara. Nadalje, pokazali su kako je ESWT siguran i bez neželjenih nuspojava. Mehanizam djelovanja ESWT-a na mišiće zahvaćene spastičnošću još uvijek nije poznat. Do danas nisu utvrđeni standardni parametri ESWT-a u spastičnosti nakon moždanog udara s obzirom na intenzitet, učestalost, mjesto i broj potrebnih sesija. Potrebna su daljnja istraživanja koja udovoljavaju najvišim standardima, kako bi se uspostavili ujednačeni parametri stimulacije mišića pomoću ESWT-a.[63]

Ostale indikacije i recentna istraživanja

Posljednjih godina, temeljem pozitivnih učinaka kod prethodno navedenih indikacija, ESWT se počinje sve više primjenjivati i kod različitih drugih mišićno-koštanih patologija. Primjerice, poremećeno posttraumatsko cijeljenje kosti je komplikacija prijeloma, a standardno liječenje je kirurška revizija. Hempe i sur. proveli su pregled literature, te su pronašli ukupno 97 bolesnika s ovim stanjem kod kojih je primijenjen ESWT. Došli su do zaključka da je ESWT obećavajuća alternativa za liječenje poremećenog cijeljenja kosti, ali kako su potrebna daljnja istraživanja kako bi se identificirali čimbenici rizika lošeg ishoda, te povećala stopa uspješnosti primjene.[64] Yue i sur. proveli su meta-analizu (10 randomiziranih kliničkih studija s ukupno 455 bolesnika) čiji je cilj bio procijeniti učinkovitost i sigurnost ESWT-a za liječenje kronične križobolje (engl. chronic low back pain, CLBP). Utvrdili su da uporaba ESWT-a u bolesnika s CLBP-om rezultira značajnim i mjerljivim smanjenjem bola i onesposobljenosti u kratkom roku.[65] Sun i sur. proveli su istraživanje gdje su usporedili učinkovitost i sigurnost ESWT-a niskog intenziteta naspram srednjeg intenziteta u ispitanika s CLBP. Utvrdili su da je tretman ESWT-om niskog intenziteta s više sesija bio učinkovitiji u ublažavanju bola i kratkoročnom poboljšanju onesposobljenosti, od tretmana srednjeg intenziteta s manje sesija, pod istom ukupnom dozom energije.[66] Zhang i sur. uradili su pregled literature kako bi procijenili potencijal ESWT-a kao dodatne terapije za smrznuto rame. ESWT se pokazao kao učinkovita metoda u pogledu smanjenja bola i povećavanja funkcije ramena, te su sugerirali da bi se ESWT mogao koristiti kao dodatna terapija, uz rutinske tretmane, iako je kvaliteta uključenih kliničkih studija bila ometena značajnom heterogenošću u pogledu dugotrajne analgezije i opsega pokreta zglobova.[67] Zhao i sur. proveli su istraživanje o procjeni učinkovitosti ESWT-a u 70 bolesnika s osteoartritisom (OA) koljena tijekom 12 tjedana, u usporedbi s placebom. ESWT se pokazao učinkovitim u smanjenju bola i poboljšanja funkcije koljena, no preporučuje se provesti dodatna istraživanja kako bi se utvrdilo u kojoj fazi OA je primjena ESWT-a najpogodnija i treba li ga koristiti samostalno ili kao dodatan modalitet uz konvencionalnu terapiju.[68] Prema meta-analizi Liaoa i sur. o primjeni ESWT-a kod osteoartritisa koljena, ESWT se pokazao učinkovitim u kombinaciji s fizikalnom terapijom i tradicionalnom kineskom

medicinom u smislu smanjenja bola, povećavanja funkcije, te smanjenja upale.[69] Forogh i sur. su pak u svom pregledu literature istražili učinke ESWT-a kod sindroma trkačke potkoljenice, tzv. shin splints, odnosno medijalnog tibijalnog stres sindroma (engl. medial tibial stress syndrome, MTSS). Na temelju ograničenog broja dostupnih istraživanja, pokazalo se da ESWT može smanjiti bol, skratiti trajanje oporavka, te povećati zadovoljstvo bolesnika MTSS-om. Nijedno istraživanje nije zabilježilo štetne učinke ESWT-a.[70] Dogru i sur. istražili su, pak, učinak radijalnog ESWT-a na liječenje škljocavog prsta (engl. trigger finger), te utvrdili da je radijalni ESWT učinkovita metoda za smanjenje bola i poboljšanje opsega pokreta i snage stiska šake kod ovih bolesnika. No, s obzirom na to da se radilo o manjoj kohorti od 18 bolesnika, potrebna su dodatna randomizirana, kontrolirana ispitivanja, kako bi se dobilo više dokaza o učinkovitosti ESWT-a za ovu indikaciju.[71] Ramon i sur. proveli su randomiziranu kliničku studiju o učinku fokusrianog ESWT-a u 103 bolesnika sa sindromom bolnog trohantera (engl. greater trochanteric pain syndrome, GTPS). Fokusirani ESWT se u kombinaciji sa specifičnim programom vježbanja pokazao sigurnim i učinkovitim za liječenje GTPS-a, sa stopom uspješnosti od 86,8% dva mjeseca nakon provedenoga tretmana.[72] Carlisi i sur. su u svom istraživanju usporedili učinak fokusiranog ESWT-a s terapijom ultrazvukom, te su njihovi rezultati također podržali tezu da je fokusirani ESWT učinkovit u smanjenju bola, te dovodi do poboljšanja funkcije donjeg ekstremiteta, s tim da se nije pokazao superiorniji terapiji ultrazvukom.[73] Paoletta i sur. ispitali su učinke ESWT-a na sindrom miofascijalne boli (engl. miofascial pain syndrome, MPS) i fibromialgiju (FM), dva podcijenjena bolna mišićno-koštana stanja koja mogu izuzetno utjecati na funkciju i kvalitetu života. Uključeno je 19 kliničkih studija, od kojih je u njih 12 korišten radijalni ESWT, a u sedam fokusirani ESWT za MPS. Utvrdili su povoljan učinak ESWT-a na poboljšanje kliničkog i funkcionalnog ishoda kod osoba s MPS-om, dok za FM nisu pronađeni dokazi. Autori su predložili da je mogući mehanizam djelovanja ESWT-a preko modulacije bioloških mehanizama bola, upale i angiogeneze u bolesnika s MPS-om.[74]

Zaključak

Brojna istraživanja potvrdila su povoljno djelovanje ESWT-a u liječenju različite mišićno-koštane patologije. Kao glavni učinak izdvaja se smanjenje bola, te poboljšanje funkcije zahvaćenog dijela tijela. Prednost ESWT-a je to što se radi o neinvazivnoj metodi liječenja koja omogućuje brz oporavak i povratak aktivnostima svakodnevnog života, uz malu stopu komplikacija. Primjena ESWT-a je danas već ustaljena za određene indikacije poput tendinopatija, epikondilitisa i plantarnog fascitisa, no zahvaljujući znanstvenom napretku i provedenim istraživanjima, ESWT se sve više primjenjuje i kod drugih stanja poput kalcificirajućeg tendinitisa ramena, te čak i spasticiteta kod bolesnika nakon moždanoga udara. Novija istraživanja sugeriraju pozitivne učinke ESWT-a i kod poremećenog cijeljenja kosti, kronične križobolje, smrznutog ramena, osteoartritisa koljena, sindroma trkačke potkoljenice, škljocavog prsta, sindroma bolnoga trohantera, te kod sindroma miofascijalne boli. Potrebno je, međutim, provesti dodatna istraživanja kako bi se utvrdila stvarna vrijednost i mjesto ESWT-a u liječenju navedenih bolesti.

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Pregledni članak
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Povezanost bolesti covid-19 i poremećaja glasa

The relation between covid-19 disease and voice disorders

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Sažetak

Utjecaj COVID-19 na fonatorni sustav još uvijek nije moguće metodološki konačno sumirati zbog premalog broja znanstvenih i/ili stručnih radova koji ih obrađuju.Cilj ovoga rada je dati preliminaran pregled za sada dostupnih spoznaja o fonijatrijskim posljedicama COVID-19 temeljem pregleda baza podataka.

Infekcija SARS-Cov-2 virusom u visokom je omjeru praćena tegobama vezanim uz upalne procese larinksa, te simptomima kao što su disfonija, osjećaj suhoće u grkljanu, zamor glasa ili afonija. Stopa prevalencije disfonije uzrokovane SARS-Cov-2 infekcijom kreće se čak do 79%, a kao glavni uzroci izdvajaju se intubacija, postviralne paralize i pareze glasnica, te postviralna laringalna senzorna neuropatija. Čini se da COVID-19, zbog utjecaja na larinks i pluća, također posredno utječe na akustičke karakteristike glasa, pa se kod bolesnika primjećuju smanjenje maksimalnog vremena fonacije, povećana šumnost u glasu, povećan jitter i shimmer, te povećan broj prekida glasa tijekom fonacije.

S obzirom na to da je disfonija kod mnogih bolesnika prisutna i nakon otpusta s bolničkoga liječenja, važno je poznavati i multidimenzionalno procijeniti moguće postojanje poremećaja glasa kod bolesnika koji imaju ili su preboljeli COVID-19. Osim toga, za odgovarajuće liječenje, kao i funkcionalni i socio-emocionalni oporavak bolesnika s disfonijom, potrebna je sveobuhvatna multidisciplinarna dijagnostika koja se ponajprije odnosi na uporabu vizualizacijskih dijagnostičkih metoda, ali ju je potrebno dopuniti objektivnom i subjektivnom analizom glasa, te samoprocjenom utjecaja kvalitete glasa na svakodnevni život. Imajući u vidu ozbiljnost posljedica poremećaja glasa na kvalitetu života, u liječenju i rehabilitaciji perzistirajuće disfonije neophodna je uska suradnja otorinolaringologa, odnosno fonijatra, te logopeda.

Ključne riječi: COVID-19, disfonija, prevalencija, uzroci, dijagnostika

Summary

The impact of COVID-19 on the phonatory system is still not possible to summarize methodologically due to the insufficient number of papers covering this topic. The aim of this paper is to provide a preliminary overview of the currently available knowledge about the phoniatric consequences of COVID-19, based on a review of databases.

The SARS-Cov-2 infection is often accompanied by complaints related to inflammatory processes of the larynx and symptoms such as dysphonia, feeling of dryness in the larynx, voice fatigue or aphonia. The prevalence rate of dysphonia caused by the SARS-Cov-2 infection is as high as 79%, and the main causes are intubation, postviral vocal cord paralysis and paresis, and postviral laryngeal sensory neuropathy. It seems that COVID-19, due to its impact on the larynx and lungs, also indirectly affects the acoustic characteristics of the voice, so patients notice a decrease in the maximum phonation time, increased

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hoarseness in the voice, increased jitter and shimmer, and an increased number of voice interruptions during phonation.

Given that dysphonia is present in many patients even after discharge from hospital treatment, it is important to know and multidimensionally assess the possible existence of voice disorders in patients who have or have recovered from COVID-19. In addition, for appropriate treatment, as well as functional and socio-emotional recovery of patients with dysphonia, comprehensive multidisciplinary diagnostics is required, which primarily refers to the use of a visual diagnostic methods, but it must be supplemented by subjective and objective voice analysis, and self-assessment of the impact of voice quality on everyday life is required.

Bearing in mind the consequences of voice disorders on the quality of life, in the treatment and rehabilitation of persistent dysphonia, close cooperation between otolaryngologists - phoniatricians and speech-language pathologists is necessary.

Key words: COVID-19, dysphonia, prevalence, causes, diagnosis

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Uvod

Pandemija koronavirusne bolesti-2019 (COVID-19), uzrokovane infekcijom teškim akutnim respiratornim sindromom coronavirus-2 (SARS-CoV-2) proglašena je 2020. godine. S obzirom na to da se radilo o novoj bolesti, ona je epidemiološki, patogenetski, patološki, klinički, komorbiditetno i terapijski bila neodređena[1]– o njoj se nisu znali čak niti osnovni podaci poput vremena inkubacije ili vremena kada inficirana osoba počinje biti zarazna za kontakte, niti koliko dugo je zarazna nakon izbijanja simptoma. Zbog brzine kojom se pandemija proširila svijetom[2] COVID-19 istraživan je „u hodu“, pa u početku njezinog izbijanja učinci na pojedine tjelesne sustave i organizam u cjelini nisu bili precizno određeni. Sukladno tome, niti učinci ove infekcije na larinks nisu bili detaljno opisani[3], iako su ubrzo, kao najčešći otorinolaringološki simptomi SARS-Cov-2 infekcije počeli biti prijavljivani kašalj, grlobolja, ageuzija, nazalna kongestija, nazalni iscjedak i problemi sa sluhom, a veliki broj zaraženih osoba prijavljivao je i tegobe vezane uz upalne procese larinksa, kao što su promuklost, osjećaj suhoće u grkljanu, zamor glasa ili afonija.[4,5] Budući da je visoko zarazna i podložna brzom širenju, od kraja 2019. godine, te posebno nakon ožujka 2020. godine (kada je Svjetska zdravstvena organizacija službeno proglasila globalnu pandemiju) do danas, infekcija uzrokovana SARS-Cov-2 virusom postala je jedno od najviše istraživanih oboljenja,[6] što je rezultiralo, ne samo mogućnošću boljeg opisivanja bolesti, već i brzim razvojem cjepiva. Brza i masovna orijentacija istraživača na COVID-19 postala je očita u naglom skoku broja istraživačkih priloga koji se njime bave u etabliranim bazama znanstvenih radova.[2] Usprkos tome, utjecaj COVID-19 na specifične tjelesne sustave poput fonatornog i danas nije moguće metodološki rigorozno sumirati zbog premalog broja prijavljenih znanstvenih priloga koji ih obrađuju, nego ih se prikazuje tek kao preliminarne preglede spoznaja. Cilj ovoga rada upravo je dati takav pregled spoznaja o fonijatrijskim posljedicama COVID-19 temeljem pregleda baza podataka Scopus, Medline, Current Contents i PsycInfo pomoću ključnih riječi „COVID-19“ i „disfonija“. Pregledi navedenih baza izvršeni su pomoću ovih ključnih riječi jer su rezultati pretraga pomoću drugih ključnih riječi bili nekoherentni s obzirom na cilj istraživanja, odnosno nedovoljno usmjereni na fonijatrijske posljedice infekcije SARS-Cov-2 virusom.

Prevalencija poremećaja glasa kod bolesnika s covid-19

Istraživanja prevalencije disfonije uzrokovane infekcijom SARS-Cov-2 virusom pokazuju različite stope prevalencije, ovisno o metodologiji, te geografskom podneblju. Stope prevalencije, kao što je vidljivo iz tablice 1, kreću se od 22,3% do čak 79%.[7,8,9,10] S obzirom na spol, neki autori prijavljuju veću prevalenciju disfonija uzrokovanih COVID-19 kod žena,[11,12] dok drugi prijavljuju podjednaku prevalenciju kod oba spola.[7,9] Ako se razmotri dob oboljelih od COVID-19, čini se da ona nije statistički značajno povezana s brojem ili izraženošću fonijatrijskih simptoma.[8,10] Poljsko istraživanje pokazalo je da je kod 3.80% bolesnika prisutna umjerena do jaka promuklost kao izolirani simptom post-COVID-a. Kod navedenih bolesnika simptomi kao afonija, promuklost i vokalni zamor perzistirali su i nekoliko mjeseci nakon preboljene infekcije SARS-Cov-2.[13]

Covid-19 kao uzročnik poremećaja glasa

Zbog utjecaja COVID-19 na funkciju larinksa i pluća dolazi do promjena u akustičkim karakteristikama glasa, kao što su MVF (maksimalno vrijeme fonacije)[14,15,16] povećana šumnost u glasu i

vrijednosti jittera i shimmera, te povećan broj prekida u glasu tijekom fonacije.[15] Iako se u literaturi spominju različiti etiološki čimbenici koji povezuju disfoniju i COVID-19, Helding i suradnici kao osnovne uzroke promuklosti uzrokovane ovom infekcijom izdvajaju intubaciju, postviralne paralize i pareze glasnica, te postviralnu laringalnu senzornu neuropatiju.[17]

Tablica 1. Prijavljena prevalencija disfonije kod oboljelih od COVID-19
Table 1 Reported prevalence of dysphonia in patients with COVID-19

Autori *Authors*	Država *Country*	N žene/*female* muškarci/*male*	Prevalencija poremećaja glasa *Voice disorder prevalence*
Al-Ani i Rashid (2021)[8]	Irak	94 (48 ž/*f*, 46 m/*m*)	22.3%
Lechien i sur. (2022)[7]	Europa	702 (496 ž/*f*, 206 m/*m*)	26.8%
Cantarella i sur. (2021)[9]	Italija	160 (110 ž/*f*, 50 m/*m*)	43.7%
Cecen i Korunur Engiz (2022)[12]	Turska	50 (25 ž/*f*, 25 m/*m*)	68%
Azzam i sur. (2021)[10]	Egipat	106 (78 ž/*f*, 28 m/*m*)	79%

Intubacija

Najčešća posljedica teške infekcije SARS-Cov-2 virusom je respiratorno zatajenje koje zahtijeva intubaciju, što za posljedicu ima različite laringalne komplikacije. Kronične posljedice intubacije i ozljeda uzrokovanih kašljem nakon infekcije SARS-Cov-2 virusom uključuju stenozu dišnih putova, abnormalnosti sluznice glasnica, fiksaciju glasnica i postintubacijsku fonatornu insuficijenciju.[17] Naunhaim i suradnici su kod 20 bolesnika koji su imali laringološke tegobe nakon COVID-19 učinili fleksibilnu laringoskopiju i stroboskopiju. Od 20 uključenih bolesnika, 65% ih je bilo intubirano prosječno u trajanju od 3 tjedna. Svi bolesnici koji su podvrgnuti fleksibilnoj laringoskopiji pokazali su abnormalnosti grkljana, najčešće u glotisu (93,8%), a oni koji su bili podvrgnuti stroboskopiji imali su abnormalnosti mukoznog vala (87,5%), periodičnosti (75%), zatvaranja (50%) i simetrije (50%). Najčešća dijagnoza kod intubiranih bolesnika bila je jednostrana paraliza glasnica (40%), uz stenozu stražnjeg glotisa (15%) i subglotisa (10%), dok kod bolesnika koji nisu bili intubirani nisu pronađene paralize glasnica ili stenoze.[18] Slične rezultate su u svom istraživanju prikazali Neevel i sur. Na uzorku od 18 bolesnika s COVID-19 kod kojih je bila potrebna endotrahealna intubacija, najveći broj njih imao je poremećaj pokreta glasnica (50%), a zatim povrede glotisa (39%), stenozu subglotisa (22%) i stenozu stražnjeg glotisa (17%).[19]

