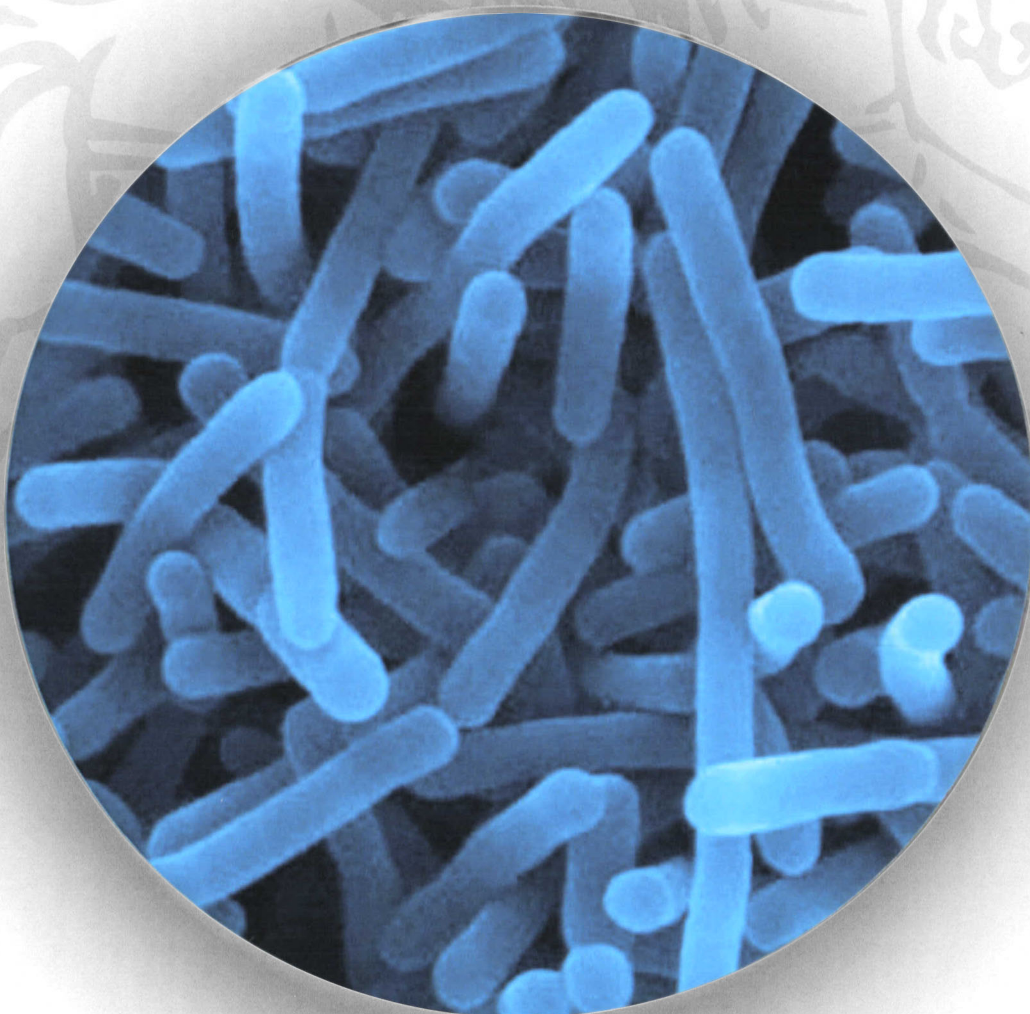
UDK 61(05)=862=20
GOD. 53/2023, 4

ISSN 0351-0093
Coden: MEJAD6

medica jadertina



Med. Jad. God 53. Br. 4 Str. 243-306 Zadar 2023.

Nakladnik
Opća bolnica Zadar

Publisher
Zadar General Hospital

UDK 61(05)=862=20 ISSN 0351-0093

GOD. 53/2023, 4 Coden: MEJAD6

Med. Jad. God 53. Br. 4 Str. 243-306 Zadar 2023.

Nakladnik *Publisher*

Opća bolnica Zadar *Zadar General Hospital*

Nakladnik
Opća bolnica Zadar

Publisher
Zadar General Hospital

Urednički odbor – *Editorial Board*
Ivan Bačić, Željko Čulina, Boris Dželalija, Robert Karlo, Ivo Klarin, Alan Medić, Jakov Mihanović, Jure Pupić-Bakrač, Nataša Skitarelić, Neven Skitarelić, Tatjana Šimurina, Dražen Zekanović

Glavni i odgovorni urednik – *Editor-in-Chief*
NEVEN SKITARELIĆ

Urednik – *Editor*
NEVEN SKITARELIĆ

Tajnik – *Secretary*
ROBERT NEZIROVIĆ

Lektor za hrvatski jezik – *Croatian language proof reading*
ROBERT NEZIROVIĆ

Lektor za engleski jezik – *English language proof reading*
JASMINKA BAJLO

Grafički urednik – *Graphic editor*
PREDRAG JELIČIĆ

Savjet časopisa – *Council of the Journal*
Klaudio Grdović, Mile Gverić, Albino Jović, Mate Kozić, Boris Labar, Petar Lozo, Neven Ljubičić, Želimir Maštrović, Zlatko Matulić, Antun Mazzi, Maja Maržić-Mazzi, Šime Mihatov, Miro Morović, Marko Mustać, Boris Petričić, Mladen Srzentić, Tatjana Vukelić-Baturić

Adresa uredništva – *Address of the Editorial Office*
MEDICA JADERTINA – Opća bolnica Zadar, 23000 Zadar, Bože Peričića 5
Telefon (023) 315-508; 505-270, fax: (023) 312-724, e-mail: opca-bolnica-zadar@zd.t-com.hr

Časopis MEDICA JADERTINA objavljuje uvodnike, izvorne znanstvene i stručne članke, prethodna priopćenja, pregledne članke, prikaze bolesnika, izlaganja sa znanstvenih skupova i druge priloge iz temeljnih i kliničkih medicinskih znanosti.