Najčešći simptom koje su oboljeli od infekcije SARS-Cov-2 virusom prijavljivali nakon intubacije su tegobe povezane s glasom (60%), a potom tegobe povezane s disanjem (35%) i gutanjem (30%).[18] Kao prediktori loše kvalitete glasa nakon intubacije pokazale su se ozljede prilikom intubacije i prijašnje respiratorne bolesti.[17]

Opservacijsko kohortno istraživanje učinjeno u Londonu uključilo je 164 odrasla bolesnika hospitalizirana radi COVID-19, koji su upućeni na logopedsku procjenu glasa i gutanja. Ukupno 78,7% ovih osoba bilo je intubirano, od čega je njih 87,5% imalo disfoniju utvrđenu perceptivnom procjenom glasa GRBAS skalom. Po otpustu iz bolnice 17% bolesnika imalo je disfoniju koja je zahtijevala daljnji logopedski tretman.[21]

Rouhani i suradnici ispitivali su perceptivne posljedice na kvalitetu glasa kod intubiranih bolesnika nakon infekcije SARS-Cov-2 virusom pomoću GRBAS skale i upitnika za samoprocjenu Indeks vokalnih teškoća (Voice Handicap Index – VHI). Iako je samo 13,2% bolesnika subjektivno smatralo svoj glas narušene kvalitete, čak za polovinu njih (53,7%) je slušno-perceptivnom procjenom od strane kliničara utvrđeno da imaju narušenu kvalitetu glasa. Najizraženija je bila astenija, što upućuje na opću slabost u glasu.[22]

Neevel i sur. navode da je promuklost najčešći problem (79%) koji navode bolesnici s COVID-19 kada su pitani o kvaliteti života povezanom s glasom upitnikomVoice Related Quality of Life (V-RQOL). Međutim, oni naglašavaju da je kod bolesnika kojima nije bila potrebna intubacija, incidencija mišićne tenzijske disfonije 67%, te da ona nije zabilježena kod intubiranih bolesnika, što navodi na zaključak da problemi s glasom nisu ograničeni samo na bolesnike kojima je bila potrebna intubacija.[19]

Postviralne paralize i pareze glasnica

Paraliza i pareza glasnica mogu biti rezultat intubacije nakon SARS-Cov-2 infekcije, a također mogu biti posljedica virusne ozljede živca vagusa ili njegovih ogranaka koji su odgovorni za funkciju mišića glasnica i osjet u dijelu grkljana.[17] Tijekom

vrhunca prvog vala pandemije COVID-19 početkom 2020. godine primijećen je nagli porast slučajeva "idiopatske" paralize ili pareze glasnica kod bolesnika koji se oporavljaju od COVID-19. Postvirusna neuropatija vagusa obično uključuje akutnu infekciju gornjeg dišnog trakta koja dovodi do senzorne i motoričke disfunkcije živca vagusa. Živac vagus je mješoviti živac, pa tako njegova post-virusna neuropatija može imati i motoričke i senzorne simptome.[23] Klinička slika anomalije u funkciji vagusa može uključivati senzorne simptome kao što su kronični kašalj, učestalo pročišćavanje grla i umor glasa,[20]te disfoniju,[24,25,26] u čijoj su pozadini pareza ili paraliza glasnica.

Rapoport i sur. su u laringološkim klinikama primijetili porast slučajeva "idiopatske" paralize i pareze glasnica kod bolesnika koji se oporavljaju od COVID-19, a nisu bili recentno intubirani. Šesnaest bolesnika čije su podatke analizirali imalo je novonastalu disfoniju tijekom i nakon oporavka od COVID-19. Kod 25% bolesnika učinjena je laringalna elektromiografija kojom je utvrđena neuropatija, što dovodi do zaključka da COVID-19 može uzrokovati post-virusnu neuropatiju vagusa, koja rezultira abnormalnom pokretljivošću glasnica.[23]

Posljednje dvije godine objavljeno je nekoliko prikaza slučajeva paralize glasnica uzrokovanih infekcijom SARS-Cov-2 virusom koji pokazuju da se idiopatska paraliza glasnica može pripisati postvirusnoj neuropatiji.[23,24,25,26,27] Stoga se savjetuje da se kod bolesnika koji se oporavljaju od COVID-19 i imaju senzorne simptome laringalne iritabilnosti (kašalj, pročišćavanje grla) ili glotalne insuficijencije (promuklost, umor glasa i/ili aspiracija), treba posumnjati na parezu glasnica i učiniti daljnje pretrage poput videostroboskopije s dinamičkom procjenom larinksa, radi dokazivanja moguće abnormalne pokretljivosti glasnica ili laringalnu elektromiografiju, kako bi se potvrdila ili odbacila sumnja na postvirusnu neuropatiju.[23] S obzirom na perzistirajući poremećaj glasa koji ima jaki bio-psiho-socijalni utjecaj na kvalitetu života, za ovakve bolesnike preporučljivo je i uključivanje u logopedsku terapiju.

Postviralna laringalna senzorna neuropatija

Uz ranije opisane motoričke neuropatije, s virusnim infekcijama se povezuju i senzorne neuropatije grkljana. Senzorna neuropatija grkljana uzrokovana infekcijom SARS-CoV-2 uzrokuje kronični kašalj i disfunkciju gutanja.[28]Smatra se da SARS-CoV-2 dovodi do fizičkog učinka na glasnice zbog akutne i kronične upale, te kasnijeg kroničnog vokalnog zamora povezanog s glasovnim tegobama. Oštećenje grkljana uzrokovano senzornom neuropatijom može biti pogoršano upalom sluznice gornjeg dišnog trakta, za koju se smatra da je posredovana samim virusom, uz upalu uzrokovanu fizičkom traumom kašlja, povezanom preosjetljivošću larinksa i laringofaringalnim refluksom. Prevalencija laringalne senzorne neuropatije nakon COVID-19 nije poznata, ali je vjerojatno da će se pojaviti kao i nakon bilo koje virusne infekcije.[17]

Moyano, Torres i Espinosa prikazali su slučaj 38-godišnje bolesnice s infekcijom SARS-CoV-2 virusom kod koje su se razvili poremećaj glasa i gutanja i neuropatska bol u području vrata. Fiberoptička nazolaringoskopija i videofluoroskopija pokazale su parezu desne glasnice, neuropatiju desetog kranijalnog živca, kao i oralnu, hipofaringalnu i supraglotičku hipesteziju. Autori smatraju da su poremećaj glasa i gutanja uzrokovani upalnim odgovorom na infekciju koji je zahvatio nervus vagus, što je dovelo do pareze glasnica i laringalne senzorne neuropatije. S obzirom na izrazitu neuropatsku bol započeto je medikamentozno liječenje, te rehabilitacijski program koji je uključivao psihološku, fizikalnu, respiratornu i glasovnu rehabilitaciju.[28]

Wong prikazuje slučaj 43-godišnje bolesnice koja se javila na bolničko liječenje zbog teškog kašlja uslijed SARS-Cov-2 infekcije. Propisana terapija nije dala rezultate. Nalazi radiograma prsnog koša, kompjuterizirane tomografije, te laboratorijski nalazi bili su uredni. Unatoč intervencijama, jaki paroksizmi kašlja su se zadržali i rezultirali povraćanjem i promuklošću. Refraktorni kašalj kod bolesnice upućivao je na neuropatsku etiologiju. Laringovideostroboskopija je pokazala blagu obostranu restrikciju mukoznog vala koja može biti povezana sa senzornom neuropatijom laringalnog živca. Podvrgnuta je blokadi desnog gornjeg laringalnog živca i medikamentoznoj terapiji, te je upućena na logopedsku terapiju.[29]

Zaključak

Infekcija SARS-Cov-2 virusom u visokom je omjeru praćena disfonijom, koja je kod mnogih bolesnika prisutna i nakon otpusta s bolničkog liječenja. Ovu činjenicu važno je poznavati, te multidimenzionalno procijeniti moguće postojanje poremećaja glasa kod bolesnika koji imaju ili su preboljeli COVID-19. Klinički neophodne informacije za odgovarajuće liječenje i maksimiziranje funkcionalnog i socio-emocionalnog oporavka bolesnika s komorbidnom (i perzistirajućom) disfonijom moguće je utvrditi tek

temeljem kombinacije vizualizacijskih dijagnostičkih metoda, subjektivne i objektivne analize glasa, te samoprocjene utjecaja kvalitete glasa na njihov svakodnevni život. S obzirom na širok spektar mogućih uzroka disfonije, kao i na ozbiljnost posljedica poremećaja glasa na kvalitetu života, neophodna je uska suradnja otorinolaringologa-fonijatra i logopeda – najprije u dijagnostičkom postupku, a potom i u liječenju, odnosno rehabilitaciji perzistirajuće promuklosti nakon otpusta iz bolnice.

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Pregledni članak
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Psychiatric approach to tinnitus

Psihijatrijski pristup tinitusu

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Summary

Tinnitus is a symptom with a significant incidence in the general population, usually of unclear etiology, that can cause serious difficulties in people's daily functioning, significantly impair the quality of life, and have a negative impact on mental health.

The paper aims to present a brief overview of current knowledge about this frequent and unpleasant phenomenon, including epidemiology, etiology, clinical presentation, diagnosis, and treatment.

The paper highlights contemporary theories of tinnitus that link damage to the peripheral organ of hearing and the consequent neuronal changes involved in the subjective experience, which are the target sites for treating psychological disorders associated with tinnitus. The psychiatric approach to tinnitus is aimed not so much at reducing the sound intensity as at reducing the negative experience of this phenomenon and preventing the development or worsening of existing psychological disorders.

The results of previous researches indicate numerous therapeutic options for treating tinnitus, including drugs, cognitive-behavioral therapy, and neuromodulation techniques with promising results.

Key words: neuromodulation, neuroplasticity, psychiatry, tinnitus

Sažetak

Tinitus je simptom sa značajnom pojavnošću u općoj populaciji, najčešće nejasne etiologije, koji može izazvati ozbiljne poteškoće u svakodnevnom funkcioniranju, značajno narušiti kvalitetu života i dovesti do negativnog utjecaja na psihičko zdravlje.

Cilj rada je prikazati kratki pregled dosadašnjih spoznaja o ovome, često neugodnom fenomenu, uključujući epidemiologiju, etiologiju, kliničku sliku, dijagnostiku i liječenje.

U radu su istaknute suvremene teorije tinitusa koje povezuju oštećenje perifernog organa sluha i posljedične neuronske promjene uključene u subjektivni doživljaj, koje su ciljno mjesto liječenja psihičkih smetnji udruženih s tinitusom. Psihijatrijski pristup tinitusu usmjeren je, ne toliko na smanjenje zvučnog intenziteta, koliko na smanjenje negativnog doživljaja ovoga fenomena i sprječavanje razvoja ili pogoršanja postojećih psihičkih poremećaja.

Rezultati dosadašnjih istraživanja ukazuju na brojne terapijske mogućnosti liječenja tinitusa, uključujući lijekove, kognitivno-bihevioralnu terapiju, te neuromodulacijske tehnike s obećavajućim rezultatima.

Ključne riječi: neuromodulacija, neuroplastičnost, psihijatrija, tinitus

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Introduction

The appearance of noise lasting longer than five minutes in one or both ears in the absence of external sound sources is called tinnitus. In terms of duration, it can be permanent and constant, or recurrent, with episodes occurring at least once a month. According to the American Academy of Otolaryngology-Head and Neck Surgery, tinnitus can be divided into primary and secondary.[1] The primary is of an unknown cause, and the secondary is always associated with an ear disease or some other systemic illness. Both external, middle, and inner ear diseases can lead to tinnitus. Middle ear inflammation, otosclerosis, and Meniere's disease are some of the most common ear disorders that can provoke tinnitus. Systemic diseases, such as atherosclerosis, cervical spine spondylosis, and anemia, may also be associated with the development of tinnitus. Secondary tinnitus is always characterized by a clear organic cause of the disorder.[2]

Tinnitus can be divided into subjective and objective types based on causative factors. Subjective tinnitus is a sound that cannot be explained by the existence of a real source of sound and is mainly associated with hearing loss. Objective tinnitus is much less frequent and is associated with sound formation near the ear due to cardiovascular abnormalities and disturbances in musculoskeletal structures. Objective tinnitus is always secondary to a clearly defined organic cause.[3] Subjective tinnitus may manifest as a sniffing, buzzing, whistling, or ringing sound. Sometimes, there may be polymorphic exchanging characteristics, and if several types of sound phenomena are present simultaneously, we can talk about complicated tinnitus. If objective tinnitus is synchronous with heart function, there will be a sense of pulsation. On the other hand, an occasional onset is a characteristic of tinnitus due to muscular-skeletal disorders.[4]

The mechanisms of sound perception are very complex; therefore, it is difficult to clarify the origin of tinnitus as a phantom sound phenomenon. The primary auditory cortex is responsible for processing auditory information. It is located bilaterally, approximately in the upper temporal lobes, and takes part in the spectro-temporal analysis of the sounds, determining the frequency and time of the stimulus.[5] The associative cortex in the parietal and frontal lobes is responsible for final sound processing and is associated with the emotional and cognitive experience of sound. The auditory cortex has a crucial but ambiguous function in hearing. Multiple sounds are simultaneously transduced during the hearing process, and it is the responsibility of the auditory system to determine which components form the sound link. A disorder in any part of the complex auditory pathway may be a possible cause of tinnitus.[6]

The absence of different sounds usually amplifies the severity of tinnitus, therefore, it is most noticeable during sleep onset. This important physiological function is impaired since the symptoms worsen in silence and before sleep. Tinnitus may lead to the development or worsening of anxiety and depression disorders. On the other hand, psychological stress is often associated with increased intensity or the occurrence of tinnitus.[7]

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) does not describe tinnitus as a separate entity, and the eleventh edition of the International Classification of Diseases (ICD-11) describes it as a non-specific symptom of hearing disorders but not as a separate disorder.[8] In 2021, the international multi-disciplinary group proposed a new definition of tinnitus as a conscious sense of sound or composite noise without an appropriate external sound source. As a disorder, tinnitus is defined only if there is an impairment of emotional, cognitive, and working functions, leading to subjective suffering.[9] This definition of tinnitus is more associated with affective disorders than with a disorder in the perception of reality. Some experts have characterized vertigo and tinnitus as hallucinations, vertigo as a spatial hallucination, and tinnitus as an acoasm. It is important to distinguish tinnitus from simple auditory hallucination.[10,11] It should be stressed that patients do not attribute any deeper psychological meaning to the sound caused by tinnitus, as they do with hallucinations. Tinnitus may provoke newer enhance existing psychological issues such as anxiety, addiction, and depression disorders. Some patients will require psychiatric treatment to overcome their tinnitus burden.[12,13]

Epidemiology

Tinnitus is a common disorder, affecting about 15% of the general population[5]. The severity of negative subjective experiences varies from slightly disturbing to extremely disturbing. Its incidence and prevalence are relatively stable worldwide, though not precise due to the wide range of intensities and polymorphic phenomena, as well as the complex and poorly understood etiology.[14]

Smokers, people exposed to chronic noise and stress, nightshift workers, and patients with various bodily comorbidities are more affected.[15] Gender prevalence studies are contradictory.[13,16] The likelihood of developing tinnitus significantly increases with ages. The general prevalence in the

population older than 65 is about 13.5%, but tinnitus occurs at all periods of life, and even children are not spared.[17] In a Polish study of 15,199 students aged seven to 12. 6% reported having tinnitus lasting five minutes or longer at least once in their lives, with no gender difference.[18]

Etiology

The cause of objective tinnitus is usually easily discovered by hearing sounds from nearby vascular and musculoskeletal structures. In subjective tinnitus, it is difficult to talk about the reason, therefore, we will talk about the reluctant phantom sensation that causes the patient's negative experience. Tinnitus may occur as a multi-level disorder. The occurrence of tinnitus is primarily related to the disturbance of the external, middle, or inner ear or the impairment or loss of hearing. The next level is in the central nervous system, which can be in the neuronal circles of the auditory and extra-auditory regions of the brain stem and cortex.[19]

The exact changes in neural activity that lead to the perception of the creation and maintenance of this phenomenon remain unknown.[20] There are several hypotheses about the formation of tinnitus, including the leading theory of degeneration at the level of sensory cells in the inner ear and the theory of neuroplasticity, which includes the impaired regulation of impaired excitation parts of the central nervous system included in the sense of sound.[21,22]The theory of neuroplasticity is followed by the theory of cortical reorganization, which recognizes changes in the structure of cortical circuits as an important factor in the psychological experience of tinnitus.[23]

Risk factors

Numerous studies have found several factors of risk associated with tinnitus, such as age, impaired or lost hearing, exposure to sound stress, psychological disorders, psychosocial stress, temporomandibular joint disorders, inflammatory diseases, head and neck trauma, ototoxic medications, viral infections, long-term smoking, and lack of sleep. Tinnitus occurs more frequently in people with comorbidities such as hyperlipidemia, asthma, osteoarthritis, rheumatoid arthritis, and thyroid dysfunction, and usually in patients with damaged hearing apparatus on all levels, from the external auditory canal, eardrum membrane, middle ear ossicles, to internal ear structures.[13] Although several risk factors for tinnitus have been discovered, not everyone with these factors experiences tinnitus or an equally profound sense of subjective suffering. Subjective psychological experience is of crucial importance for the sensation of tinnitus-related discomfort.[24]

As we live during the COVID-19 pandemic, it is important to emphasize the connection between viral infections and tinnitus. Viruses can harm the cells of the inner ear or the brain region involved in the sense of hearing in various ways. The varicella-zoster virus and human immunodeficiency virus are two examples of viruses that can directly damage neuronsorvascular endothelium,[25] whereas SARS-Co-V2 has been shown to cause hyper coagulability as one of the mechanisms of damage to peripheral hearing organs and central nervous system structures.[26]

There have been few studies on audio vestibular symptoms in SARS-CoV2 patients, but more patients with these problems can be expected in the future, especially after treatment in intensive care units with ototoxic drugs such as chloroquineanda-minoglycosides.[27] Preliminary results of the Italian study by Viola et al. on a small sample of 185 patients who were infected by COVID-19 at the beginning of the pandemic were published; 23.2% of patients had a different intensity and duration of tinnitus during and after the disease.[25]

Disorders within the Central Nervous System

Modern theories associate tinnitus with disorders of the central nervous system. The occurrence of tinnitus is explained by the spontaneous activation of neurons after peripheral damage to the organs of hearing and consequential regulatory disorders between the limbic system and the central auditory cortex.[17]

The dominant theory put forth by Jastreb offdates back to 1990, according to which damage to the peripheral organs of the hearing leads to changes in the audio vestibular path, which further leads to spontaneous hyperactivity in the brain stem and auditory cortex.[19,28] Subsequently, reorganizational changes in the brain stem and cortical areas occur as a neuroplastic response, which can enhance the subjective feeling of tinnitus. It is assumed that the displeasure of tinnitus induces a reorganization of neuronal activity that strengthens neural connections in brain areas related to the emotional experience.[29]