The journal MEDICA JADERTINA publishes editorials, original scientific and professional articles, earlier announcements, reviewed articles, case reports, presentations from scientific conferences and other enclosures basic and applied medical sciences.

Medica Jadertina izlazi četiri puta godišnje. Godišnja pretplata iznosi 14 €. Broj žiro računa: HR5924020061100879223 kod Erste&Steiermärkische Bank d.d., s naznakom: Za Medica Jadertina i adresom 23000 Zadar, B. Peričića 5, p.p. 291.

Medica Jadertina is published four times a year. The annual subscription is 14 € payable to Erste&Steiermärkische Bank, account number HR5924020061100879223, SWIFT: ESBCHR22 for Medica Jadertina and the address Croatia, 23000 Zadar, B. Peričića 5, p.p. 291.

Medica Jadertina je indeksirana u EMBASE/Excerpta Medica, Scopus, Hrčak – portal hrvatskih znanstvenih i stručnih časopisa. Medica Jadertina član je registracijske agencije Crossref putem sustava za DOI.

Medica Jadertina is indexed in EMBASE/Excerpta Medica, Scopus. Hrčak - portal of Croatian scientific and professional journals. Medica Jadertina is a member of the Crossref registration agency through the DOI system.

Digitalna verzija časopisa ISSN 1848-817X (Online) dostupna je na portalu znanstvenih časopisa Republike Hrvatske: https://hrcak.srce.hr/medica-jadertina

The digital version of the magazine ISSN 1848-817X (Online) *is available at the portal of the scientific papers of Croatia: https://hrcak.srce.hr/medica-jadertina*

Rješenje i priprema korica: NILO KARUC
Priprema: PREDRAG JELIČIĆ
Tisak: FG GRAFIKA, Zadar
Naklada 85 primjeraka
Printed in Croatia

SADRŽAJ
Contents

IZVORNI ZNANSTVENI ČLANCI
Original scientific papers

Vedrana Terkeš, Željko Čulina, Ana Ribarović, Jurica Arapović
ISHOD BOLESTI U COVID-19 BOLESNIKA LIJEČENIH REMDESIVIROM U OPĆOJ BOLNICI ZADAR U RAZDOBLJU OD 1. KOLOVOZA 2020. DO 1.KOLOVOZA 2021. GODINE 247
Disease outcome in COVID-19 patients treated with remdesivir in Zadar General Hospital in the period from August 1, 2020 to August 1, 2021

PREGLEDNI ČLANCI
Review

Mario Ćorić, Mara Tešanović, Luka Matak, Magdalena Matak, Ivana Jurković, Gordan Zlopaša, Mislav Mikuš
PRIMJENA DIODNOG LASERA U HISTEROSKOPIJI: ŠTO TRENUTNO ZNAMO I ŠTO MOŽEMO OČEKIVATI U BUDUĆNOSTI? 251
Use of diode laser in gynecology: what do we alredyy know and what could we expect in the future?

Dražen Shejbal, Tajana Gudlin Sbull, Davor Vagić
BAROTRAUMA OF THE EAR AND PARANASAL SINUSES 257
Barotrauma uha i paranazalnih šupljina

STRUČNI ČLANCI
Professional papers

Tihana Nađ, Nora Pušeljić, Krešimir Šantić, Lea Arambašić, Darjan Kardum
IMPACT OF EARLY CALORIC INTAKE ON GROWTH PARAMETERS IN EXTREMELY PRETERM NEONATES..263
Utjecaj ranog kalorijskog unosa na parametre rasta u izrazito nezrele nedonoščadi

Mirta Peček, Siniša Stevanović, Marijana Peček Vidaković, Andro Košec
UTJECAJ BOLESTI UZROKOVANE KORONAVIRUSOM NA PRIMARNU I TERCIJARNU RAZINU ZDRAVSTVENE ZAŠTITE IZ PERSPEKTIVE OTORINOLARINGOLOGA 271
The impact of coronavirus disease on primary and tertiary healkth care levels from an otorhinolaryngological perspective

Sonja Iža, Ines Ivanković, Marija Crnković Knežević
UČINAK TERAPIJSKOG ULTRAZVUKA KOD SIMPTOMA SINDROMA KARPALNOG TUNELA 279
Effect of therapeutic ultrasound in symptoms of carpal tunnel syndrome

Fatima Juković Bihorac, Anhel Koluh, Emir Begagić
A CASE REPORT OF APPENDICEAL ADENOMA – A RARE ENTITY 285
Prikaz bolesnice s adenomom apendiksa – rijedak entitet

Jakov Ajduk, Mirta Peček, Marija Pierobon, Iva Mažić, Tomislav Gregurić, Andro Košec
MULTIFOCAL METACHRONOUS OCCURENCE OF DIFFERENT HYSTOLOGIC SINONASAL-TYPE PAPILLOMA: A CASE REPORT 289
Multifokalna metakrona pojava različitih histoloških sinonazalnih pailoma: prikaz bolesnice

Filip Miletić, Vladimir Bauer, Andro Košec, Sonja Radić
LONG LASTING ATROPHIC GLOSSITIS DUE TO AUTOIMMUNE ATROPHIC GASTRITIS 293
Atrofični glositis kao prvi znak autoimunog atrofičnog glositisa

UPUTE AUTORIMA 299
Instructions for authors

Izvorni znanstveni rad
Original scientific paper

ISSN 0351-0093
Coden: MEJAD 53 (2023) 4

Ishod bolesti u COVID-19 bolesnika liječenih remdesivirom u Općoj bolnici Zadar u razdoblju od 1. kolovoza 2020. do 1. kolovoza 2021. godine

Disease outcome in COVID-19 patients treated with remdesivir in Zadar General Hospital in the period from August 1, 2020 to August 1, 2021

Vedrana Terkeš, Željko Čulina, Ana Ribarović, Jurica Arapović*

Sažetak

Bolest uzrokovana SARS-CoV-2 (COVID-19) izrazito je zarazna bolest, koja zadnje tri godine ima izuzetno loš utjecaj na svjetsku demografiju, rezultirajući s gotovo 6,5 milijuna umrlih diljem svijeta. U ovom trenutku još uvijek ne postoji učinkoviti ciljani lijek, a liječenje određuje težina bolesti. Terapija remdesivirom pokazala je određeno kliničko poboljšanje, zbog čega ga je *Food and Drug Administration* odobrio kao prvi ispitivani lijek u liječenju COVID-19. Ovo retrospektvno opservacijsko istraživanje uključilo je bolesnike liječene remdesivirom u Općoj bolnici Zadar u razdoblju od 1. kolovoza 2020. do 1. kolovoza 2021. godine. Primarni cilj bio je utvrditi komorbiditete i klinički ishod bolesnika liječenih remdesivirom. Najčešće kronične bolesti bile su arterijska hipertenzija (80; 58,4%), dijabetes (44; 32,1%) i maligne bolesti (14; 10,2%). Ukupno je 86 bolesnika (62,7%) pripadalo skupinama teško i kritično bolesnih, a preostalih 51 (37,2%) bili su umjereno bolesni. Smrtnost je bila značajno veća u skupini teško bolesnih i iznosila je 23,4%, dok je u skupini umjereno bolesnih bila 5, 9% (*p*=0,0287).

Ključne riječi: remdesivir, COVID-19, komorbiditeti, ishod bolesti.

Summary

The disease caused by SARS-CoV-2 (COVID-19) is an extremely contagious disease, which for the last three years has had an extremely bad impact on world demography, resulting in almost 6.5 million deaths worldwide. At the moment, there is still no effective targeted drug, and the treatment is determined by the severity of the disease. Remdesivir therapy has shown some clinical improvement, which is why the Food and Drug Administration approved it as the first investigational drug in the treatment of COVID-19. This retrospective observational study included patients treated with remdesivir at Zadar General Hospital in the period from August 1, 2020 to August 1, 2021. The primary objective was to determine the comorbidities and clinical outcome of patients treated with remdesivir. The most common chronic diseases were arterial hypertension (80; 58.4%), diabetes (44; 32.1%) and malignant diseases (14; 10.2%). A total of 86 patients (62.7%) belonged to the severely and critically ill groups, and the remaining 51 (37.2%) were moderately ill. Mortality was significantly higher in the severely ill group and was 23.4%, while in the moderately ill group it was 5.9% (p=0.0287).

Key words: remdesivir, COVID-19, comorbidities, disease outcome

Med Jad 2023;53(4):247-250

* **Opća bolnica Zadar, Odjel za infektologiju** (Vedrana Terkeš, dr.med.; Ana Ribarović, dr.med.); **Opća bolnica Zadar, Služba za interne bolesti, Odjel za pulmologiju** (Željko Čulina, dr.med.); **Sveučilišna klinička bolnica Mostar, Klinika za infektivne bolesti** (Prof.dr.sc. Jurica Arapović, dr.med.)

Adresa za dopisivanje / *Corresponding address:* Vedrana Terkeš, dr.med. Opća bolnica Zadar, Odjel za infektologiju, Bože Peričića 5, 23 000 Zadar E-mail: vedranafalak@yahoo.com

Primljeno/*Received* 2023-08-03; Ispravljeno/*Revised* 2023-11-02; Prihvaćeno/*Accepted* 2023-11-03

Uvod

Odmah po otkriću koronavirusne bolesti (engl. *SARS-CoV-2* ili COVID 19) koji uzrokuje teški akutni respiratorni sindrom, isti je klasificiran globalnom prijetnjom s pandemijskim potencijalom. Pandemija je postavila velike izazove pred socijalnu kulturu i zdravstvene sustave u cijelom svijetu.[1] Nedostatak zapreka između prirodnog rezervoara i aktivnosti čovjeka, može dovesti do pojave brojnih drugih CoV virusa.[2] SARS-CoV-2 je RNA virus koji pripada rodu beta koronavirusa, a koji se pomoću šiljatih glikoproteina (engl. *spike protein*) veže na angiotenzin-konvertirajući enzim 2 (ACE 2) receptore. Nakon vezivanja virus ulazi u stanicu.[3] Prvi registrirani slučaj bolesti zabilježen je u prosincu 2019. godine u gradu Wuhanu u Kini. Od tada se bolest vrlo brzo proširila po svijetu, rezultirajući time da je 11. ožujka 2020. godine Svjetska zdravstvena organizacija (SZO) proglasila pandemiju.[4] U ovom trenutku još uvijek ne postoji učinkoviti ciljani lijek, a liječenje određuje težina bolesti po aktualnim smjernicama Nacionalnog instituta zdravlja (engl. *National Insitutes of Health*).[5] Uz simptomatsko liječenje, provodi se protuupalno, protuvirusno, te ovisno o potrebi, i antimikrobno liječenje.[5,6] Nukleozidni analog remdesivir pokazao je učinovitost u SARS-CoV-2 na životinjskom modelu, kao i u infekciji koronavirusom koji uzrokuje Bliskoistočni respiratorni sindrom (engl. *Middle East Respiratory Syndrome,* MERS), jer dovodi do prekida sinteze virusne RNA.[7] Remdesivir se koristi u više država, a u većini nacionalnih smjernica preporučuje se i kao lijek izbora u teško i kritično oboljelih.[6]