Changes in the central nervous system remain the target areas of the investigation of tinnitus etiology, but still without a full explanation. The complexity of the pathophysiology of tinnitus and its consequential changes in neuroplasticity and subjective experience is partly explained by the difficulties in treating this complex disorder. The failure to treat only one

cascade in this complex enchanted circle explains the persistence of tinnitus even after the treatment of hearing disorders. As mentioned earlier, future treatments must simultaneously focus on several aspects of tinnitus pathophysiology.[30] Research shows that changes in neuronal activity are not limited only to the auditory system but also include non-auditory brain areas such as the frontal lobe, which is involved in emotional experiences.[31,32]

Genetics

The number of genetic studies of tinnitus is increasing. A large Swedish cohort study from 2019 using data from the National Register between 1964 and 2015 suggests that tinnitus is related to genetic factors in 32% of cases. This study did not find a link between common environmental factors and the development of tinnitus.[33]There is a link between several genes and polymorphisms related to oxidative stress and the inflammatory response to tinnitus.[6]

The genetic research on tinnitus is focused on gene sequencing, bioinformatics analysis, and understanding gene regulation through epigenetic mechanisms. Examples of genes that may be associated with the occurrence of tinnitus are genes for pro-inflammatory cytokines and growth factors, whereas the example of epigenetic regulation of gene expression involved in the development of tinnitus may be the significant difference detected in the ratios of the methylation of cytosine gene sections for the brain-derived neurotrophic factor (BDNF) between the control group and patients with tinnitus.[24]

The function of BDNF is to inhibit neuronal damage and promote neuronal regeneration after a lesion, whereas damage to the auditory nerve system is a major pathophysiological cause of tinnitus. Changes in BDNF expression in patients with tinnitus could reflect the repair process following injuries to parts of the brain involved in hearing sensation. The genetic basis for the development of tinnitus requires further research.[34]

Clinical presentation

Tinnitus is a highly heterogeneous disorder with no significant success in classifying its clinical presentation. Problems related to tinnitus are described in a continuous gradation with no apparent boundaries. These patients may perceive a soft background or a loud external noise. The intensity of interference and functional limitations may vary from case to case, while approximately 20% of patients are severely disabled in everyday functioning.[12]

Subjective tinnitus is usually called tinnitus, and objective tinnitus is often called somatosound. Most tinnitus sounds resemble sniffing, buzzing, whistling, or ringing. Tinnitus patterns are stored in the auditory memory and are associated with limbic system emotions. Patients with tinnitus have significantly higher levels of depression and anxiety on psychological scales. Other mental disorders, such as alcohol abuse, dysfunction, and social function, including suicide, are more frequent among these patients.[35]

In objective tinnitus, physical movements such as turning the eyes, clenching the jaw, or applying pressure to the head and neck can change the frequency or intensity of the ringing. Objective tinnitus may be caused by neck muscle contractions or clenching of the jaw, which may disappear during sleep but usually returns within a few hours.[4] The occasional onset of tinnitus is characteristic of disorders in the nasopharynx or middle ear muscle contractions. Pulsatile somatosounds associated with heartbeats in objective tinnitus may result from carotid or vertebrobasilar stenosis.[13]

Tinnitus can be induced after noise exposure, and this acute-induced tinnitus duration ranges from minutes to weeks. If tinnitus lasts over two years, it is considered permanent and irreversible. Chronicity of tinnitus is associated with a negative treatment response.[3]

Diagnosis

The diagnosis of tinnitus is based on anamnestic data, such as duration, location, and sound frequency. It is primarily important to distinguish objective from subjective tinnitus. To rule out possible cardiovascular causes of occasional present-day tinnitus, it is critical to determine whether it is caused by a pulse wave. Stimulating and mitigating factors such as neck movements, swallowing, and head position speak in favor of a musculoskeletal etiology.[36]

Imaging radiological methods such as magnetic resonance imaging and computerized tomography are used to determine the etiology of cardiovascular and musculoskeletal diseases. The simultaneous appearance of other symptoms with tinnitus, such as loss of hearing, vertigo, pain, and ear discharge, indicates an otologic etiology.[19] Neurological damage may also cause tinnitus and should be excluded. It is important to assess the effects of tinnitus on patients, their mental experience, and their association with mental disorders such as anxiety, depression, and insomnia. Risk factors for tinnitus development, such as noise exposure, changes in diving or airplane travel pressure, infection, and ear or central nervous system

injuries, may indicate the level at which tinnitus developed.[35]

Unilateral tinnitus that has been present for six months or more or in the presence of a hearing disorder should have an extensive audiological assessment. If an objective cause is not found, we can discuss subjective tinnitus as an idiopathic phenomenon lacking objective diagnostic tools.[36]

Treatment

Different methods are currently used to treat tinnitus: medications, cognitive-behavioral therapy, neurofeedback therapy, and neuromodulation. There are now no strong guidelines or specific treatments for tinnitus. The current recommendations aim to treat mental comorbidities, including insomnia, anxiety, and depression, and improve microcirculation to lessen suffering.[37] Anticonvulsants, local anesthetics, antiarrhythmics, antihistamines, antidepressants, antipsychotics, anxiolytics, calcium channel blockers, diuretics, vasodilators, and vitamins are among the medications used to treat tinnitus.[38] So far, no medicinal product has been authorized by the Food and Drug Administration for the specific treatment of tinnitus.[39]

The use of anticonvulsants is based on the assumption of hyperactivity in brain pathways involved in sound sensation, but Cochrane's study has led to the conclusion that anticonvulsants are ineffective in treating tinnitus and have a significant risk of numerous adverse reactions that were manifested by as many as 18% of patients.[40]

Lidocaine, a local anesthetic and antiarrhythmic, is effective in treating tinnitus but carries a high risk of dangerous side effects.[41]

Antihistamines affect microcirculation, and studies have been conducted to prove their efficacy in treating tinnitus. Betahistine, a potent histamine H3 receptor antagonist and histamine H1 receptor agonist used to treat Meniere's disease, does not treat tinnitus successfully.[42]

The use of antidepressants in tinnitus treatment is widespread and particularly effective in treating comorbid symptoms of anxiety, depression, and insomnia but less significant in reducing the feeling of an unpleasant sound phenomenon. Several studies have found that tricyclic antidepressants and selective serotonin reuptake inhibitors effectively reduce tinnitus-related subjective suffering,[43] while trazodone has shown no effect.[44]

Sulpirideas an antipsychotic was noted in the treatment of tinnitus, which significantly reduced the tinnitus sensation in the study by Lopez-Gonzalez et al. by 56%, in addition to hydroxyzine by 86%.[45]

The most frequently prescribed medicines for tinnitus-related problems are benzodiazepines, which are significantly effective in treating anxiety disorders and insomnia. The occurrence of tinnitus after discontinuation of benzodiazepine therapy for anxiety supports the theory of disturbed neuronal circuits as an important cause of the occurrence of tinnitus and the increase in its intensity. Clonazepam has been shown to significantly reduce the subjective intensity of tinnitus.[32]

Calcium channel blockers, diuretics, and vasodilators reduced tinnitus intensity but had a negative impact due to numerous adverse cardiovascular reactions.[39]

Vitamin B preparations often alleviate tinnitus problems, but different studies confirm and deny their effectiveness.[46,47]

Tinnitus treatment can be divided into two categories based on the goal of therapy. The first is to reduce or eliminate the perception of tinnitus. The second focuses on the effect of tinnitus on the patient's life and aims to reduce anxiety and the consequent development of low mood, anxiety, and insomnia. Cognitive-behavioral therapy in tinnitus treatment focuses on changing the patient's negative experience by correcting negative and unrealistic beliefs and behaviors. Cognitive-behavioral therapy aims not to reduce negative experiences but to help create more positive thoughts in this situation.[48]

Numerous neuromodulation techniques that have emerged during the past twenty years have been recognized as promising new approaches for treating tinnitus. Neurofeedback, transcutaneous stimulation of the vagus nerve, transcranial electrical stimulation, and repetitive transcranial magnetic stimulation are new and promising treatment options.[2] Some of these techniques have demonstrated encouraging findings regarding prospective treatment and understanding the pathophysiology of various conditions within the brain's structure, which may be included in the pathophysiology of tinnitus. To obtain considerable and long-lasting improvement in tinnitus therapy, neuromodulation techniques become an effective therapeutic option.[8]

Conclusion

Tinnitus is a significant burden due to an unpleasant subjective experience that can limit everyday functioning and exacerbate mental disorders such as depression, anxiety, and insomnia. Tinnitus etiology is very complex, but it is always associated with hearing impairment, whether it is a disturbance in the peripheral organ, the audio vestibular nervous pathway, or brain areas related to

hearing sensation. After hearing damage, changes occur in neuronal circles important for the emotional and subjective sense of tinnitus.

The personal experience of tinnitus has a wide range of intensities, ranging from almost inconspicuous to incapacitating with a strong sense of suffering. Psychological structure and psychic comorbidities play an important role in the experience of tinnitus.

The treatment today is aimed at reducing sound perception and subjective suffering. Benzodiazepines and antidepressants play a special role in reducing emotional suffering. Cognitive-behavioral therapy aims to correct negative beliefs and unacceptable behaviors associated with tinnitus. Neuromodulation techniques have also been developed as an alternative treatment, with promising results. Numerous studies on the efficacy of various treatments have been conducted, some of which could be more consistent. Further studies are necessary to shed light on the development's causes and determine the appropriate therapeutic approaches.

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Review
Pregledni članak

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Herlyn-Werner-Wunderlich syndrome with pyohematocolpos: a case report and review of literature

Herlyn-Werner-Wunderlichov sindrom s piohematokolposom: prikaz bolesnice i pregled literature

Damir Zudenigo, Ingrid Marton, Petar Lozo, Dubravko Habek*

Summary

Herlyn-Werner-Wunderlich syndrome (HWWS) is a rare malformation syndrome of the women reproductive tract characterized by uterus didelphys with obstructed hemivagina and ipsilateral renal agenesis. We report here a case of a 20 year-old patient presented to the emergency department with pain in the right lower quadrant. The clinical exam showed a vaginal fluctuant painful mass obliterating the right part of the vagina. Transvaginal ultrasound showed uterus didelphys, the right uterus was dilated with a dense fluid collection which corresponded to pyohematometra. It also revealed a dense vaginal collection which corresponded to pyohematocolpos. Abdominal ultrasound showed the absence of a right kidney. The laparoscopy showed uterus didelphys with a large right uterus. We performed the resection of the vaginal septum to reconstruct one vagina. The first follow-up visit revealed a healthy wound with no adhesion of the vaginal wall. Prompt and accurate diagnosis of female reproductive tract disorders, including HWWS, is necessary to prevent complications and preserve future fertility.

Key words: Herlyn-Werner-Wunderlich syndrome, pyohematocolpos, pyohematometra, ultrasound, laparoscopy

Sažetak

Herlyn-Werner-Wunderlichov sindrom (HWWS) je rijetka malformacija ženskog reproduktivnog sustava karakterizirana uterusom didelfisom, opstrukcijom hemivagine i istostranom agenezom bubrega. Prikazujemo slučaj 20-godišnje bolesnice koja se javila u hitnu službu s bolovima u donjem desnom kvadrantu. Klinički pregled ukazao je na bolnu fluktuirajuću masu koja je obliterirala desni dio rodnice. Transvaginalni ultrazvuk pokazao je prisutnost uterusa didelfisa, s time da je desni uterus bio dilatiran uslijed gustog tekućeg sadržaja koji je odgovarao piohematometri. Također je nađena vaginalna nakupina gustog tekućeg sadržaja koja je odgovarala piohematokolposu. Abdominalni ultrazvuk ukazao je na odsutnost desnog bubrega. Laparoskopija je pokazala uterus didelfis s uvećanim desnim uterusom. Resecirali smo vaginalni septum kako bi rekonstruirali jednu vaginu. Prvi kontrolni pregled je pokazao uredno cijeljenje rane bez priraslica vaginalne stijenke. Promptna i precizna dijagnoza malformacija ženskog genitalnog sustava, uključujući HWWS, potrebna je u svrhu prevencije komplikacija i očuvanja buduće plodnosti.

Ključne riječi: Herlyn-Werner-Wunderlichov sindrom, piohematokolpos, piohematometra, ultrazvuk, laparoskopija

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Introduction

Herlyn-Werner-Wunderlich syndrome (HWWS) is a rare congenital malformation syndrome characterized by a triad of uterus didelphys with obstructed hemivagina and ipsilateral renal agenesis, also known as OHVIRA.[1] In 1922., Purslow first described this syndrome in a young woman who presented with gradually increasing pelvic pain and a pelvic mass with regular menstruation.[2] The triad was reported in 1971. by Herlyn and Werner[3] and again in 1976. by Wunderlich.[4] The reported incidence for this anomaly is 0.1 to 3.8%.[5] The mean age of onset in patients with complete obstruction of the hemivagina is 13 years, with average time of four months from menarche to symptoms.[6] In cases of incompletely obstructed hemivagina the onset of symptoms may occur at a later time. Clinical manifestations are unspecific and most often include abdominal pain, painful menstruation and a palpably vaginal mass secondary to hematocolpos. Rarely, patients may develop pyohematocolpos, pyosalpinx and peritonitis as a result of an ascending infection due to retained discharge or menstrual blood in the obstructed hemivagina.[7] Ultrasound, magnetic resonance imaging and laparoscopy are used to establish the diagnosis.

Case report

A 20 year-old girl presented to the emergency department with pain in the right lower quadrant and fever 37.7°C. The laboratory test showed leukocytosis (leukocits were 23700×10^9/L). C reactive protein was 10.6 mg/L. She was on the fourth day of menstrual bleeding. Her medical history was uneventful. She had menarche at 13 years and a normal menstrual cycle of 28/5 days. The clinical exam showed normal external genitalia and a vaginal fluctuant painful mass obliterating the right part of the vagina. In the right vaginal wall, there was a defect through which bad-smelling purulent discharge mixed with the blood flowed. Normal cervix was identified on the speculum exam. The pelvic ultrasound showed uterus didelphys, the right uterus was dilated with a dense fluid collection which corresponded to pyohematometra. It also showed a dense vaginal collection of 10×4 cm which corresponded to pyohematocolpos (Figure 1). Abdominal ultrasound showed the absence of the right kidney. The patient was scheduled for surgical treatment. The laparoscopy showed uterus didelphys with a large right uterus (Figure 2). The ovaries were normal. No endometriosis implants were identified. The fluid collection in the blocked vagina was drained, evacuating a bloody and purulent content. We performed resection of the vaginal septum to reconstruct one vagina (Figure 3). After that treatment, the right cervix became visible. A final vaginoscopy showed a unique vaginal cavity with double cervix. The patient tolerated the procedure well and was discharged from hospital on the 3rd postoperative day. The first follow-up visit was four weeks after the operation. She had no symptoms and no complications were observed and the right hemivagina had collapsed. Vaginal examination revealed a healthy wound with no adhesion of the vaginal wall. Thus, her recovery was uneventful.

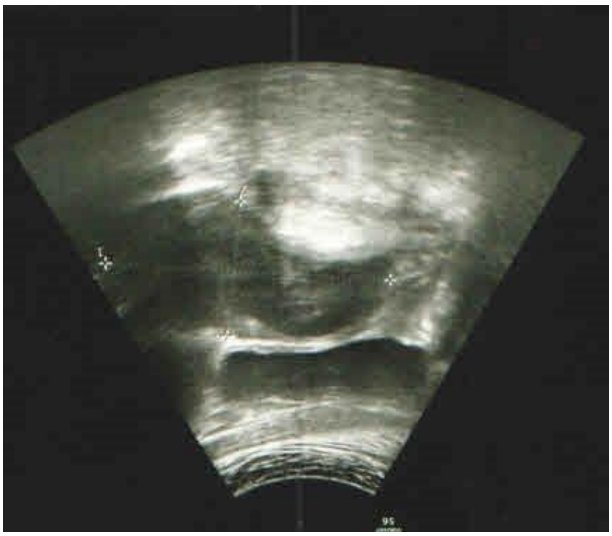

Figure 1 Ultrasound finding of the dilated, hemiobstructed vagina with fluid collection 10×4 cm (pyohematocolpos)

Slika 1. Ultrazvučni prikaz dilatirane, djelomično opstruirane vagine s nakupinom tekućine 10×4 cm (piohematokolpos)

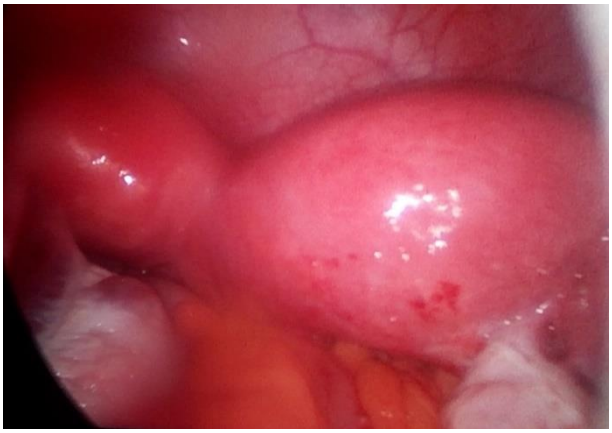

Figure 2. Intraoperativelly laparoendoscopic finding: left normal uterus, right large uterus (pyohematometra)

Slika 2 Intraoperativni laparoendoskopski nalaz: lijevo normalan uterus, a desno povećan uterus (piohematometra)

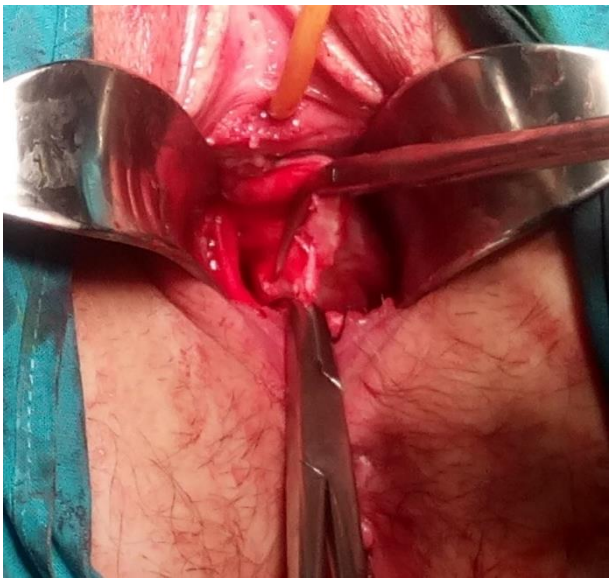

Figure 3 Intraoperative finding of the incised and resected vaginal septum
Slika 3. Intraoperativni prikaz incidiranog i reseciranog vaginalnog septuma

Discussion

HWWS is a rare complex congenital anomaly of the urogenital tract that involves abnormal development of the Mullerian and mesonephric ducts in female embryos. It is also known as the OHVIRA syndrome (Obstructed hemivagina and ipsilateral renal agenesis). The syndrome falls under type III Mullerian duct anomaly classification system of the American Society for Reproductive Medicine. In HWWS there is an insult to the paramesonephric system and metanephros. The uterus, fallopian tube, cervix, and upper two-thirds of the vagina develop from the paired paramesonepric ducts. The duct arises from the urogenital ridge. Then, caudally, it runs lateral to the mesonephric duct, and finally, in the midline, it comes in close contact with the upper part of the vagina.[8] When they fail to fuse, they produce two hemiuteri and hemicervicis, resulting in mulerian anomalies associated with HWWS.[9] An insult to the metanephric diverticulum results in ipsilateral agenesis of the ureter and kidney.[10] The simultaneous insult to the paramesonephric system and metanephros could suggest a multifactorial origin. Renal agenesis related genes such as CHD1L, TRIM32, RET and WNT 4 may be associated with HWWS.[11] Other anomalies include horseshoe kidney, pelvic kidney, renal dysplasia, duplication of the kidneys and ureters, ectopic ureter, high-riding aortic bifurcation, IVC duplication, intestinal malrotation and ovarian malposition.[12] Rarely, adenocarcinoma of the obstructed side of the uterine cervix and clear cell carcinoma of the obstructed portion of the vagina are also noted.[13,14] According to the proposed classification system based on a review of 79 patients[15], HWWS is categorized as: Classification 1 – a completely obstructed hemivagina (1.1-with blind hemivagina; 1.2-cervicovaginal atresia without communicating uteri) and Classification 2-an incompletely obstructed hemivagina (2.1-partial resorption of the vaginal septum; 2.2-with communicating uteri). A right-sided prevalence has been described.[16] Our case falls under classification 2.1.(Figure 4).