Bolesnici i metode

Retrospektivno su analizirani podaci 137 bolesnika liječenih antivirusnom terapijom remdesivirom na COVID odjelima Opće bolnice Zadar u razdoblju od 1. kolovoza 2020. do 1. kolovoza 2021. godine. Uključeni bolesnici bili su stariji od 18 godina s potvrđenom SARS-CoV-2 infekcijom putem reverzne transkripcije i lančane reakcije polimeraze. Analizirali su se demografski čimbenici (dob, spol), kronične bolesti, težina bolesti, radiološki nalazi i ishod bolesti. Po klasifikaciji Nacionalnog instituta zdravlja (engl. *National Insitutes of Health,* NIH*)* bolesnike smo podjelili na blaže, umjereno, teško i kritično bolesne.[5] Za sve statističke analize koristili su se *PASW Statistics for Windows* (verzija 18.0 SPSS Inc. Chicago, IL, SAD) i *Microsoft Excel* (verzija *Office 2019, Microsoft Corporation*, Redmont, WA, SAD).

Rezultati

Demografske i kliničke karakteristike bolesnika liječenih remdesivirom prikazane su u Tablici 1. Srednje vrijeme hospitalizacije bilo je 15 dana (raspon; 1-59 dana), a srednja dob bolesnika 65 godina (raspon; 22-94); muški spol 81% bolesnika, bolesnici su bili većinom stariji od 65 godina i to njih 58, 4%. Najčešće kronične bolesti bile su hipertenzija (80; 58, 4%), dijabetes (44; 32,1%) i maligne bolesti (14; 10, 2%). Ukupno 86 (62,7%) bolesnika pripadaju skupinama teško i kritično bolesnih, a preostali dio bolesnika (51; 37,2%) su bili umjereno bolesni. Obostrana upala pluća bila je prisutna u 131 bolesnika (95; 6%).

Tablica 1. Demografska i klinička obilježja 137 hospitalizirana bolesnika liječenih remdesivirom
Table 1 Demographic and clinical characteristics of 137 hospitalized patients treated with remdesivir

Obilježje/*Characteristics*	
Dob: median, (raspon) – godine *Age: median (range) - years*	65 (22-94)
Spol-muški, n (%) *Gender - male*	111 (81)
Kronične bolesti, n (%) *Chronic diseases*	
Hipertenzija/*Hypertension*	80 (58,4)
Dijabetes/*Diabetes*	44 (32,1)
Hipertenzija i diabetes *Hypertension and diabetes*	30 (21,9)
Maligne bolesti *Malignant diseases*	14 (10,2)
Težina bolesti, n (%) *Disease severity*	
Umjerena/*Moderate*	51 (37,2)
Teška/Severe	47 (34,3)
Kritična/*Critical*	39 (28,5)
Radiologija/*Radiology*	
RTG pluća, obostrana upala pluća, n (%) *Lung X-Ray, bilateral pneumonia*	131 (95,6)

Klinički ishodi bolesnika liječenih remdesivirom prikazani su u Tablici 2. Smrtnost je bila značajno veća u skupini teško bolesnih (11/47 bolesnika je umrlo; 23, 4%), nego u skupini umjereno bolesnih (3/51 bolesnika je umrlo; 5,9%, *p*=0,0287).

Tablica 2. Smrtnost u bolesnika liječenih remdesivirom
Table 2 Mortality in patients treated with remdesivir

Karakteristike *Characteristics*	Umrli N (%) *Deceased*	*p*-value
Težina bolest *Disease severity*		
Umjereni/*moderate*	3/51 (5.9)	0.0287*
Teški/*severe*	11/47 (23.4)	
Kritični/*critical*	19/39 (48.7)	0.0003**

* umjereni *vs* teški **umjereni *vs* teški/kritični
** moderate vs severe ** moderate vs severe/critical*

Rasprava

Sadašnje mogućnosti liječenja COVID-19 možemo podijeliti u dvije skupine: antivirusne lijekove i modifikatore imunološkog sustava.[8] Remdesivir je prvi antivirusni lijek odobren u liječnju COVID-19 bolesnika.[9] Početna istraživanja pokazala su visok udio hospitalizacija i smrtnosti, ali uz sadašnje liječenje i cijepljenje, rizici od hospitalizacije, mehaničke ventilacije i smrtnosti značajno su se smanjili.[10] Mortalitet u naših bolesnika je bio 24%, a većina bolesnika pripadala je skupini teško i kritično bolesnih. COVID-19 bolesnici najčešće imaju obostranu upalu pluća(do 76%).[11-13] Većina naših bolesnika, njih 95,6% također je imala obostranu upalu pluća. Postoje kontradiktorna izvješća o dobrobitima remdesivira u COVID-19 bolesnika. S jedne strane, određena randomizirana klinička istraživanja nisu pokazala kliničku korist od primjene remdesivira.[14] Također nedavno, faza 3, randomizirano istraživanje na 857 bolesnika nije pokazalo kliničku korist remdesivira kod bolesnika koji su hospitalizirani unutar sedam dana od pojave simptoma, a bili su respiratorno insuficijentni.[15] Nadalje, solidarno istraživanje SZO koje je kao primarni cilj imalo učinak liječenja na bolničku smrtnost, također je pokazalo da remdesivir nema učinka na ukupnu smrtnost.[16] S druge strane, faza 3, dvostruko slijepo, placebom kontrolirano ispitivanje - *Adaptive COVID-19 Treatment Trial* (ACTT-1) pokazalo je da je remdesivir bio superiorniji od placeba u skraćivanju vremena oporavka u bolesnika koji su bili hospitalizirani s COVID-19, štoviše, ovo je istraživanje pokazalo veću korist remdesivira kada se daje ranije, unutar 10 dana od početka simptoma, nego kod onih koji su liječeni kasnije.[17] Retrospektivna studija Mehta pokazala je smanjeni mortalitet u COVID-19 bolesnika liječenih remdesivirom, ako su lijek dobili untar devet dana od početka simptoma.[18] Jedno je istraživanje pokazalo kraće vrijeme do kliničkog poboljšanja (7, 3 dana) i dobar ishod u više od dvije trećine bolesnika liječenih remdesivirom, ako su liječeni u ranoj fazi COVID-19.[19]

Naše istraživanje ima određene nedostatke jer nije imalo kontrolnu skupinu bolesnika, tako da se nije mogao usporediti ishod bolesnika koji jesu ili nisu liječeni remdesivirom.

Zaključak

Istraživanja i dalje ukazuju na učinkovitost remdesivira i ostalih antivirusnih lijekova, kao i na povezanost remdesivira sa smanjenom smrtnošću u različitim valovima COVID-19, te kraće vrijeme do kliničkog poboljšanja, ukoliko su liječeni u ranoj fazi COVID-19.[20] U liječenju COVID-19 bolesnika, možemo reći da ipak najveću korist od antivirusnog lijeka remdesivira u smanjenju smrtnosti imaju bolesnici koji imaju lakši oblik COVID infekcije, te oni koji su liječeni u ranoj fazi bolesti.

Literatura

1. Majumder J, Minko T. Recent Developments on Therapeutic and Diagnostic Approaches for COVID-19. AAPS J 2021;23:14.
2. de Almeida SMV, Santos Soares JC, Dos Santos KL.et al. COVID-19 therapy: What weapons do we bring into battle? Bioorg Med Chem 2020;28:115757.
3. Matricardi PM, Dal Negro RW, Nisini R. The first, holistic immunological model of COVID-19: Implications for prevention, diagnosis, and public health measures. Pediatric Allergy Immunol 2020;31::454-470.
4. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19). 2022 May 4. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.
5. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed.Datum pristupa. 19.1.2022.
6. Nicola M, O'Neill N, Sohrabi C, Khan M, Agha M, Agha R. Evidence based management guideline for the COVID-19 pandemic - Review article. Int J Surg 2020;77:206-216.
7. Brown AJ, Won JJ, Graham RL. et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. Antiviral Res 2019;169:104541.
8. Lamontagne F, Agarwal A, Rochwerg B. et al. A living WHO guideline on drugs for covid-19. BMJ. 2020;370:m3379.
9. Robinson J. Everything you need to know about the... - Google znalac [Internet]. Available from: https://scholar.google.com/scholar?q=Robinson+J.+E

verything+you+need+to+know+about+the+COVID-19+therapy+trials.+Pharm+J.++2020+.+DOI:+10.1211/PJ.2021.20208126+Datum pristupa:30.1.2023.
10. CDC. Centers for Disease Control and Prevention. 2020 Coronavirus Disease 2019 (COVID-19). Available from: https://www.cdc.gov/coronavirus/2019-ncov/index.html Datum pristupa: 27.1.2023.
11. Wong HYF, Lam HYS, Fong AHT. et al. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. Radiology 2020;296:E72–E78.
12. Vancheri SG, Savietto G, Ballati F. et al. Radiographic findings in 240 patients with COVID-19 pneumonia: time-dependence after the onset of symptoms. Eur Radiol 2020;30:6161–69.
13. Sadiq Z, Rana S, Mahfoud Z, Raoof A. Systematic review and meta-analysis of chest radiograph (CXR) findings in COVID-19. Clin Imaging 2021;80:229–38.
14. Wang Y, Zhang D, Du G.et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569-1578. doi: 10.1016/S0140-6736(20)31022-9. Epub 2020 Apr 29. Erratum in: Lancet 2020;395:1694.
15. Spinner CD, Gottlieb RL, Criner GJ.et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA 2020;324:1048-1057.
16. WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med 2021;384:497–511.
17. Beigel JH, Tomashek KM, Dodd LE.et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020;383:1813–26.
18. Mehta RM, Bansal S, Bysani S, Kalpakam H. A shorter symptom onset to remdesivir treatment (SORT) interval is associated with a lower mortality in moderate-to-severe COVID-19: A real-world analysis. Int J Infect Dis 2021;106:71-77.
19. Terkes V, Lisica K, Marusic M, Verunica N, Tolic A, Morovic M. Remdesivir Treatment in Moderately Ill COVID-19 Patients: A Retrospective Single Center Study. J Clin Med 2022;11:5066.
20. Dobrowolska K, Zarębska-Michaluk D, Brzdęk M.et al.. Retrospective Analysis of the Effectiveness of Remdesivir in COVID-19 Treatment during Periods Dominated by Delta and Omicron SARS-CoV-2 Variants in Clinical Settings. J Clin Med 2023;12:2371.