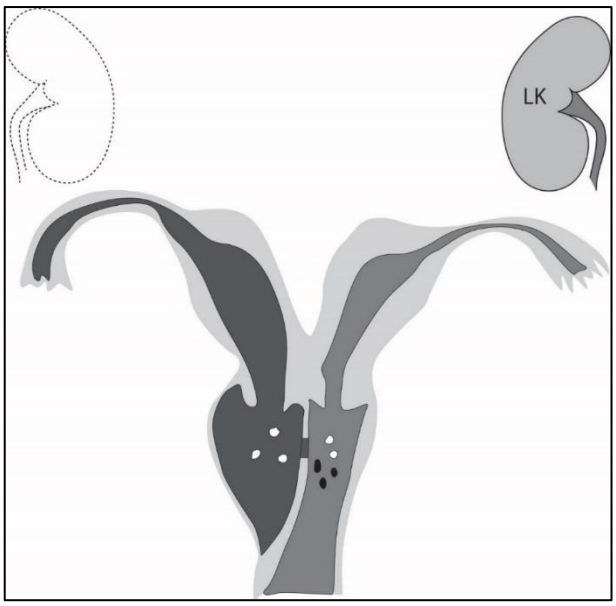

Figure 4 Diagrammatic representation of OHVIRA. On the right side pyohematometra, pyohematocolpos, incompletely obstructed hemivagina and renal agenesis are clearly visible.
Slika 4. Shematski prikaz OHVIRA-e. Na desnoj strani se jasno vide piohematometra, piohematokolpos, djelomično opstruirana hemivagina i renalna ageneza.

Classically, a patient with HWWS can present with severe dysmenorrhea a few months to 1 year after attaining menarche.[17] Other patients can present with a pelvic or vaginal mass secondary to hematocolpos, abnormal vaginal discharge, acute retention of urine, infertility, complicated pregnancy and labor or endometriosis. Usually, HWWS remains undiagnosed and asymptomatic during early childhood with normal external genitalia. Compared to patients with incomplete obstruction, patients with completely obstructed hemivagina are diagnosed earlier (often soon after menarche) and more likely present with symptoms of abdominal pain, fever and emesis than with mucopurulent vaginal discharge common in patients with incomplete obstruction. Pyocolpos can occur in patients with HWWS due to

secondary infection of retained menstrual blood in the obstructed hemivagina. The two vaginal cavities can communicate through partially fenestrated septum, or the two cervicies can communicate through fistula.[18] Additionaly, women with complete obstruction are more susceptible to complications such as hematometra, hematosalpinx, hemoperitoneum and even pelveoperitonitis, as obstruction causes retention of the menstrual flow in the internal female genitalia.[19] Another uncommon presentation is urinary retention which occurs because the mass of hematocolpos is quite large. At that size, it causes urethra angulation which leads to an obstruction.[20] In the absence of treatment, the natural course of the disease also includes complications such as endometriosis and pelvic adhesions.[21] The fertility of patients with HWWS with early diagnosis and treatment is usually not impaired.[22] Some authors mentioned that in 87% of HWWS cases pregnancy could be achieved and 62% of them had delivery at term.[23] However, premature labour in patients with HWWS occurs more commonly compared than in the general population, although the prevalence of misscarriages does not differ.[24] Approximately 84% of pregnancies require caesarean section. The most common indication is breech presentation, which is reported in 51% of cases.[22] Fetal growth restriction is a possible complication that can increase the rate of caesarean section.[22] Clinical suspicion and awareness of the syndrome are imperative to make a timely diagnosis and prevent complications. Ultrasound and MRI are the most widely used diagnostic tools.[24-26] It is reported to note that CT imaging is not recommended for syndrome diagnosis as it less accurate and subjects the patient to ionizing radiation.[26] Ultrasound examination is an inexpensive and convenient method of screening for HWWS. Sonographic features include uterine anomalies (didelphis/bicornuate uterus), hematometra, hematocolpos, pelvic fluid collection (often hemoperitoneum), and ipsilateral renal agenesis with compensatory hypertrophy of the contralateral kidney.[27] MRI is considered to be more sensitive for imaging soft-tissue anatomy and delineating subtle findings seen in congenital anomalies. MRI is the imaging modality of choice for the diagnosis and classification of HWWS as it provides details about uterine morphology, including contour and intrauterine cavity shape and continuity with each vaginal lumen, and nature of the fluids in these cavities. Evaluation of the genital tract using MRI scanning is recommended in all girls with known renal abnormalities detected antenatally or after that, before the onset of menstruation. This enables us to diagnose some patients before menarche and carry out a surgical correction of the obstruction before any damage has occured because of hematocolpos, hematometra and retrograde menstruation.[27-29] It can also identify associated pathologies such as endometriosis, pelvic inflammation and adhesions, as well as renal abnormalities. Laparoscopy is not mandatory but could help confirm the diagnosis when radiologic imaging is inconclusive.[1] Resection of the vaginal septum is the treatment of choice for obstructed hemivagina. Candiani and coauthors have suggested marsupializing the vaginal margins after excision of the septum to allow ample drainage of the purulent material and better expose the cervix.[30] Smith and Laufer reported of 27 cases, there were six cases underwent two-stages vaginoplasty due to anatomical distortion, infection and stenosis.[1] Rarely, unilateral hysterectomy may be considered in case of reccurent stenosis.[31] Surgery is important to relieve the obstruction, alleviate symptoms and prevent complications of retrograde flow. Some authors prefer a hysteroscopic incision. The advantages of the last method include, among others, avoiding the risk of the use of general anesthesia in an operating room setting and the possibility of performing in the office. Boyraz and coauthors performed laparoscopic resection of the vaginal septum to preserve virginity.[32] Regular gynecological control is important in postoperative management, aimed at assessing the patency of the residual vagina. In some cases, it is necessary to expand the formed passage to avoid its secondary closure.

Prompt and accurate diagnosis of female reproductive tract disorders, including HWWS, is necessary to prevent complications and preserve future fertility. Early recognition of this relatively rare syndrome would lead to the immediate, proper surgical intervention. A multidisciplinary approach guided by a gynecologist, radiologist, pediatric specialist and pediatric surgeon is fundamental to avoid complications and achieve a better outcome.

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Lipid profile of postmenopausal women

Lipidni profil kod žena u u postmenopauzi

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Summary

Objectives: The main objectives of the research are to examine the incidence of hyperlipoproteinemia in postmenopausal women and to determine the differences in lipid profile considering age, duration of menopause and body mass index in postmenopausal women.

Respondents and methods: The research is structured as cross-sectional with historical data. The research used data collected during regular check-ups in primary health care clinics in Osijek Health Center from November 2021 to March 2022. Collected data: demographic data, information on the duration of menopause, body mass, body height, body mass index, values of total, LDL, HDL cholesterol and triglycerides, and data on associated diseases.

Results: 98 postmenopausal women were included in the research, of which over 50% had elevated total and LDL cholesterol values, and 39.8% had elevated triglyceride values. Subjects aged 45 to 65 years and subjects with a duration of menopause of 10 or more years had significantly higher values of total and LDL cholesterol while no difference was observed in the lipid profile with regard to the body mass index. Using the SCORE2 table, it was estimated that 65% of the subjects had a very high cardiovascular risk, and only 6% of the subjects achieved the target values of LDL cholesterol in accordance with the cardiovascular risk.

Conclusion: There is a very high incidence of hyperlipoproteinemia in postmenopausal women, and the age and duration of menopause have an impact on the poorer achievement of the target values of the lipid profile, while the body mass index showed no impact. Given the high prevalence of subjects with a very high cardiovascular risk (SCORE 2 tables), intensive interventions are needed at all levels of health care, especially at the primary level of health care, which include non-pharmacological and pharmacological methods of treating hyperlipoproteinemia.

Key words: cardiovascular diseases; hyperlipoproteinemia; HMG-CoA reductase inhibitors; postmenopause

Sažetak

Cilj istraživanja: Osnovni ciljevi istraživanja jesu ispitati incidenciju hiperlipoproteinemije u žena u postmenopauzi i utvrditi razlike u sastavnicama lipidnog profila obzirom na dob, trajanje menopauze i indeks tjelesne mase.

Ispitanici i metode: Istraživanje je ustrojeno kao presječno s povijesnim podacima. Za istraživanje su se koristili podaci prikupljeni u ambulantama primarne zdravstvene zaštite u Domu zdravlja Osijek, od studenoga 2021. do ožujka 2022. g. a prikupljeni su na redovitim kontrolama. Prikupljeni podaci: demografski podaci, podaci o trajanju menopauze, tjelesna masa, tjelesna visina, indeks tjelesne mase, vrijednosti ukupnog, LDL, HDL kolesterola i triglicerida, te podaci o pridruženim bolestima.

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Rezultati: U istraživanje je uključeno 98 ispitanica od kojih preko 50 % njih ima povišene vrijednosti ukupnog i LDL kolesterola, a 39,8 % povišene vrijednosti triglicerida. Ispitanice starosti 45 do 65 godina i ispitanice s trajanjem menopauze od 10 ili više godina imaju značajno više vrijednosti ukupnog i LDL kolesterola, dok nije uočena razlika u lipidnom profilu obzirom na indeks tjelesne mase. Upotrebom SCORE2 tablice procijenjeno je da 65 % ispitanica ima vrlo visok kardiovaskularni rizik, a samo 6 % ispitanica postiglo je ciljne vrijednosti LDL kolesterola u skladu s kardiovaskularnim rizikom.

Zaključak: Incidencija hiperlipoproteinemije u postmenopauzalnih žena je vrlo visoka, a starija dob i dulje trajanje menopauze povezani su sa slabijim postizanjem ciljnih vrijednosti lipidnog profila, dok indeks tjelesne mase nije pokazao utjecaj. Obzirom na visoku zastupljenost ispitanica s vrlo visokim kardiovaskularnim rizikom (SCORE 2 tablice), potrebne su intenzivne intervencije na svim razinama zdravstvene zaštite, posebice primarnoj razini zdravstvene zaštite, a koje uključuju i nefarmakološke i farmakološke metode liječenja hiperlipoproteinemija.

Ključne riječi: hiperlipoproteinemija; inhibitori HMG-CoA reduktaze; kardiovaskularne bolesti; postmenopauza

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Introduction

Menopause is the last period in a woman's reproductive age and is caused by the gradual loss of ovarian function. Menopause is diagnosed retrogradely (when a woman has not had a period for the past twelve months). The average age of women in the Republic of Croatia is 77 years, and the average age at which menopause occurs is 50 years, which means that women spend almost a third of their life in postmenopause.[1] Postmenopause refers to the period that occurs after the last menstruation, and consists of early postmenopause and late postmenopause (occurs after the age of 70). The postmenopausal period is characterized by numerous hormonal changes that include a decrease in the levels of estradiol, progesterone, androgens and growth hormones, which leads to a multitude of symptoms such as hot flashes, night sweats, difficult sleeping, lack of concentration, decline in sexual function, while late consequences include cardiovascular changes, osteoporosis and dementia.[1,2]

In postmenopause, there are also significant changes in the lipid profile that favor increased atherogenesis, namely an increase in the level of total cholesterol, low-density lipoprotein (LDL) cholesterol and a decrease in the level of high-density lipoprotein (HDL) cholesterol.[1,3] In addition, with the onset of menopause, the ratio of total cholesterol to HDL cholesterol increases, and it is considered a better indicator of cardiovascular diseases than the value of total cholesterol.[3] The effect of estrogen in the regulation of vascular resistance and the regulation of thrombogenesis has been proven; via estrogen α receptors, it stimulates the synthesis of cyclooxygenase 1 (COX-1) and prostacyclin synthase and inhibits the production of prostaglandin H2 and thromboxane A2, which results in vasodilation and antiaggregation effects.[4] In the absence of estrogen, the values of factor VII, fibrinogen and plasminogen activation inhibitor increase, all of which increase the risk of cardiovascular diseases.[1]

The risk increases significantly if the woman is obese (a special risk is obesity of the central type), suffers from diabetes, hypertension or polycystic ovary syndrome.[1] The connection between type II diabetes and hypoestrogenism in postmenopause is multiple. Postmenopause itself, due to estrogen deficiency, is susceptible to disturbances in glycemic homeostasis.[5] An increase in glycosylated hemoglobin was observed in the group of postmenopausal women, but it should be taken into account that aging itself, together with obesity and smoking, is associated with an increased risk of developing type II diabetes.[6] In women with preexisting type II diabetes, global metabolic, oxidative, and inflammatory damage low estrogen levels increases susceptibility to developing postmenopausal complications such as cardiovascular disease (CVD), osteoporosis, and metabolic syndrome.[7,8]

Due to all of the above, it is extremely important to promptly recognize and treat dyslipidemia in postmenopausal women with increased cardiovascular risk. Prevalence of dyslipidemia in premenopausal women is 35%, while in postmenopausal women it is 65.2%. Dyslipidemia is highly correlated with the development of hypertension and diabetes and represents a high risk factor for the occurrence of cardiovascular disease.[9] In a woman aged 50, the probability of developing coronary disease during her lifetime is 46%, and the probability of death from it is 31%. The probability of developing a cerebrovascular insult in the postmenopausal age is 20%, and the probability of death is 8%.[1]

The main therapeutic approach in patients with dyslipidemia, also in postmenopausal women, is to

lower the level of LDL cholesterol, all in order to reduce the risk of developing or progressing cardiovascular disease. For this reason, special target values were set based on the associated cardiovascular risk determined according to the SCORE2 tables.[10] Target values are listed in Table 1.

Table 1 Target values and therapeutic goals for the prevention of cardiovascular diseases
Tablica 1. Ciljne vrijednosti i terapijski ciljevi za prevenciju kardiovaskularnih bolesti

Cardiovascular risk *Kardiovaskularni rizik*	Target values and therapeutic goals *Ciljne vrijednosti i terapijski ciljevi*
Low/*niski*	LDL cholesterol/*LDL kolesterol*< 3.0 mmol/L
Moderate/*umjereni*	LDL cholesterol /*LDL kolesterol*< 2.6 mmol/L
High/*visoki*	LDL cholesterol < 1.8 mmol/L and/or reduction of initial LDL values 50% or more *LDL- kolesterol < 1.8 mmol/L i/ili smanjenje početnih vrijednosti LDL kolesterola za 50 % i više*
Very high/*vrlo visoki*	LDL cholesterol < 1.4 mmol/L and/or reduction of initial LDL values by 50 % or more *LDL- kolesterol < 1.4 mmol/L i/ili smanjenje početnih vrijednosti LDL kolesterola za 50 posto ili više*

Current recommendations are to screen for hyperlipidemia during systematic examinations in all persons with an increased risk of developing hyperlipidemia, all men over 40 years of age and all women over 50 years of age, regardless of the presence of possible comorbidities.[11]

The goals of our research were to examine the frequency of hyperlipoproteinemia in postmenopausal women and to determine differences in the lipid profile in relation to age, duration of postmenopause and body mass index.

Respondents and methods

The research was organized as a cross-sectional study with historical data and was conducted in the Osijek Health Center, in primary health care clinics, in the period from November 2021 to March 2022. The research was approved by the Ethics Committee of the Faculty of Medicine Osijek, J.J. Strossmayer University in Osijek. Data was collected through regular controls from the database "Central Health Information System of the Republic of Croatia" (CEZIH) in primary health care clinics in Osijek Health Center. The collected data is anonymous. Collected data: demographic data, data on duration of postmenopause, body mass, body height, body mass index (BMI), values of total cholesterol, LDL cholesterol, HDL cholesterol, triglyceridesand data on associated comorbidities.

Categorical data are represented by absolute and relative frequencies. Differences in categorical data were tested with Fisher's exact test. The normality of the distribution of continuous variables was tested with the Shapiro - Wilk test. Due to the distribution of continuous variables that do not follow a normal distribution, continuous data are described by the median and interquartile range. Differences in numerical variables between two independent groups were tested with the Mann Whitney U test, and between three or more groups with the Kruskal Wallis test (post hoc Conover). All P values are two-sided. The significance level was set at Alpha = 0.05. For statistical analysis we used the statistical program MedCalc® Statistical Software version 20.026 *(MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022)* and SPSS ver. 23 *(IBM Corp. Released 2015. IBM SPSS, Ver. 23.0. Armonk, NY: IBM Corp.).*

Results

The research was conducted on 98 female subjects with a median age of 68, while the median duration of postmenopause was 17 years. The median body height of the test subjects is 166 cm, and the body weight is 73 kg. The median body mass index in the test subjects is 27.67 kg/m^2.

The largest number of respondents, 43% of them, belong to the age group of 45 to 64 years, while in 57% of respondents, menopause lasts from 10 to 29 years. 24% of the subjects were of normal body weight, as many as 59% were overweight (BMI 25.0 - 29.9 kg/m^2), and 17% were obese. 2% of the subjects had third-degree obesity with a body mass index greater than 40 kg/m^2.

The most common comorbidity is arterial hypertension, which is present in 80.6% of the respondents, while in second place are thyroid diseases and type 2 diabetes (31.6%). 10.2% of the subjects had a diagnosis of atrial fibrillation, and 8.2% had a diagnosis of chronic kidney disease. 12.2% of the subjects had a history of acute myocardial infarction or cerebrovascular incident.The values of the lipid profile are shown in detail in Table 2.