Pregledni članak
Review

ISSN 0351-0093
Coden: MEJAD 53 (2023) 4

Primjena diodnog lasera u histeroskopiji: što trenutno znamo i što možemo očekivati u budućnosti?

Use of diode laser in gynecology: what do we already know and what could we expect in the future?

Mario Ćorić, Mara Tešanović, Luka Matak, Magdalena Matak, Ivana Jurković, Gordan Zlopaša, Mislav Mikuš*

Sažetak

Histeroskopija je metoda vizualizacije šupljine maternice koja se koristi u svrhu dijagnosticiranja i liječenja intrakavitarne patologije. Zahvaljujući razvoju tehnike uloga histeroskopije mijenjala se od dijagnostičke, preko operativne u operacijskoj dvorani, do operativne u ambulantnom okruženju.

Cilj ovog preglednog članka je analizirati uporabu diodnog lasera u histeroskopiji i minimalno invazivnim postupcima u području ginekologije, raspravljajući o pozitivnim i negativnim aspektima ove tehnologije s posebnim osvrtom na buduće primjene i perspektive u području ambulantne kirurške histeroskopije.

Ključne riječi: histeroskopija, diodni laser, minimalno invazivna kirurgija, histeroskopska polipektomija.

Summary

Hysteroscopy is a method of visualization of the uterine cavity that is used for the purpose of diagnosing and treating intracavitary pathology. Thanks to the development of the technique, the role of hysteroscopy changed from diagnostic through operative in the operating room, to operative in the ambulatory environment.

The aim of this review article is to analyze the use of the diode laser in hysteroscopy and minimally invasive procedures in the field of gynecology, discussing the positive and negative aspects of this technology, with special reference to future applications and perspectives in the field of ambulatory surgical hysteroscopy.

Keywords: hysteroscopy, diode laser, minimally invasive surgery, hysteroscopic polypectomy

Med Jad 2023;53(4):251-256

Uvod

Histeroskopija je metoda vizualizacije šupljine maternice koja se koristiu u svrhu dijagnosticiranja i liječenja intrakavitarne patologije.[1,2] Indikacije za histeroskopiju su obilno krvarenje iz maternice, anomalije Mullerovih kanala, zaostalo strano tijelo u maternici, neplodnost i sumnja na intrauterinu

* **Klinički bolnički centar Zagreb, Klinika za ženske bolesti i porode** (prof.dr.sc. Mario Ćorić, dr.med., Mara Tešanović, dr.med., Ivana Jurković, dr.med., doc.dr.sc. Gordan Zlopaša, dr.med., dr.sc. Mislav Mikuš, dr.med.); **Opća bolnica Zadar, Odjel za ginekologiju i porodništvo** (Luka Matak, dr.med.); **Sveučilište u Zadru, Odjel za zdravstvene studije** (naslovni asistent Luka Matak, dr.med.); **Opća bolnica Zadar, Odjel za interne bolesti, Dermatovenerologija** (Magdalena Matak, dr.med.)

Adresa za dopisivanje / *Corresponding address:* Luka Matak, dr.med.; Opća bolnica Zadar, Odjel za ginekologiju i porodništvo, Bože Peričića 5, 23000 Zadar E-mail: lmatak.gin@gmail.com

Primljeno/*Received* 2023-02-27; Ispravljeno/*Revised* 2023-11-13; Prihvaćeno/*Accepted* 2023-11-27

patologiju (polip, miom).[3-5] Osim za vaginoskopiju, koristi se za pregled endometrija, cervikalnog kanala i analizu tubarnih ušća.[6,7] Kontraindikacije za histeroskopiju su purulentni endometritis i trudnoća.[3] Zahvaljujući razvoju tehnologije, uloga histeroskopije mijenjala se od dijagnostičke, preko operativne u operacijskoj dvorani, do operativne u ambulantnom okruženju.[8]

Za razvoj ambulantne histeroskopije (engl. *Office Hysteroscopy*) ključna je bila redukcija promjera instrumenata, uključujući smanjenje veličine resektoskopa s 8,5 na 5 mm, uz korištenje bipolarne radiofrekvencije.[9] Ambulantnom histeroskopijom smanjuje se upotreba anestezije i korištenje operacijske dvorane, a omogućava klinički pristup "vidjeti i liječiti" (eng. *See and treat*).[6,7,9] Ambulantna operacijska histeroskopija prihvaćena je kao izvediv, isplativ i praktičan način liječenja intrauterine patologije. Za potrebe ambulantne histeroskopije razvijeni su miniresektoskopi, intrauterini morselatori i drugi sustavi za uklanjanje tkiva.[7,9,10] Istraživanje koje su proveli Torok i sur. sugerira da se percepcija boli i nelagode tijekom histeroskopije u ambulanti može povećati kada se uoči bilateralna opstrukcija jajovoda pri selektivnoj kromopertubaciji i tubarnoj kanilaciji i u tom slučaju, histeroskopiju treba provesti pri nižem intrauterinom tlaku, kako bi se smanjili grčevi mišića i bol.[4]

Razvoj ginekološke kirurgije uveo je u upotrebu kirurške lasere za uklanjanje intrauterinih lezija, a u svojoj skupini najkorišteniji je diodni laser.[10,11] Laser se također može koristiti za vrijeme histeroskopskih procedura. U ovom području korištene su različite vrste lasera: Nd-Yag laser, argonski laser i diodni laser.[12] Diodni laser predstavlja najznačajniju novost, jer reže i koagulira postižući hemostazu značajno bolje od CO_2 lasera.[9,12] Diodni laser koristi se za histeroskopsku metroplastiku, polipektomiju endometrija i enukleaciju submukoznih mioma, pokazujući sigurnost, izvedivost, učinkovitost i potencijalnu prevenciju stvaranja intrauterinih priraslica i smanjen rizik od recidiva.[12]

Cilj ovog preglednog članka je analizirati uporabu diodnog lasera u histeroskopiji i minimalno invazivnim postupcima u području ginekologije, raspravljajući o pozitivnim i negativnim aspektima ove tehnologije, s posebnim osvrtom na buduće primjene i perspektive u području ambulantne kirurške histeroskopije.

Materijali i metode

Relevantna istraživanja objavljena u posljednjih 20 godina identificirana su putem pretraživanja PubMed/Medline koristeći različite kombinacije sljedećih pojmova za pretraživanje: "histeroskopija", "laser" i "kirurgija".Dodatni radovi identificirani su pregledom popisa referenci relevantnih publikacija. Poseban naglasak stavljen je na izvornaistraživanja koja istražuju pitanja učinkovitosti i/ili sigurnosti.Sažeci svojstava lijeka (SmPC) korišteni su za provjeru odobrenih indikacija. Publikacije koje nisu na engleskom jeziku bile su isključene.Nije proveden sustavan pristup odabiru istraživanja.Umjesto toga, podaci su izdvojeni na temelju njihove relevantnosti za temu.

Rezultati

Pretraživanjem relevantnih medicinskih elektroničkih baza podataka, uz uklanjanje duplikata, izdvojili smo ukupno 102 publikacije. Analizom sažetaka isključeno je 87 radova koji ne ulaze u definirane uključne kriterije, uglavnom vezane uz sadržaj članka. Ukupno 15 radova analizirano je u svrhu ovog preglednog članka i to kako bismo prikazali fizikalne osnove diodnog lasera, njegove primjene u histeroskopskoj kirurgiji s naglaskom na polipektomiju i miomektomiju, laserskumiolizu kao novi kirurški pristup, ulogu diodnog lasera u liječenju anomalija maternice, te smo analizirali potencijal u budućoj kliničkoj primjeni.

Rasprava

Diodni laser: Od fizikalnih osnova do glavnih primjena u histeroskopskoj kirurgiji

Laserska tehnologija temelji se na pojačanju određene valne duljine svjetlosti koja generira emisiju snopa fotona. Kontakt laserske zrake s organskim tkivom stvara molekularne vibracije, izazivajući prekid kemijskih veza i proizvodnju topline.[12,13]

Prethodnici diodnog lasera su CO_2 i Nd:YAG laser.[12] Monopolarna frekvencija uzrokuje veće kolateralno toplinsko oštećenje miometrija od fleksibilnog CO_2 laserskog vlakna. Nd:YAG laser proizvodi najglađe lezije s dobro definiranim rubovima u usporedbi s monopolarnom frekvencijom koja je češće povezana s nepravilnim i ispucalim rubovima.[12,14]

Korištenje lasera u ginekološkoj minimalno invazivnoj kirurgiji tijekom godina ograničeno je visokim troškovima, niskom dostupnošću i dugom krivuljom učenja, no tehnološki napredak i smanjenje troškova potrebni su za daljnje proširenje njegove primjene u ginekološkoj endoskopiji.[13] Diodni laser je snage 15 W, valne duljine 1470 nm, radi samo kontaktom s disperzijskom toplinom od 0,5-1 mm, uz