Table 2 Lipid profile of postmenopausal women who participated in the research
Tablica 2. Lipdni profil postmenopauzalnih žena uključenih u istraživanje

	Median (interquartile range) *Medijan (interkvartilni raspon)*	Range (minimum – maximum) *Raspon (minimum – maksimum)*
Total cholesterol (mmol/L) *Ukupni kolesterol (mmol/L)*	5.60 (4.50 – 6.80)	2.70 – 9.60
HDL cholesterol (mmol/L) *HDL-kolesterol (mmol/L)*	1.50 (1.20 – 1.70)	0.70 – 3.40
LDL cholesterol (mmol/L) *LDL-kolesterol (mmol/L)*	3.25 (2.48 – 4.33)	1.20 – 6.40
Triglycerides (mmol/L) *Trigliceridi (mmol/L)*	1.50 (1.10 – 2.10)	0.60 – 6.10

Regarding the lipid status values, it can be observed that more than 50% of the subjects have total cholesterol and LDL cholesterol above the recommended values, while triglyceride values are above the recommended values in 39.8% of the subjects (Table 3). The recommended values used in our study were as follows: total cholesterol < 5 mmol/L, LDL cholesterol < 3 mmol/L, triglycerides < 1.7 mmol/L, HDL cholesterol > 1 mmol/L in men and > 1.5 mmol /L in women.

The values of total cholesterol (Kruskal Wallis test, P = 0.001) and LDL cholesterol (Kruskal Wallis test, P = 0.01) are significantly higher in the group of respondents aged 45 to 64 years, compared to older respondents (Table 4) while no significant differences were found in the lipid profile in relation to the duration of postmenopause and the level of nutrition. Statin therapy is used by 40 (40.8%) women, and considering the type and dose, the most common therapy is atorvastatin in a dose of 20 mg (Table 5). Most of the respondents, 65% of them, have a very high cardiovascular risk, 24% of the respondents have a high cardiovascular risk, and 10% of the respondents have a moderate cardiovascular risk. Target values of LDL cholesterol according to the associated cardiovascular risk were achieved by only 6% of the subjects. Subjects who did not reach the target values are significantly older compared to the subjects who reached the lipid profile target values (Mann Whitney U test, P = 0.01). Also, subjects who did not achieve the target values were significantly longer in postmenopause compared to subjects who achieved the target values (Mann Whitney U test, P = 0.009). No association of body mass index with the achievement of lipid profile target values was found (Table 6).

Table 3 Distribution of the respondents according to the reference values of lipoproteins
Tablica 3. Raspodjela ispitanica prema referentnim vrijednostima lipoproteina

	Number (%) of respondents *Broj (%) ispitanica*	
	Within the recommended values *Unutar preporučenih vrijednosti*	Above the recommended values *Izvan preporučenih vrijednosti*
Total cholesterol (mmol/L) *Ukupni kolesterol (mmol/L)*	34 (34.7)	64 (65.3)
HDL cholesterol (mmol/L) *HDL-kolesterol (mmol/L)*	38 (38.7)	60 (61.2)
LDL cholesterol (mmol/L) *LDL – kolesterol (mmol/L)*	44 (44.9)	54 (55.1)
Triglycerides (mmol/L) *Trigliceridi (mmol/L)*	59 (60.2)	39 (39.8)

Table 4 Lipid profile of postmenopausal women in relation to age groups
Tablica 4. Lipidni profil postmenopauzalnih žena obzirom na dobne skupine

	Median (interquartile range) according to age groups *Medijan (interkvartilni raspon po dobnim skupinama*			*P**
	45 – 64	65 - 79	80 and more *80 i više*	
Total cholesterol (mmol/L) *Ukupni kolesterol (mmol/L)*	6.15 (5.4 – 7.1)	5,0 (4.4 – 6.6)	4.8 (4.2 – 5.5)	**0.001**†
HDL cholesterol (mmol/L) *HDL-kolesterol (mmol/L)*	1,6 (1.3 - 1.9)	1,4 (1.2 – 1.60)	1.4 (1.1 – 1.5)	0.06
LDL cholesterol mmol/L) *LDL-kolesterol (mmol/L)*	3.9 (2.9 – 4.7)	2.8 (2.2 – 4.2)	2.6 (2.2 – 3.4)	**0.01**†
Triglycerides (mmol/L) *Trigliceridi (mmol/L)*	1.6 (1.1 – 2.2)	1.5 (1.1 – 1.8)	1.36 (0.9 – 2.1)	0.28

*Kruskal Wallis test (post hoc Conover); Bold denotes statistical significance/*Podebljano označava statističku značajnost*
†at the P<0.05 level, higher values are significant in the 45-64 age group/*†na razini P<0.05 značajne su više vrijednosti u skupini od 45 – 64 godine*

Table 5 Use of statin therapy in postmenopausal women
Tablica 5. Korištenje statinske terapije u postmenopauzalnih žena

Therapy – dose *Terapija - doza*	Number (%) of respondents *Broj (%) ispitanica*
atorvastatin – 10 mg	4 (4.1)
atorvastatin – 20 mg	13 (13.3)
atorvastatin – 40 mg	8 (8.2)
atorvastatin – 80 mg	1 (1)
rosuvastatin – 10 mg	4 (4,1)
rosuvastatin – 20 mg	8 (8.2)
rosuvastatin – 40 mg	2 (2)
ezetimib - 10 mg	3 (3.1)

Table 6 Differences in age, duration of postmenopause and body mass index in relation to achieving the target values of all components of the lipid profile
Tablica 6. Razlike u dobi, trajanju menopauze i indeksu tjelesne mase u odnosu na postizanje ciljnih vrijednosti svih sastavnica lipidnog profila

	Median (interquartile range) *Prosjek (interkvartalni raspon)*		Difference *Razlika*	95 % confidence interval of the difference *95% interval pouzdanosti razlike*		*P**
	Did not achieved target values *Nisu postigle ciljne vrijednosti*	Achieved target values *Postigle su ciljne vrijednosti*		From/*od*	To/*do*	
Age (years) *Dob (godine)*	69 (61 – 77)	56 (54 – 58)	-10	-19	-3	**0.01**
Postmenopause duration (years) *Trajanje postmenopauze (godine)*	18 (10 – 27)	5 (3 – 6)	-10	-19	-3	**0.009**
Body mass index (kg/m^2) *Indeks tjelesne mase (kg/m^2)*	27.74 (25.2 – 29.1)	26.65 (22.23 – 27.43)	-1.62	-5.46	0.99	0.21

*Mann Whitney U test; Bold denotes statistical significance/*Podebljano označava statističku značajnost*

Considering the present comorbidities, subjects with arterial hypertension achieved significantly less lipid profile target values (Fisher's exact test, P = 0.01), while there is no significant difference in achieving target values compared to other comorbidities.

Discussion

Cardiovascular diseases are the leading cause of death in women and are responsible for 50% of deaths of which 20% are attributed to ischemic heart disease and 15% to cerebrovascular insult. Ischemic heart disease appears on average 7-10 years later in the female population compared to the male population, and this is attributed to the protective effects of estrogen on the progression of atherosclerotic processes.[12] Many studies have shown a significant increase in the prevalence of dyslipidemia associated with a woman's older age; in the third decade of life, the prevalence is 14.9%, and by the age of 60, this percentage rises to 56.4%.[13]

In our research, data was collected on 98 women in the postmenopausal period. The youngest respondent was 46 years old and the oldest 87 years old, therefore the median age is 68 years. The most frequently recorded comorbidity in this study was arterial hypertension, which was recorded in 80.6% of the subjects. Also, subjects with associated arterial hypertension achieved the target values of lipid parameters less. Other recorded comorbidities did not have the same impact. The increased prevalence of hypertension in the perimenopausal and postmenopausal period has been undoubtedly proven, but there are divided opinions about the role of menopause itself in the development of hypertension.[14,15] The increased prevalence of hypertension may be a consequence of the aging process itself and the associated reduced vascular elasticity and atherogenic processes.[16] Some studies suggest that an increased body mass index and the presence of metabolic syndrome contribute to the increased prevalence of hypertension in perimenopausal women more than menopause itself.[15] On the other hand, it is known that the prevalence of hypertension and cardiovascular diseases is significantly lower in premenopausal women compared to the male population of the same age, but this advantage is lost after the age of 45 when morbidity rates from cardiovascular diseases increase faster in the female population.[14,16,17] The next comorbidity in terms of frequency in our patients is thyroid disease, with 31 subjects suffering from it, and the same number suffering from diabetes. Thyroid diseases occur more often in the female population, their incidence is 5-20 times more common in women than in men.Research showed that the incidence of increased TSH in the general female population is 7.6%, while it is 17% in women over 70 years old.[18] Most studies also have found that total cholesterol, triglyceride, low-density and very low-density lipoprotein cholesterol levels are higher in clinical hypothyroidism and lower in clinical hyperthyroidism.[19,20] Changes in the lipid profile have also been extensively reported in subclinical thyroid function, but no consistent conclusion has been reached. Some studies found no significant differences in lipids between patients with subclinical hypothyroidism and those with normal thyroid function.[21]

It was observed that more than half of the subjects had total and LDL cholesterol values above the recommended values, while triglyceride values were above the reference value in 39.8% of the subjects. Our results are supported by earlier studies, and the above is explained by the well-established modulation of the LDL receptor by estrogen, which is lost in menopause. Older age is associated with less achieved target values of lipid profile parameters. In this study, elderly subjects have significantly worse lipid profile values overall. Significantly higher values of total cholesterol and LDL cholesterol were observed in the age group of 45-64 years. Longer duration of postmenopause (10 years and more), in line with older age, is also associated with worse lipid profile values. It is difficult to determine how much influence the menopause has on the proatherogenic lipid profile, and thus on the increased cardiovascular risk, compared to the biological processes of aging, since the two processes mentioned are closely related and dependent on each other.[22] In this study, the body mass index did not show an influence on the achievement of the target values of the lipid profile parameters.

In our study, 40.8% of the subjects used statin therapy, and the most frequently prescribed therapy was atorvastatin in a dose of 20 mg. The given dose of atorvastatin belongs to the category of moderate intensity therapy, which is expected to reduce the value of LDL cholesterol by 30 to 49%.[13] The reduction in the value of LDL cholesterol is proportional to the values before the start of therapy, therefore, when choosing the intensity of statin therapy, the percentage of reduction in the value of serum LDL cholesterol is considered. In a study conducted on 35 postmenopausal women, after 8 weeks of atorvastatin therapy at a dose of 20 mg, the vast majority of subjects achieved LDL target values. The remaining test subjects received an increased dose of atorvastatin of 40 mg in the next 8 weeks, and

they also achieved the target values after a total of 16 weeks of statin treatment.[23]

To assess cardiovascular risk, SCORE (Systemic Coronary Risk Estimation) tables are used, which estimate the ten-year risk of developing the first fatal atherosclerotic event.[24] The latest guidelines published in 2021 by the European Society of Cardiology contain new SCORE2 tables, that estimate the ten-year risk of fatal and non-fatal cardiovascular events. In this study, the SCORE2 table for high-risk countries (Croatia) was used to assess cardiovascular risk. Out of 98 test subjects, 64 of them had an estimated very high risk. According to the estimated cardiovascular risk and the associated values of LDL cholesterol, it was determined that only 6 subjects achieved the target values of LDL cholesterol. A possible explanation for the above results is the short period of time between the publication of the latest guidelines and their implementation in clinical practice.

In one study, estimates of cardiovascular risk in patients with systemic lupus erythematosus obtained using the SCORE2 tables were compared with the previously used SCORE table. According to the SCORE table, 3% of respondents pertain to the high risk category, and 8% of them pertain to the very high risk category. When a new assessment was made according to the SCORE2 table, 29% of the respondents now are in the high risk category and 1% of the respondents are in the very high risk category. In addition to the mentioned differences, further research revealed that even 63% of respondents in the high and 74% of respondents in the very high category according to the SCORE2 table did not have statin therapy. SCORE2 tables change not only the approach to the assessment of cardiovascular risk, but also the target value of LDL cholesterol, which needs to be adjusted to the latest guidelines in accordance with the estimated cardiovascular risk, and thus the indications for the use of pharmacological therapy.[25]

A similar study was conducted in which 1168 patients with rheumatoid arthritis participated. According to the SCORE table, 12% of the respondents belonged to the high risk category, and 8% of the respondents belonged to the very high risk category. According to the re-evaluation (SCORE2 table) 34% of the respondents pertain to the high risk category, and 8% of the respondents pertain to the very high risk category.[26] As both studies showed significant differences between the percentages of subjects in certain categories, it is certainly necessary to emphasize the need to adapt to the latest guidelines and to change the existing therapy in the subjects in order to achieve the target values of LDL cholesterol. Due to estrogen deficiency, postmenopausal women are at an increased risk of developing cardiovascular diseases, which is certainly influenced by increased waist circumference, hypertension, hypertriglyceridemia, hyperglycemia, and reduced HDL cholesterol values, which are often present.[27] In a study conducted on 271 postmenopausal women, it was shown that waist circumference and waist-to-hip ratio exceeded the recommended values in normolipemic and hyperlipemic women. The same study proved the association of genetic polymorphisms with eating habits of postmenopausal women with dyslipidemia. In the aforementioned study, dyslipidemia was proven for the first time in 80% of the subjects.[28] The beneficial effects of moderate physical activity on reducing the progression of atherosclerosis and the stiffness of blood vessels are known. Study also showed that 30 minutes of moderate intensity training on a treadmill over 3 months increased HDL cholesterol values by 30%, decreased LDL cholesterol values by 30% and triglyceride values by 18%. In addition to the above, physical activity in postmenopausal women can help in the development of muscle mass, thereby improving the symptoms of osteoporosis and the overall quality of life.[29]

Conclusion

Based on the conducted research, it can be concluded that postmenopausal women have a high incidence of hyperlipidemia and LDL cholesterol values are significantly higher in the age group between 45 and 64 years. Older test subjects and those whose postmenopause lasts for 10 or more years are less likely to achieve the target values of all components of the lipid profile, while the influence of the body mass index in this case was not observed. Also, subjects with associated arterial hypertension have significantly higher lipid profile values.

Although women generally have a lower cardiovascular risk, due to postmenopausal changes, this risk increases and LDL cholesterol levels may be higher than in men of the same age. That is why it is crucial to control postmenopausal women and their lipid profile, especially if they belong to the category of high and very high cardiovascular risk. It is therefore crucial to adequately assess cardiovascular risk (SCORE2 tables) preventively at all levels of health care and, based on them, to categorize patients into risk groups so that we can recommend and introduce adequate pharmacotherapy and intervene to change lifestyle (diet and physical activity).

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Efekti antiagregacijske i antikoagulacijske terapije trombofilija u trudnoći

The effects of anti-aggregation and anticoagulation therapy for thrombophilia in pregnancy

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Sažetak

Uvod: Trombofilija povećava rizik od ponovnog pobačaja i drugih ozbiljnih opstetričkih komplikacija kao što je preeklampsija, abrupcija posteljice i zastoj u rastu fetusa.

Cilj: istražiti učinkovitost antiagregacijske i antikoagulacijske terapije u odnosu na: pojavu i težinu opstretičkih komplikacija i ishod trudnoće.

Ispitanice i metode: Multicentrična retrospektivno/prospektivna studija. Istraživanje je provedeno u razdoblju 2018-2021. godine na području Zeničko-dobojske županije, Federacija Bosne i Hercegovine. Laboratorijske analize obavljene su u Kantonalnoj bolnici Zenica (Ginekološko-akušerski odjel) i Općoj bolnici Tešanj (Ginekološko-akušerski odjel). U istraživanje je uključeno 180 ispitanica. Formirane su dvije osnovne skupine: radna (skupina ispitanica) i kontrolna skupina. Radnu skupinu činilo je ukupno 120 ispitanica (N=120). Kontrolnu skupinu činilo je ukupno 60 ispitanica (N=60).

Rezultati:Primjena antikoagulacijske terapije u profilaktičkim i terapijskim dozama utjecala je na smanjenje učestalosti i težine komplikacija, pozitivan učinak u postizanju terminske trudnoće, te pozitivan učinak u profilaksi tromboembolijskih bolesti. Primjenom antiagregacijske terapije postignut je pozitivan učinak profilakse tromboze, ali ne i smanjenje broja komplikacija.

Zaključak:Utvrđen je bolji učinak antikoagulacijske u odnosu na antiagregacijsku terapiju u postizanju terminske trudnoće, smanjenja broja komplikacija i tromboze.

Ključne riječi: antiagregacijska i antikoagulacijska terapija, trombofilija, trudnice

Summary

Introduction: Thrombophilia increases the risk of recurrent miscarriage and other serious obstetric complications such as preeclampsia, placental abruption, and fetal growth retardation.

Aim: to investigate the effectiveness of antiplatelet and anticoagulation therapy in relation to: the occurrence and severity of obstetric complications and the outcome of pregnancy.

Respondents and methods: A multicenter retrospective/prospective study. The research was conducted in the period 2018-2021 on the territory of Zenica-Doboj Canton, Federation of BiH. Laboratory analyses were performed at Zenica Cantonal Hospital (Department of Gynecology and Obstetrics) and Tešanj General Hospital (Department of Gynecology and Obstetrics). 180 respondents were included in the study. Two basic groups were formed: Working (group of respondents) and control group. The working group consisted of a total of 120 respondents (N = 120). The control group consisted of a total of 60 respondents (N = 60).

Results: The use of anticoagulant therapy in prophylactic and therapeutic doses had an effect on reducing the frequency and severity of complications, a positive effect in achieving term pregnancy and a positive effect of thromboembolic disease prophylaxis. The application of anti-aggregation therapy

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achieved a positive effect of thrombosis prophylaxis, but not a reduction in the number of complications. The use of anti-aggregation therapy has had a positive effect on the prevention of early pregnancy loss.

Conclusion: A better effect of anticoagulation compared to anti-aggregation therapy was found in achieving term pregnancy, reducing the number of complications and thrombosis.

Key words: anti-aggregation and anticoagulant therapy, thrombophilia, pregnant women

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Uvod

Trombofilija je pojam kojim se opisuje sklonost pojedinca razvoju arterijske ili venske tromboze. Predstavlja urođeni ili stečeni poremećaj hemostatskog sustava koji povećava sposobnost zgrušavanja krvi. Nasljedne trombofilije smatraju se genetski uvjetovanim poremećajima hemostatskih mehanizama koji rezultiraju povećanom sklonošću nastanku tromboza, dok se stečenim podrazumjevaju stanja stečene hiperkoagulabilnosti uzrokovane različitim poremećajima i bolestima.[1]

Klinička i osnovna medicinska istraživanja povezuju nasljednu trombofiliju i negativan ishod trudnoće: preeklampsija, zastoj u rastu fetusa, prijevremeni porod, abrupcija posteljice i mrtvorođenče.[2] Kao posljedica navedenih stanja, povećano je obolijevanje u populaciji žena, te rizik od umiranja tijekom trudnoće i poroda, kao i u puerperiju.[3] Gledamo li daljnji rast i razvoj novorođenčeta, postoji mogućnost pogoršanja postojećeg genetskog kapaciteta novorođenčadi i poticanje razvoja određenih bolesti u odrasloj dobi.[4]

Otkriće tehnike lančane reakcije polimerazom (PCR) dovelo je do veće spoznaje o promjenama na razini gena koje su uzrok poremećaja koagulacijskog sustava. Do sada opisane nasljedne trombofilije su: nedostatak antitrombina III (AT III), nedostatak proteina C (PC), nedostatak proteina S (PS), mutacija gena faktora V Leidena (FVL), mutacija gena protrombina (FII).[2]

Venska tromboembolija važan je uzrok morbiditeta i mortaliteta tijekom trudnoće i purperija. Učestalost se kreće od 0,7–1,0/1000 trudnoća. Pojava trombofilije povećava ovu učestalost pet puta ili više, ako postoji više od jednog uzroka trombofilije. Svi nasljedni uzroci trombofilije značajno su povezani s venskom tromboembolijom. Najjača povezanost i najveći relativni rizik za vensku tromboemboliju prisutan je shomozigotnom mutacijom faktor V Leiden gena i iznosi 34–40. Kod drugih nasljednih uzroka trombofilije, (FII) G20210A i nedostatka antitrombina(AT III), rizik od venske tromboembolije je manji. U žena s kombiniranim mutacijama FVL i PT G20210A rizik je značajno veći nego kod bilo kojeg pojedinačnog defekta.[5] Trudnice s nasljednim uzrokom trombofilije imaju visok relativni rizik za razvoj venske tromboembolije tijekom trudnoće.[6]

Liječenje akutne tromboembolije tijekom trudnoće zahtijeva potpunu antikoagulantnu terapiju koja se obično provodi s nefrakcioniranim heparinom (LMWH). Heparin niske molekulske mase je antikoagulans izbora u trudnoći, zbog svog vrhunskog sigurnosnog profila. Kada je indicirano, farmakološku tromboprofilaksu treba održavati tijekom cijele trudnoće. Nakon porođaja, liječenje treba nastaviti najmanje šest tjedana.[6] Sve komplikacije u trudnoći koje sa sobom nosi trombofilija često su povezane s nedostatnom uteroplacentnom cirkulacijom.[7,8] Prisutnost povećanog otpora kroz umbilikalnu arteriju i venu prisutna je u komplikacijama trudnoće bolesnica s trombofilijom.[8]

Primjena LMWH u trudnica s antifosfolipidnim sindromom potiče invaziju trofoblasta i smanjuje učestalost tromboze, te sprječava komplikacije u trudnoći.[9] Primjena niske doze acetilsalicilne kiseline (ASA) do 16. tjedna gestacije u bolesnica s ultrazvučno otkrivenom lošom placentacijom smanjuje učestalost prijevremenog poroda.[10]

Primjena LMWH smanjuje broj komplikacija u trudnoći kod trudnica s antifosfolipidnim sindromom, te se pokazala sigurnom tijekom trudnoće.[11] Također, utvrđeno je da uporaba LMWH smanjuje komplikacije i povećava stopu živorođene djece za 69-83%.[12] Kada je riječ o stopi živorođene djece kod koje je profilaktički primijenjen LMWH, ona iznosi 78% kod trudnica s mutacijom FV Leiden i 84,4% s mutacijom MTHFR C677T. Primjenom LMWH smanjuje se rizik od krvarenja i stopa prijevremenih poroda.[11,12]

Pri odlučivanju o antikoagulantnoj profilaksi tijekom trudnoće postoje dva stava. Prvi se temelji na nekontroliranim objavljenim studijama koje uspoređuju bolesnice s prethodnim lošim ishodom trudnoće i savjetuju primjenu antikoagulantne terapije tijekom sljedeće trudnoće.[11,13] Drugo stajalište, koje zbog nepostojanja kontroliranih studija ne podupire profilaksu LMWH-om.[14] Primjena LMWH značajno je učinkovitija kao mjera profilakse u sprječavanju naknadnog gubitka trudnoće u usporedbi s primjenom ASA.[15,16]

Randominizirana studija novijeg datuma došla je

do zaključka da u usporedbi sa standardnim nadzorom, uporaba LMWH nije rezultirala višim stopama živorođene djece u žena koje su imale dva ili više prekida trudnoće i potvrđenu nasljednu trombofiliju. Na temelju nalaza ne savjetuje se rutinsku upotrebu LMWH u žena s ponovljenim prekidom trudnoće i potvrđenom nasljednom trombofilijom, kao ni rutinsko testiranje na nasljednu trombofiliju u žena s ponovljenim prekidom trudnoće.[17]

Cilj je istražiti učinkovitost antiagregacijske i antikoagulacijske terapije u odnosu na pojavu i težinu opstetričkih komplikacija, te ishod trudnoće.

Ispitanice i metode

Multicentrična retrospektivna/prospektivna studija. Istraživanje je provedeno u razdoblju 2018.-2021. godine na području Zeničko-dobojske županije, Federacija Bosne i Hercegovine. Laboratorijske analize rađene su u Kantonalnoj bolnici Zenica (Ginekološko-akušerski odjel) i Općoj bolnici Tešanj (Ginekološko-akušerski odjel). U istraživanje je bilo uključeno 180 ispitanica. Formirane su dvije osnovne skupine: radna (skupina ispitanica) i kontrolna skupina. Radnu skupinu činilo je ukupno 120 ispitanica (N=120). Kontrolnu skupinu činilo je ukupno 60 ispitanica (N=60)

Prema težini kliničke slike trombofilije, radna skupina podijeljena je u dvije podskupine: podskupina A (blagi poremećaj) i podskupina B (teški poremećaj). Podskupinu A činilo je ukupno 60 ispitanica (N=60). Te su trudnice imale jedan od sljedećih poremećaja ili kombinaciju ovih poremećaja:

a) nositeljice HETEROZIGOTNE mutacije samo jednog od gena odgovornih za trombofiliju.

Prema terapiji koja im je dodijeljena, dijele se u dvije podskupine:

Podskupinu A1 činilo je ukupno 30 ispitanica (N=30). Ispitanice su primale antiagregacijsku terapiju u dozi od 100 mg acetilsalicilne kiseline (ASA).

Podskupinu A2 činilo je ukupno 30 ispitanica (N=30). Ispitanice su primale antikoagulacijsku terapiju, u profilaktičkoj dozi od 40 mg heparina niske molekulske mase (LMWH).

Podskupinu B činilo je ukupno 60 ispitanica (N= 60). Ispitanice koji su:

A) nositeljice HOMOZIGOTNE mutacije jednog ili više gena odgovornih za trombofiliju

B) nositeljice HETEROZIGOTNIH mutacija na više gena odgovornih za trombofiliju

Istodobno, sve ispitanice podskupine B mogu imati i nedostatak endogenih antikoagulansa proteini S i C i/ili pozitivna antifosfolipidna protutijela.

Podskupinu B1 činilo je ukupno 30 ispitanica (N=30). Ispitanice su primale kombiniranu antiagregacijsku i antikoagulantnu terapiju (ASA) u dozi od 100 mg dnevno i profilaktičku dozu (LMWH) od 40 mg.

Podskupinu B2 činilo je ukupno 30 ispitanica (N=30). Ispitanice su primile antikoagulacijsku terapijsku dozu (LMWH) koja je bila prilagođena za svakog ispitanika prema standardnom terapijskom protokolu. Ova skupina uključuje ispitanice s prethodnim gubitkom trudnoće zbog opstetričkih komplikacija povezanih s trombofilijom: jedan ili više spontanih pobačaja, preeklampsije i eklampsije, intrauterini zastoj u rastu, intrauterina fetalna smrt, kao i ispitanice u prvoj trudnoći.

Kontrolnu skupinu činilo je ukupno 60 ispitanica (N=60). Radilo se o ispitanicama koje su prethodno imale jedan ili više spontanih pobačaja i/ili gubitak trudnoće zbog intrauterinog zastoja u rastu, preeklampsije, eklampsije, abrupcije posteljice, koje nisu primale antikoagulantnu i antiagregacijsku terapiju i kod kojih je naknadno dijagnosticirana trombofilija.

Kontrolnu skupinu činile su dvije podskupine: C1 i C2.

Podskupina C1 ukupno 30 ispitanica (N=30) koje su nositeljice HETEROZIGOTNE mutacije samo jednog od gena odgovornih za trombofiliju.

Podskupina C2, ukupno 30 ispitanica (N=30) koje su nositeljice HOMOZIGOT mutacije jednog ili više gena odgovornih za trombofiliju ili su nositeljice HETEROZIGOT mutacije na više gena odgovornih za trombofiliju.

Statistička obrada podataka

Baza podataka sastavljena je u programu IBM SPSS Statistics v. 21.0 za Windows. Podaci se prikazuju u obliku tablica i grafikona, klasičnim metodama deskriptivne statistike, ovisno o prirodi podataka i mjerilu mjerenja. Za opis uzorka korištene su odgovarajuće metode klasične deskriptivne statistike, ovisno o prirodi podataka: aritmetička sredina (A.S.), standardna devijacija (S.D.), medijan (Med.), interkvartilni raspon (25. postotak i 75. postotak), apsolutne frekvencije (N), relativne frekvencije (%).

Statistička analiza kategorijskih varijabli provedena je pomoću χ^2 testa. Pearsonov koeficijent korelacije korišten je za ispitivanje linearnog odnosa između omjera i ordinalnih karakteristika. Prag statističke značajnosti postavljen je na konvencionalnoj razini α=0,05.

Rezultati

Ispitanice su bile podijeljene u tri dobne skupine. U najmlađoj dobnoj skupini od 20-25 godina istraživanjem je obuhvaćeno 17 ispitanica, od čega 15 u radnoj skupini i dvije u kontrolnoj skupini. U dobnoj skupini od 26-30 godina istraživanjem su obuhvaćene 102 ispitanice, od čega 64 u radnoj i 38 u kontrolnoj skupini. U najstarijoj dobnoj skupini od 31-40 godina u istraživanju je sudjelovala 61 ispitanica, od čega 41 u radnoj, a 20 u kontrolnoj skupini. U omjeru broja ispitanica u dobnoj skupini između ispitivanih skupina (p>0,05) (r=4,273 p=0,118) nije utvrđena statistička značajnost, što ukazuje na homogenost skupina (Tablica 1).

Krvarenje je bilo dominantan simptom kod ispitanica radne i kontrolne skupine. U skupini A krvarenje je imalo 17, u skupini B 34, a u kontrolnoj skupini tri ispitanice. Intrauterini zastoj rasta (IUGR) bio je prisutan u skupini B kod šest, a u kontrolnoj skupini kod sedam ispitanica. EPH gestoze prisutne u skupini B kod jedne, a u kontrolnoj kod sedam ispitanica. Eklampsija je nađena u jedne ispitanice u skupini B i u pet ispitanica u kontrolnoj skupini (Tablica 2).

Tablica 1. Starosna dob ispitanica
Table 1 Age of respondents

Starosna dob ispitanica po skupinama *Age of respondents by group*		Starosna dob *Age*			Ukupno *Total*
		20 - 25 godina/*years*	26 - 30 godina/*years*	31 - 40 godina/*years*	
Skupine *Group*	Skupina ispitanica *Group of respondents*	15	64	41	120
	Kontrolna skupina *Control group*	2	38	20	60
Ukupno/*Total*		17	102	61	180

Tablica 2. Broj ispitanica s trombofilijom i simptomima vezanim za trombofiliju
Table 2 Number of respondents with thrombophilia and thrombophilia-related symptoms

Simptomi *Symptoms*	Ispitanice *Respondents* n= 120			Kontrolna skupina *Control group* n=60
	Grupa A *Group A*	Grupa B *Group B*	Ukupno *Total*	
Krvarenje/*Bleeding*	17	34	**51**	**3**
IUGR	0	6	**6**	**7**
EPH	0	1	**1**	**7**
Eklampsija/*Eclampsia*	0	1	**1**	**5**
Ukupno/*Total*	17	42	**59**	22

Komplikacije prethodne trudnoće predstavljaju vrlo važan parametar za razvoj trombofilije. U prethodnoj trudnoći EPH gestoza je registrirana kod jedne ispitanice (1%) u radnoj skupini, te kod sedam ispitanica (5%) u kontrolnoj skupini. Eklampsija/preeklampsija dijagnosticirana je kod jedne ispitanice (1%) u radnoj skupini i kod pet (3%) ispitanica u kontrolnoj skupini. Ablacija posteljice dijagnosticirana je u dvije ispitanice (1%) u radnoj skupini i u njih pet (3%) u kontrolnoj skupini. IUGR je dijagnosticiran u šest ispitanica (4%) u porođajnoj skupini i u njih sedam (3,9%) u kontrolnoj skupini. Nije utvrđena statistička značajnost u pojavi komplikacija prethodne trudnoće u odnosu na radnu i

kontrolnu skupinu (p>0,05) (Tablica 3).

Rezultati pokazuju analizu pojedinačnih genskih mutacija. Heterozigotne mutacije faktora V nađene su u 0,6% ispitanika u podskupinama B1 i C2. Homozigotne mutacije faktora V nađene su kod 6,1% ispitanica podskupine B1, kod 7,2% ispitanica podskupine B2 i kod 7,8% ispitanica podskupine C1. Heterozigotne mutacije faktora II nađene su u 2,2% ispitanica u podskupinama A1 i B1, u 4,4% ispitanica u podskupini B2 i u 2,8% bolesnica u podskupini C2. Homozigotne mutacije faktora II nađene su u 7,2% ispitanica u podskupinama B1 i B2, te u 6,7% bolesnica u podskupini C2.

Utvrđeno je da učinci terapije ASA na ishod trudnoće, komplikacije i trombozu imaju jaku negativnu korelaciju s ishodom trudnoće, što znači da kontinuirano uzimanje ASA nije povećalo pozitivan ishod trudnoće. Također, utvrđena je jaka pozitivna korelacija između uzimanja ASA i prisutnosti komplikacija, što ukazuje na to da se bez obzira na kontinuitet uzimanja ASA, broj komplikacija povećao. Također je utvrđena niska negativna korelacija u odnosu između uzimanja ASA i pojave tromboze. Primjena ASA nije spriječila pojavu tromboze kod ispitanika (Tablica 4).

Učinci primjene LMWH imaju jaku pozitivnu korelaciju s pozitivnim ishodom trudnoće, jaku negativnu korelaciju s prisutnošću komplikacija, te nisku negativnu korelaciju s pojavom tromboze (Tablica 5).

Primjena kombinirane antikoagulantne i antiagregacijske terapije ima nisku pozitivnu korelaciju s pozitivnim ishodom poroda i pojavom komplikacija, ali ima umjerenu pozitivnu korelaciju s pojavom tromboze (Tablica 6).

Tablica 3. Komplikacije prethodne trudnoće
Table 3 Complications in previous pregnancy

Komplikacije u prethodnoj trudnoći *Complication in previus pregnancy*		Grupe/*Group*					
		Skupina ispitanica *Group of respondents*		Kontrolna skupina *Control group*		Ukupno/*Total*	
		N	%	N	%	N	%
EPH gestoze *Gestosis*	Ne/*No*	89	59	53	35	142	94
	Da/*Yes*	1	1	7	5	8	6
	Ukupno/*Total*	90	60	60	40	150	100.0
Preeklampsija/Eklampsija *Preeclampsia/Eclampsia*	Ne/*No*	89	59	55	37	144	96
	Da/*Yes*	1	1	5	3	6	4
	Ukupno/*Total*	90	60	60	40	150	100.0
Ablacija posteljice *Placental ablation*	Ne/*No*	88	59	55	37	143	96
	Da/*Yes*	2	1	5	3	7	4
	Ukupno/*Total*	90	60	60	40	150	100.0
IUGR	Ne/*No*	84	56	53	35	137	91
	Da/*Yes*	6	4	7	5	13	9
	Ukupno/*Total*	90	60	60	40	150	100,0

Tablica 4. Korelacija antiagregacijske terapije s komplikacijama i ishodom trudnoće
Table 4 Correlation of antiaggregation therapy with complications and outcome of pregnancy

Pearsonov test korelacije *Pearson's correlation test*		Ishod trudnoće *Pregnancy outcome*	Prisustvo komplikacija *The presence of complications*	Tromboza *Thrombosis*
ASA	Korelacija *Correlation*	-0.898**	0.450**	-0.074
	Sig.	0.0001	0.0001	0.422
	N	119	32	119
Ishod trudnoće *Pregnancy outcome*	Korelacija *Correlation*	1	-0.487**	0.087
	Sig.		0.0001	0.283
	N		153	153
Komplikacije *Complications*	Korelacija *Correlation*		1	0.049
	Sig.			0.760
	N			42

*p>0,05

Tablica 5. Korelacija antikoagulacijske terapije s komplikacijama i ishodom trudnoće
Table 5 Correlation of anticoagulation therapy with complications and pregnancy outcome

Pearsonov test korelacije *Pearson's correlation test*		Ishod trudnoće *Pregnancy outcome*	Prisustvo komplikacija *The presence of complications*	Tromboza *Thrombosis*
LMWH	Korelacija *Correlation*	0.439**	-0.276**	-0.111
	Sig.	0.0001	0.001	0.145
	N	153	179	172
Ishod trudnoće *Pregnancy outcome*	Korelacija *Correlation*	1	0.487**	0.078
	Sig.		0.0001	0.335
	N		153	172
Komplikacije *Complications*	Korelacija *Correlation*		1	0.002
	Sig.			0.978
	N			172

Tablica 6. Korelacija kombinirane terapija s komplikacijama i ishodom trudnoće
Table 6 Correlation of combined therapy with complications and pregnancy outcome

Pearsonov test korelacije *Pearson's correlation test*		Ishod trudnoće *Pregnancy outcome*	Prisustvo komplikacija *The presence of complications*	Tromboza *Thrombosis*
Kombinirana terapija *Combined therapy*	Korelacija/*Correlation*	0.142	0.345	0.230*
	Sig.	0.122	0.053	0.012
	N	119	32	119
Ishod trudnoće *Pregnancy outcome*	Korelacija/*Correlation*	1	0.732**	0.087
	Sig.		0.0001	0.283
	N		42	153
Komplikacije *Complications*	Korelacija/*Correlation*		1	0.049
	Sig.			0.760
	N			42

Rasprava

Rezultati studije pokazali su da je 94% ispitanica i bolesnica kontrolne skupine koje su imale neku od komplikacija vezanih uz trombofiliju imalo potvrđenu mutaciju gena ili manjak prokoagulacijskih čimbenika, što korelira s podacima koje nalazimo u literaturi.

Heterozigotne mutacije faktora V nađene su u 0,6% ispitanica u podskupinama B1 i C2. Homozigotne mutacije faktora V nađene su kod 6,1% ispitanica podskupine B1, kod 7,2% ispitanica podskupine B2 i kod 7,8% ispitanica podskupine C1. Slične podatke nalazimo i u literaturi, odnosno rezultatima drugih autora.[18] Prevalencija heterozigotnog faktora V Leidena je 5-8% europske populacije i povećava rizik od tromboze 4 do 8 puta, dok se homozigotna mutacija nalazi u 1% nositelja mutacije i povećava rizik od tromboze 40 do 80 puta.[19] Tri retrospektivne kohortne studije pokazale su da žene koje nose faktor V Leiden imaju dvostruko veći rizik od gubitka trudnoće[20-22], dok nositeljice homozigotne mutacije imaju dvostruko veći rizik od gubitka trudnoće od heterozigotnih nositeljica.[18] Oko 40% žena koje imaju vensku tromboemboliju u trudnoći većinom su heterozigoti za G1691A mutaciju faktora V Leiden gena.[23] Mutacija gena za protrombin G20210A druga je najčešća nasljedna trombofilija, a rezultira povišenom koncentracijom protrombina u serumu: za 30% u heterozigotnih i 70% u homozigotnih kliconoša.[19] Prevalencija mutacije je 1-3% u općoj populaciji[19] i nosi trostruko do osmerostruko veći rizik od venske tromboze u heterozigotnih nositelja i 18 do 80 puta veći rizik u homozigotnih nositelja.[24] Mutacija gena za protrombin nađena je u 17% žena s dubokom venskom trombozom tijekom trudnoće[25] i u 4-9% žena s ponovljenim pobačajima.[18] Podaci iz nekoliko studija pokazuju povezanost između mutacije G20210A gena za protrombin i ponovljenih pobačaja, kao i preeklampsije i duboke venske tromboze.[26]

Podaci o utjecaju ove trombofilije na ishod trudnoće i komplikacije u trudnoći pokazuju da nedostatak antitrombina povećava rizik od fetalne smrti, ali nisu čvrsti i konzistentni. Također postoji malo podataka o povezanosti s preeklampsijom, zastojem u rastu fetusa i abrupcijom posteljice s obzirom na nisku prevalenciju ove trombofilije.[19]

Utvrđena je jaka negativna korelacija između primjene ASA i ishoda trudnoće, što znači da ASA ne daje pozitivan terapijski učinak, jer njegova primjena nije povećala broj pozitivnih ishoda trudnoće. Ovi podaci do kojih smo došli istraživanjem temelje se na istraživanju provedenom na malom uzorku koje je dovelo do sličnog zaključka.[27]

Utvrđena je jaka pozitivna korelacija između primjene ASA i prisutnosti komplikacija, što znači da je u skupini u kojoj je terapijski korišten aspirin došlo do većeg broja komplikacija, a podaci koreliraju s literaturnim navodom. Utvrđena je umjereno negativna korelacija između terapijske primjene ASA i pojave tromboze, što znači da terapijska primjena ASA dovodi do manjeg broja tromboza. Podaci također koreliraju s literaturom.[27]

Utvrđena je jaka pozitivna korelacija između terapijske primjene LMWH i ishoda trudnoće, što

znači da terapijska primjena LMWH utječe na pozitivan ishod trudnoće.

Utvrđena je jaka negativna korelacija između terapijske primjene LMWH i pojave komplikacija, što znači da je u skupini u kojoj je terapijski korišten LMWH broj komplikacija bio manji. Ovi podaci koreliraju s nekoliko nedavnih studija provedenih diljem svijeta.[11,12,28]

Utvrđena je slaba negativna korelacija između terapijske primjene LMWH i pojave tromboze, što znači da njegova terapijska primjena dovodi do rjeđeg pojavljivanja tromboze. Podaci također koreliraju s podacima iz literature.[11,12]

Na temelju naših rezultata primjena terapijskih doza antikoagulacijske terapije smanjuje učestalost i težinu opstetričkih komplikacija trombofilije.

Nađena je umjerena pozitivna korelacija u odnosu terapijske primjene kombinirane terapije i ishoda trudnoće, što znači da primjena kombinirane terapije povećava pozitivan ishod trudnoće. Utvrđena je umjerena korelacija u odnosu između primjene kombinirane terapije i komplikacija, što znači da primjena kombinirane terapije umjereno povećava pojavu komplikacija. Utvrđena je jaka korelacija između primjene kombinirane terapije i tromboze, što znači da primjena kombinirane terapije kod ispitanika ne smanjuje trombozu.

U podskupini u kojoj je u terapijske svrhe korištena ASA, postignut je pozitivan učinak smanjenja tromboze, a u podskupini u kojoj je u terapijske svrhe davan LMWH, postignut je pozitivan učinak u smanjenju komplikacija i tromboze. Kombinirana terapija koja se daje u podskupini daje pozitivne učinke na smanjenje komplikacija i tromboze, uz značajnu vrijednost LMWH u odnosu na ASA.

Meta-analiza, koja je uključivala šest ispitivanja, nije bila posebno ograničena na žene s trombofilijom, već je također uključivala trudnice koje su imale komplikacije u trudnoći uključujući preeklampsiju, abrupciju posteljice, nisku težinu fetusa za gestacijsku dob, gubitak trudnoće u drugom i trećem tromjesečju. U ovoj studiji zabilježeno je značajno smanjenje nepovoljnih ishoda trudnoće u žena koje su primale terapiju (18,7% u skupini LMWH, naspram 42,9% u kontrolnoj skupini - smanjenje relativnog rizika 0,52; 95% CI 0,32-0,86). Ovo pokazuje potencijal LMWH u smislu dobrobiti za žene s prethodnim komplikacijama u trudnoć i zbog insuficijencije placente, ali zahtijeva podršku visokokvalitetnih multicentričnih studija.[29]

Dobrobiti primjene terapije utvrđene su istraživanjem provedenim 2004. godine.[11] Gubitak više od dvije trudnoće definira se kao ponavljajući gubitak trudnoće (RPL). Istraživanjem je analizirano 108 bolesnica koje su imale RPL, od kojih je kod njih 98 ASA davana u kombinaciji s LMWH, dok kod bolesnica kod kojih nije pronađen uzrok nije primjenjivana terapija. U bolesnica s trombofilijom uspješnost rađanja žive djece bila je 83%, a broj spontanih pobačaja smanjen je u odnosu na kontrolnu skupinu (13% prema 28%). Preeklampsija je bila značajno češća u bolesnika s trombofilijom (15%). Broj prijevremeno rođene djece bio je statistički značajno veći u skupini bolesnika s trombofilijom u odnosu na kontrolnu skupinu (23%) *vs* (10%), uz statistički značajnu razliku. Kod bolesnica s dokazanom nasljednom trombofilijom prosječno vrijeme poroda bilo je u 35. tjednu gestacije, dok je u kontrolnoj skupini prosječno vrijeme poroda bilo oko 38. tjedna gestacije, sa statistički dokazanom značajnošću. Autori studije zaključuju da u slučaju nasljednih trombofilija, ako su koristile ASA u kombinaciji s LMWH, imaju manji broj spontanih pobačaja i veći broj živorođene djece u trenutnoj trudnoći. Međutim, nema objašnjenja za još uvijek visoku prevalenciju preeklampsije među njihovim ispitanicama.[30] Rezultati istraživanja slični su rezultatima našeg istraživanja. U randomiziranim studijama, kao i opservacijskim studijama, dokazane su određene dobrobiti primjene LMWH u stanju nasljednih trombofilija u trudnoći. Međutim, to je suprotno podacima iz nedavnih randomiziranih ispitivanja. Ispitivanje TIPPS (Thrombophilia in Pregnancy Prophylaxis) Study) proučavalo je žene s trombofilijom i prethodnim komplikcijama trudnoće posredovanim placentom ili VTE u randomiziranoj studiji koja je uključivala 146 žena koje su prije poroda dobile LMWH, kao i 143 žene koje nisu primile navedeni tretman. Postojao je veći udio upotrebe LDA u kontrolnoj skupini (40% naspram 30%). S obzirom na činjenicu da se ranije nije pokazalo da LDA koristi takvim ženama, razlika u korištenju LDA između ove dvije skupine ne bi trebala utjecati na rezultate ispitivanja u smislu potencijalne pristranosti. Ispitivanje nije pokazalo značajno smanjenje nepovoljnih ishoda trudnoće u žena liječenih LMWH. Što se tiče sigurnosti, velika krvarenja nisu se razlikovala između dvije skupine, ali su manja krvarenja bila češća u skupini LMWH (razlika rizika 10,4%, 95% CI 2,3-18,4; p=0,01), te je ta razlika bila statistički značajna.[31]

Dokazi o prednostima antikoagulantne terapije također su utvrđeni u nekim stečenim oblicima trombofilije, kao što je antifosfolipidni sindrom. U žena s ponovljenim pobačajima zbog sindroma antifosfolipidnih protutijela, rezultati dobro osmišljenog randomiziranog kontroliranog ispitivanja pokazali su apsolutno povećanje postotka živorođene djece s 41% na 72%, pri korištenju

kombinacije niskih doza nefrakcioniranog heparina i aspirina, u usporedbi s primjenom same ASA (32).

Zaključak

Intrauterina fatalna smrt je u pozitivnoj korelaciji s heterozigotnom mutacijom faktora II. Prisutnost mutacija nije negativno utjecala na ishod trudnoće, dok je porast homozigotnih i heterozigotnih mutacija FII povećao broj komplikacija.

Primjena antikoagulantne terapije u profilaktičkim i terapijskim dozama utjecala je na smanjenje učestalosti pojave i težine komplikacija, pozitivan učinak u postizanju terminske trudnoće, te pozitivan učinak u profilaksi tromboembolijskih bolesti. Primjenom antiagregacijske terapije postignut je pozitivan učinak profilakse tromboze, prevencija ranog gubitka trudnoće, ali ne i smanjenje broja komplikacija.

Kombinirana terapija nije imala očekivane pozitivne učinke u smanjenju broja komplikacija, ali je pozitivno djelovala na težinu kliničke slike komplikacija.

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Primary arachnoid cyst – an early postoperative complication after microsurgical resection: a case report and review of literature

Primarna arahnoidna cista – rana postoperativna komplikacija nakon mikrokirurške resekcije: prikaz slučaja i pregled literature

Fahrudin Alić, Hakija Bečulić*

Summary

Arachnoid cysts (AC) are benign, non-neoplastic fluid-filled malformations of the arachnoid tissue. Approximately 50-65% occur in the middle cranial fossa and predominantly on the left side, followed by retrocerebellar and convexity locations. Tremendous development and usage of cross-sectional imaging modalities suggest a higher prevalence of AC than previously thought. Since large arachnoid cysts express mass effect on surrounding neurovascular structures, a surgical approach is preferred to passive observation. Nevertheless, the symptomatology is frequently subjective and difficult to validate, and the causal link between symptoms and an arachnoid cyst is often dubious. Therefore, the operative indication and the best surgical modality for patients with AC remain controversial. Surgical options include open-craniotomy or endoscopic cyst fenestration, cystoperitoneal, cystosubdural, ventriculoperitoneal shunt insertion, or marsupialization via a craniotomy. The complications of these procedures include subdural hematomas, hygromas, hydrocephalus, cerebral edema, postoperative secondary arachnoid cyst, and, more rarely, remote intraparenchymal or subarachnoidal hemorrhage.

Key words: middle fossa arachnoid cyst, microsurgical resection and fenestration, remote site intraparenchymal and subarachnoidal hemorrhage

Sažetak

Arahnoidalne ciste (AC) su benigne, ne-neoplastične malformacije arahnoidnog tkiva ispunjene tekućinom. Otprilike 50-65% ih se javlja u srednjoj lubanjskoj jami i pretežno na lijevoj strani, a potom retrocerebelarnim i konveksnim lokalizacijama. Ogroman razvoj slikovnih pretraga ukazuje na veću prevalenciju AC nego ranije. Budući da velike AC izražavaju kompresivni efekt na okolne neurovaskularne strukture, kirurški pristup poželjniji je od pasivnog promatranja. Ipak, simptomatologija je često subjektivna i teško ju je utvrditi, a uzročna veza između simptoma i AC često je sumnjiva. Stoga indikacija za operaciju i najbolji kirurški modalitet za bolesnike s AC ostaju kontroverzni. Kirurške opcije uključuju otvorenu kraniotomiju ili endoskopsku fenestraciju ciste, cistoperitonealno, cistosubduralno ili ventrikuloperitonealno plasiranje šanta ili marsupijalizaciju putem kraniotomije. Komplikacije ovih zahvata uključuju subduralne hematome, higrome, hidrocefalus, cerebralni edem, postoperativnu sekundarnu arahnoidnu cistu i rjeđe udaljena intraparenhimalna ili subarahnoidalna krvarenja.

Ključne riječi: arahnoidna cista srednje jame, mikrokirurška resekcija i fenestracija, intraparenhimalno i subarahnoidalno krvarenje na udaljenom mjestu

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Introduction

Arachnoid cysts (AC) are benign congenital malformations first described in 1831. They are formed by the splitting or duplication of the arachnoid membrane allowing a clear fluid, resembling normal cerebrospinal fluid, to fill its space.[1] They can occur also secondary as a complication following trauma, infection, bleeding, or surgical manipulation. In all intracranial space-occupying lesions only 1% fall on them with the prevalence in adults at approximately 1.4% and in children at 2.6%.[2] The clinical presentation of AC is variable from asymptomatic up to nonspecific symptoms such as headache, dizziness, balance impairment, and cognitive or behavioral impairment. The diagnosis is set through cerebrospinal imaging and it reveals a sharply demarcated, non-enhancing, extra-axial cyst, with a density/signal similar to the CSF.[3] Computed tomography (CT) can be helpful, but magnetic resonance imaging (MRI) is the gold standard as a definitive diagnostic tool for the evaluation of AC. It shows homogenous T2-weighted signal hyperintensity within the cyst similar to that of CSF which is also confirmed by the fluid attenuated inversion recovery sequences (FLAIR). Galassi proposed a classification scheme for AC based on their communication with the adjacent cisterns on CT scan into three basic types: type I (small, spindle-shaped; limited to the anterior portion of the middle cranial fossa (MCF); free communication of subarachnoid space); type II (superior extent along Sylvian fissure; displacement of the temporal lobe; slow communication with subarachnoid space); type III (large, fills the whole MCF; displacement of temporal, frontal and parietal lobes, little communication with subarachnoid space (Figure 1).[4]

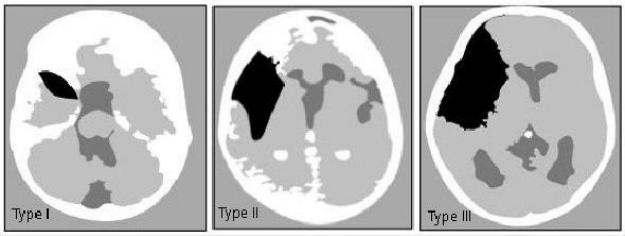

Figure 1 CT classification of Sylvian fissure arachnoid cysts[5]
Slika 1. CT klasifikacija arahnoidnih cisti Silvijeve fisure[5]

Controversy still exists about the best treatment modality for intracranial AC. There are 3 major surgical methods: craniotomy (opening or micro resection) with marsupialization into the subarachnoid spaces, basal cisterns or ventricles; neuro endoscopic fenestration or stereotactic aspiration and shunt surgery (cystoperitoneal, cystosubdural or ventriculoperitoneal).[5] The qualities of each are still a matter of debate. Table 1 shows data from the largest surgical series published in the past 10 years. The complications of these procedures include subdural hematomas, hygromas, hydrocephalus, cerebral edema, postoperative secondary AC**,** and more rarely intraparenchymal or subarachnoidal hemorrhage.[6]

We report large, unilateral MCF AC (Gallasi score III) linked with mild undefined symptoms and treated surgically via micro resection and fenestration of cyst walls followed by remote intraparenchymal and subarachnoid hemorrhage as an initial early postoperative complication.

Table 1 Largest surgical series in the past ten years with results of retrospective studies
Tablica 1. Najveće kirurške serije u posljednjih deset godina s rezultatima retrospektivnih studija

Largest surgical series *Najveće kirurške serije*	No pts *Broj bol*	OSG	EG	SG	OSG +SG
Different Surgical Options for the Management of Intracranial Arachnoid Cysts: retrospective study (2011-2019) *Različite kirurške opcije za liječenje intrakranijalnih arahnoidnih cista: retrospektivna studija (2011.-2019.)* Kayhan, Sait, and Adem Doğan (2022)	44	34		2	8
Results of surgical treatment in patients with intracranial arachnoidal cysts: retrospective study (2015-2019), single center experience *Rezultati kirurškog liječenja bolesnika s intrakranijalnim arahnoidnim cistama: retrospektivna studija (2015.-2019.), iskustvo jednog centra* Masoudi, Mohammadsadegh, Omid Yousefi, and Pouria Azami (2021)	29	26	2	1	
Experience with Management of Intracranial Arachnoid Cysts: retrospective observational study (2004-2020)	56	10	35	11	

Largest surgical series *Najveće kirurške serije*	No pts *Broj bol*	OSG	EG	SG	OSG +SG
Iskustvo s liječenjem intrakranijalnih arahnoidnih cista: retrospektivna opservacijska studija (2004.-2020.) Deopujari, Chandrashekhar E., et al. (2021)					
Surgical management of brain arachnoid cysts: retrospective study (2014-2019) *Kirurško liječenje arahnoidnih cista mozga: retrospektivna studija (2014.-2019.)* Aljubour, Raed M., et al. (2022)	65	18	23	24	
Comparison of Surgical Techniques for Intracranial Arachnoid Cysts: A Volumetric Analysis (2010-2020) *Usporedba kirurških tehnika za intrakranijalne arahnoidne ciste: volumetrijska analiza (2010.-2020.)* Kirmizigoz, Sahin, et al. (2023)	66	32	17	11	6

No pts- number of patients / *broj bolesnika*, OSG- Open surgical group /*otvorena kirurška grupa*, EG- Endoscopic group/ *endoskopska grupa*, SG- Shunt group / *šant grupa*, OSG+ SG- Open surgical group+ surgical group / *otvorena kirurška grupa + kirurška grupa*

Case report

A 44-year-old female Caucasian presented with a 2-year history of blunt, intermittent headache accompanied by anxiety and impaired verbalization. Several times examined and treated by a family practitioner and neuropsychiatrist with partial alleviation of problems. Since ailments did not pass, she was referred to a neurosurgeon. On admission, she was Glasgow Coma Score 15 with no signs of focal neurological deficit. Laboratory tests had referent values. MRI revealed right Gallasi III stage frontotemporal AC (Figure 2).

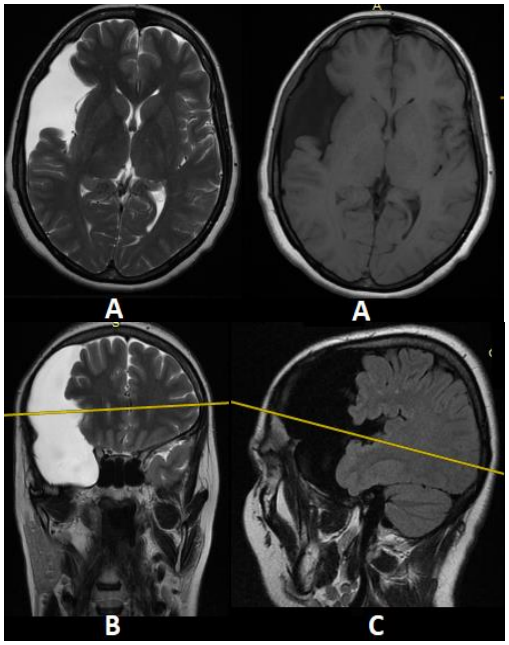

Figure 2 Axial T2, T1(A), coronal T2 (B), and sagittal T1 (C) non-contrast-enhanced magnetic resonance imaging (MRI) indicates a large right frontotemporal arachnoid cyst (Department of Radiology, Zenica Cantonal Hospital, 2020)

Slika 2. Aksijalna T2, T1(A), koronalna T2 (B) i sagitalna T1 (C) sekvenca magnetne rezonance (MRI) bez kontrasta ukazuje na veliku desnu frontotemporalnu arahnoidnu cistu (Odjel za radiologiju, Kantonalna bolnica Zenica, 2020.)

Surgical treatment was considered as one of the modalities of treatment. After a large right-sided open craniotomy and durotomy, cystic wall with a tiny fibrous wall was observed. Initial fenestration of the cyst showed the bright fluid under high pressure. Sylvian and prepontine cisterns were fenestrated after micro resection of the cystic wall in order to establish communication with the subarachnoid spaces in several places. A histopathological specimen showed classical features of delicate cystic structure (Figure 3).

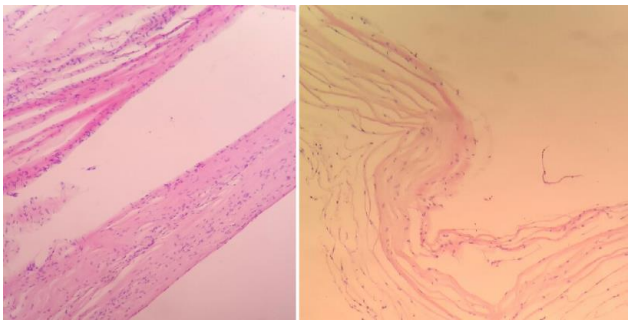

Figure 3 Microphotography of a pathohistological section showing histological features of a delicate cystic structure lined by a flattened or cuboidal epithelium. Cystic wall stained with hematoxylin and eosin (HE), original magnification of × 10 (Department of Pathology, Zenica Cantonal Hospital, 2020)

Slika 3. Mikrofotografija patohistološkog presjeka koji pokazuje histološke karakteristike delikatne cistične strukture obložene spljoštenim ili kockastim epitelom. Cistični zid obojen hematoksilinom i eozinom (HE), originalno uvećanje × 10 (Odjel za patologiju, Kantonalna bolnica Zenica, 2020.)

Due to aggravated awakening during the early postoperative period, urgent head CT imaging was performed, which revealed signs of ex vacuo supra et infratentorial subarachnoid hemorrhage linked with intraparenchymal hemorrhage and 8mm midline shift (Figure 4) after which the patient was retained in the intensive care unit (ICU).

For the next three days, the patient was cardiorespiratory stable under neuro intensivist monitoring. On the 5th postoperative day, the patient gradually woke up, sluggish, with no signs of lateralization, satisfactory respiratory and pupil status and aggravated verbalization. Since the clinical-neurological status was gradually improving and control head CTs were satisfactory, after a few days, the patient was transferred to the parent department and after that, to the regional rehabilitation center for further treatment in a solid physical condition without clear signs of neurological deficit. On a regular control, one year after discharge, the patient's general condition was better, a neurological condition satisfying and radiologically with signs of refilling at the site of the prior cystic cavity (Figure 5).

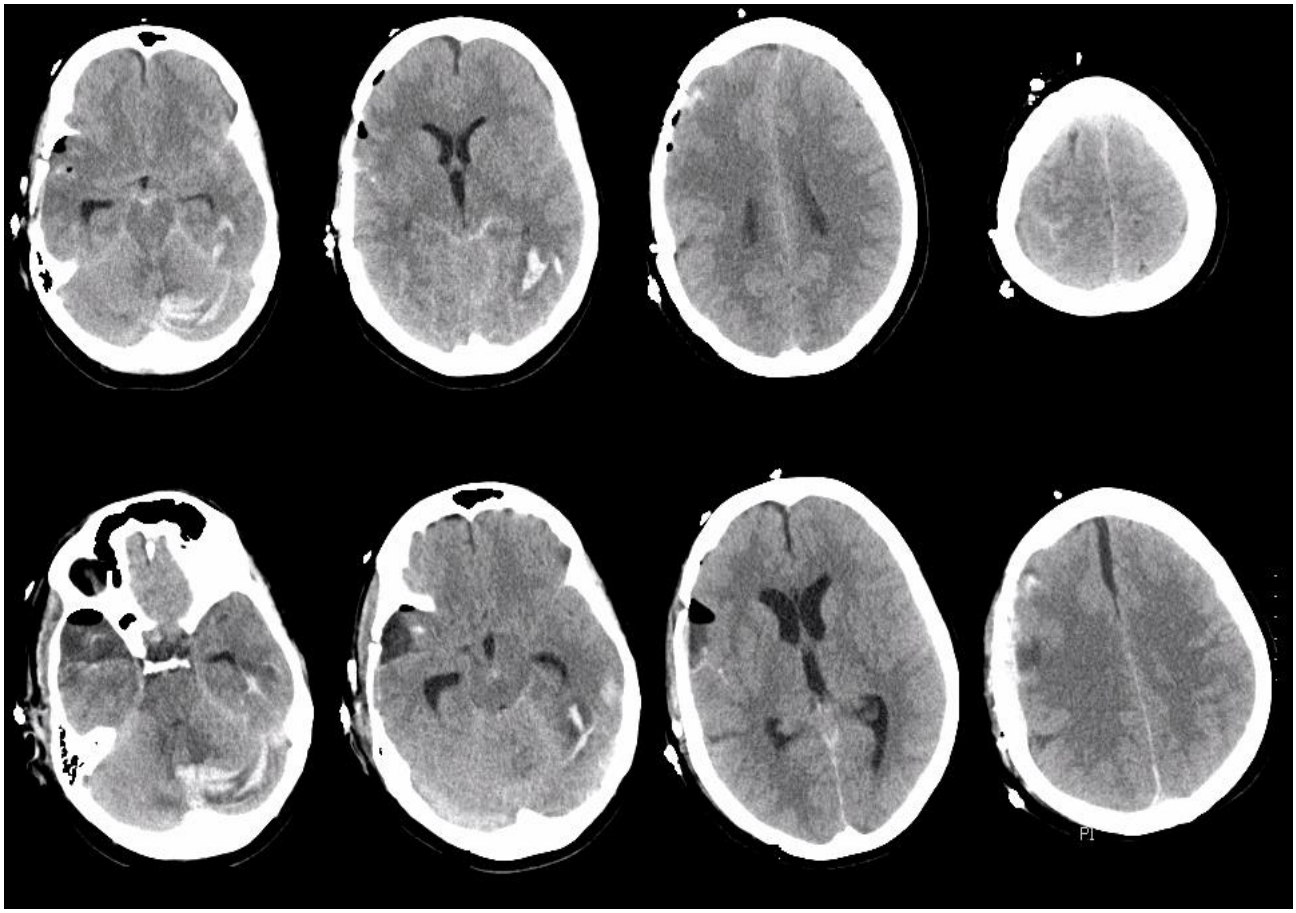

Figure 4 Postoperative axial non-contrast-enhanced computed tomography (CT) shows signs of supra and infratentorial subarachnoidal hemorrhages linked with left temporooccipital intraparenchymal hematoma (Department of Radiology, Clinical Center University of Sarajevo 2020.)

Slika 4. Postoperativna aksijalna kompjuterizovana tomografija (CT) bez kontrasta pokazuje znakove supra i infratentorijalnog subarahnoidalnog krvarenja povezanog sa lijevim temporookcipitalnim intraparenhimalnim hematomom (Odjel za radiologiju, Kantonalna bolnica Zenica, 2020.)

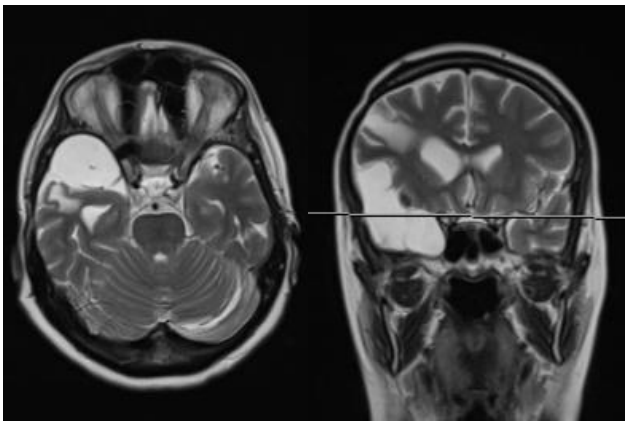

Figure 5 Axial (T2) and coronal (T2) non-contrast-enhanced magnetic resonance imaging (MRI) indicates refilling at the site of the prior cystic cavity one year later (Department of Radiology, Zenica Cantonal Hospital, 2020).
Slika 5. Aksijalna (T2) i koronalna (T2) magnetna rezonanca (MRI) bez kontrasta ukazuje na ponovno punjenje na mjestu prethodne cistične lezije godinu dana kasnije (Odjel za radiologiju, Kantonalna bolnica Zenica, 2020.)

Discussion

Arachnoid cysts are benign, extra parenchymal, intra arachnoidal collections of fluid developed by splitting or duplication of the arachnoidal membrane. They exhibit a male predominance with a 3:1 ratio within the left cerebral hemisphere which did not confirm our case.[7] It can be located anywhere with preponderance in the MCF (50%), usually unilateral and single.[8]

Our case study presents a middle-age female Caucasian with large right-sided MCF AC whose symptoms are thought to be the result of long-term pressure on surrounding brain tissue, changes in CSF dynamics, or dysgenesis of the brain. Two theories describe the pathogenesis of AC. Robinson's theory proposes primary temporal lobe agenesis, while Starkman proposes the AC as the primary abnormality leading to eventual temporal lobe hypoplasia secondary to cyst expansion.[9]

Due to the more widespread use of cross-sectional imaging modalities, the number of newly discovered patients with AC has increased significantly. Morris et al., through a meta–analysis of 16 studies of incidental brain MRI, concluded that AC are the single most prevalent incidental finding, which did not confirm our case.[10]

The lack of evidence-based data has led to considerable controversy regarding the appropriate treatment protocol for AC which mostly remain asymptomatic over time. After all, it is not questionable what to do with small asymptomatic or larger symptomatic arachnoid cysts. The most challenging treatment decision is to treat patients with a medium-sized arachnoid cyst and mild, undefined symptoms when it is unclear whether the symptoms are causally related to the presence of the cyst.

Since our patient had mild, undefined symptoms, we believed that the symptoms were the result of cyst enlargement and consecutive pressure to the brain parenchyma, leading to a combination of symptoms. Controversy still exists about the best treatment modality for intracranial AC mentioned above in the introduction. Open surgery with complete excision of the cyst membrane seems to be the logical treatment modality by most neurosurgeons, but it is unfortunately rarely performed because of the close anatomical relationship between the membrane and the underlying neural tissue.

A prospective study from Rabiei Katrin et al. concluded that fenestration/resection surgery is controversial in the absence of cerebrospinal fluid-pathway blockage and objective signs of clinical improvement.[11] Another prospective, population-based study from Rabiei Katrin et al. speaks against objectively verifiable improvement following surgical treatment in adults with intracranial AC and that it does not justify surgical treatment.[12]

Despite the results of these studies and as surgical treatment is partly a subjective decision, we decided to perform cyst resection with multiple fenestrations toward cisternal spaces and as a result of the sudden decompression we had signs of ex vacuo remote subarachnoid and intraparenchymal hemorrhage.

The rapid decompression with the craniotomy produces a rapid rise in cerebral perfusion, and changes in the intracranial dynamics with venous hyperemia resulting in consecutive parenchymal hemorrhage distant from the site of operation due to "shift of the brain". This is the explanation for intraparenchymal hemorrhage in the report of Živković N. et al.[13] Bahl Anuj et al. have shown that intraparenchymal hemorrhage in remote areas following the evacuation of a large AC indicates that chronic high cerebral perfusion pressure exists and there is a poor local auto-regulatory response surrounding an AC. It has been postulated that this complication probably represents a reperfusion injury similar to the normal perfusion pressure breakthrough syndrome following surgery for arterio-venous malformations.[14] Published data from the last decade, 2013-2022, revealed only one case of remote intraparenchymal hemorrhage after fenestration of an intracranial arachnoid cyst.[15]

Peter L. et al. confirmed the thesis that if the clinical-neurological status is not convincing, the

resection of the giant AC can lead to a vicious circle without a final solution. They described the enlargement of the ventricles and CT signal changes consistent with periventricular edema.[16]

Conclusion

Our report confirms that, given the potential of serious postoperative complications, surgical treatment should be indicated in a very narrow range of clinically symptomatic patients taking into account the previous medical history, localization, and cyst behavior and the surgeon's familiarity with all possible surgical procedures and potential complications. This statement is particularly convincing if you consider that the cystic lesion returned one year later, which ultimately leaves doubt on the correctness of the assessment and justification of the mentioned treatment.

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Kada je moguće, rad podijeliti na: uvod, bolesnici (materijal) i metode, rezultati, rasprava, zaključak i literatura. U uvodu se navodi svrha rada i razlog provođenja ispitivanja. Poglavlje bolesnici i metode obuhvaća sve važne karakteristike ispitivanja. Nužno je navesti koje je etičko povjerenstvo dalo pristanak za provođenje ispitivanja, te da je ono provedeno u skladu s etičkim načelima Helsinške deklaracije. Treba naznačiti da su ispitanici dali svoj informirani pristanak za sudjelovanje u ispitivanju, kao i priložiti pismeni pristanak pacijenta za objavljivanje njegovih podataka u "Prikazu slučaja". Potrebno je opisati korištene statističke metode kao i statistički program koji je korišten za obradu podataka. Značajnost rezultata potrebno je statistički potkrijepiti. Mjerne jedinice moraju biti izražene prema SI sustavu. Rasprava treba naglasiti nove i važne spoznaje koje proizlaze iz ispitivanja te ih usporediti s rezultatima iz literature. Kratice u tekstu mogu se koristiti tek nakon drugog spominjanja potpune riječi u tekstu. Iznimno je moguće koristiti istaknute riječi u tekstu italic fontom. Potrebno je označiti mjesta na kojima će se tiskati tablice i slike, navodeći u tekstu zagradu – npr. (Tablica 1.). Sve priloge uz tekst rada treba svesti na razuman broj (najviše šest tablica, odnosno slika).

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Čupić V, Čupić N, Dražančić A i sur. Neuropsihološki razvoj nedonoščadi. Liječ Vjesn 1983;105:343-6.

Članak na webu

Liang T, ur. Priručnik za prevenciju i liječenje COVID-19 2020 Dostupno na adresi: https://www.bolnica-zadar.hr/wp-content/uploads/2020/03/Manual-for-Covid19-Patients-from-First-Zhejiang-University4986927707241581013.pdf Datum pristupa: 20.3.2020.

Zajednički autor

The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma glutamyl transferase in blood. Scand J Clin Lab Invest 1967;36:119-25.

Nepoznati autor

Anonymous. Fetal nicotine poisoning. J Amer Med Ass 1938;110:143-45.

Bez autora

Coffee drinking and cancer of the pancreas (editorial). Br Med J 1981;283:628.

Suplement časopisa

Poje G, Kovač Bilić L. Computer assisted endoscopic sinus and skull base surgery. Med Jad 2020;50 (Suppl 1):41.

Novinski članak

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Richter B. Medicinska parazitologija. 3. izd. Zagreb: Liber, 1982;112-3.

Urednik

Zergollern-Čupak Lj, ur. Humana genetika. Zagreb: Jumena, 1983;17-60.

Poglavlje u knjizi

Sunter V, Yigit O, Skitarelić N. Combined Open and Endoscopic Approach to the Paranasal Sinus. In: Cingi C, Bayar Muluk N. Ed. All Around the Nose. Berlin: Springer, 2019;629-633.

Zbornik radova

Alter M. The epidemiology of multiple sclerosis. An overview. In: Hartog Jager WA, Bruyn GM, Heijstee APJ, Ed. Proceedings of the 11th World Congress of Neurology. Amsterdam: Excerpta medica, 1978;330- 50.

Doktorski rad

Šimurina T. Model predviđanja povraćanja nakon opće anestezije pri laparoskopskim ginekološkim zahvatima [doktorski rad]. Medicinski fakultet Sveučilišta u Zagrebu, 2011;98.

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Soter Na Wasserman SJ, Austebn KF. Cold urticarial: release into the circulation of histamine and eosinophil chemostatic factor of anaphylaxis during cold challenge.

N Engl J Med. 1976;194:687-90.

Čupić V, Čupić N, Dražančić A et al. Neuro-psihološki razvoj nedonoščadi. Liječ Vjesn 1983; 105:343-6.

Web article

Daszak P, Olival KJ, Li H. A strategy to prevent future epidemics similar to the 2019-n CoV outbreak. Bioasafety Health 2020 Accessible at the address: http://dx.doi.org/10.1016/j.bsheal.2020.01.003 Date accessed: March 22, 2020

Mutual author

The Committee of Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma glumly transferase in blood. Scand J Clin Lab Invest 1967;36:119-25.

Unknown author

Anonymous. Fetal nicotine poisoning. J Amer Med Ass 1938;110:143-45.

Without author

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Journal Supplement

Poje G, Kovač Bilić L. Computer assisted endoscopic sinus and skull base surgery. Med Jad 2020;50 (Suppl 1):41.

News article

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One book author

Richeter B. Medicinska parazitologija. 3. izd. Zagreb: Liber, 1982;112-3.

Editor

Zergollen-Čupak Lj, ed. Humanica genetica. Zagreb: Jumena, 1983;17-60.

Chapter in the book

Sunter V, Yigit O, Skitarelić N. Combined Open and Endoscopic Approach to the Paranasal Sinus. In. Cingi C, Bayar Muluk N.Ed.All Around the Nose. Berlin: Springer, 2019;629-633.

Proceedings

Alter M. Epidemiology of multiple sclerosis. An overview. In: Hartog Jager Wa, Bruyn GM, Heijstee APJ, Ed. Proceedings of the 11th World Congress of Neurology. Amsterdam: Excerpta medica, 1978;330-50.

Doctoral thesis

Šimurina T. Model predviđanja povraćanja nakon anestezije pri laparoskopskim ginekološkim zahvatima [dotorski rad]. Medicinski fakultet Sveučilišta u Zagrebu, 2011;98.

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