minimalno oštećenje okolnih tkiva, posebice miometrija.[15,16] Diodni laser već se sigurno i uspješno primjenjivao u liječenju patologija endometrija poput fibroida, polipa i septuma.[16] Angioni i sur. otkrili su da diodni laserski sustav osigurava sigurnu i učinkovitu laparoskopsku disekciju dubokih endometrijskih lezija. Preporučili su, međutim, daljnja opsežna randomizirana ispitivanja kako bi se potvrdili ovi preliminarni podaci u smislu učinkovitosti, stope recidiva i ishoda trudnoće.[17] Nappi i sur. procijenjuju utjecaj na rezervu jajnika upotrebe hemostaze laserskog sustava s dvije valne duljine (eng. *Dual wave laser spectrum*) nakon tehnike strippinga monolateralnog endometrioma, doziranjem anti-Mullerovog hormona (AMH). Njihovi rezultati sugeriraju da odgovarajuća kirurška tehnika, uz primjenu laserske hemostaze, ne dovodi do značajnog smanjenja ovarijske rezerve.[18] Tijekom posljednja dva desetljeća laserski instrumenti uvedeni su u područje endoskopskih postupaka. Postoji nekoliko vrsta lasera, uključujući argon, kripton, neodimij-itrij aluminij granat (Nd:YAG), i diodni laseri i svi se uspješno koriste, no međutim, samo je Nd:YAG laser našao široku primjenu u histeroskopskim zahvatima.[19] Leonardo® laserski sustav (eng. *Dual Wave Laser Spectrum*; Leonardo®, Biolitec®, Jena, Njemačka) predstavlja najsvestraniji i najčešće korišten diodni laser za uspješne miomektomije, polipektomije endometrija, pa čak i metroplastike u ordinacijskom okruženju.[9] Sorrentino i dr. prikazali su slučaj uspješno liječene trudnoće u ožiljku od carskog reza, koja je liječena angiografskom embolizacijom materničke arterije nakon koje je uslijedila histeroskopska resekcija diodnim laserom. Čini se da ova kombinacija nudi učinkovito, sigurno i minimalno invazivno kirurško liječenje.[20] Jedan od napredaka je razvoj RevoLixa (LISA Laser, Pleasanton, CA, SAD), 2-mikronskog kontinuiranog valnog lasera čvrstog stanja s diodnim crpkama (eng. *diode-pumpedsolid-state* -DPSS), koji objedinjuje sve prednosti postojećih laserskih principa u pojedinačnoj jedinici.[19] RevoLix laser navodno ima superiorne karakteristike preciznog rezanja i ablacije, dobru sposobnost hemostaze, izravnu vaporizaciju bez dubokog prodiranja, te manje mjehurića i stvaranja ostataka tkiva, što omogućuje mnogo bolju vidljivost kirurškog polja.[19] RevoLix laser pokazuje dobru apsorpciju vode, ovaj mehanizam štiti tkivo i organe u blizini reza, a udaljenost od 2 mm je sigurna granica. Na tkivo dalje od 2 mm RevoLix laser ne utječe. Glavni nedostatak za kliničku primjenu RevoLix lasera mogla bi biti cijena laserske opreme koja je trenutno skupa.

Histeroskopska miomektomija pomoću diodnog lasera – primjena izvan uobičajenog kliničkog okvira?

Chen i sur. su u njihovoj studiji procijenili sigurnost i učinkovitost RevoLix 2-mikronskog lasera s kontinuiranim valom za histeroskopsku miomektomiju, te je utvrđeno da se uporaba ovog lasera čini sigurnom i učinkovitom u liječenju simptomatskih submukoznih mioma.[19]

Haimovich i sur. u svojoj su studiji razvili ordinacijsku histeroskopsku resekciju intrakavitarnih G1 ili G2 submukoznih mioma u dva koraka, kao ambulantni postupak bez anestezije. U ovoj studiji korištenje histeroskopa od samo 4,3 mm uključuje ostavljanje enukleiranog mioma unutar šupljine maternice.[21] Dobili su da je srednji promjer mioma izmjeren ultrazvučnim pregledom bio 22,6 mm. Nakon prosječnog praćenja od dva mjeseca, nijedna bolesnica nije pokazala rezidualni miom unutar šupljine maternice. Zaključili su da je ostavljanje laserski enukleiranog submukoznog mioma u šupljini maternice izvediva i sigurna terapijska opcija.[21]

Laserska mioliza: Novi histeroskopski pristup

Mioliza podrazumijeva koagulaciju fibroida umjesto njihovog kirurškog uklanjanja. Prvo je korišten Nd:YAG laser za miolizu, a zatim termomiolizu. Sljedeća razvijena metoda miolize bila je fokusirana ultrazvučna kirurgija vođena magnetskom rezonancijom (eng. *Magnetic resonance guided focused ultrasound* - MRgFUS), potom mikrovalna, radiofrekventna mioliza.[22,23] Trenutno su diodni laseri pokazali mnoge prednosti u histeroskopskoj kirurgiji.[9] Odnedavno je dostupna nova vrsta lasera koji generira dvije valne duljine (eng. *Dual Wave Laser Spectrum-DWLS*). D'Alterio i sur. Osmislili su eksperimentalni sustav za karakterizaciju učinka ablacije vlakana miolize s određenim vlaknom (Myolysis®, Biolitec®, Jena, Njemačka) za liječenje fibroida i pomoć u budućem planiranju liječenja.[22] Nadalje, ista skupina autora provela je prvu ex vivo studiju koja je nastojala procijeniti tehnike ablacije za liječenje mioma.[22] Osmislili su eksperimentalni sustav za karakterizaciju učinka ablacije vlakana miolize. Pokusi su provedeni na ekscidiranim miomima nakon totalne histerektomije. Utvrdili su dobre makroskopske rezultate za fibrome volumena 60 $cm^{3,}$ ablirane sa sljedećim postavkama: 10 W / 980 nm i 10 W / 1470 nm, a za uzorke volumena 15 cm^3 ablirane s 5 W / od 980 nm 5 W / 1470 nm. Ova *ex vivo* studija omogućila je razumijevanje koje se od DWLS

postavki može preporučiti za najsigurnije i najbolje makroskopske rezultate u miolizi.[22]

Histeroskopska polipektomija i diodni laser

Polipi endometrija (EP) povezani su s abnormalnim krvarenjem iz maternice, neplodnošću, te premalignim i malignim stanjima.[5,24] Transvaginalni ultrazvuk i color doppler uobičajeni su načini otkrivanja EP-a.[24,25] Ordinacijska histeroskopija bez anestezije izvediva je i sigurna za dijagnostiku i liječenje EP.[26] Učinkoviti i sigurni tehnološki alati za resekciju EP uključuju histeroskop s monopolarnom i bipolarnom radiofrekvencijom, diodni laser, mini-resektoskope, morcelatore, MyoSure® (Hologic Inc., Marlborough, MA), TruClear™ (Medtronic, Parkway, USA) i škare/hvataljke.[3,8,27]

Lara-Dominguez i sur. u svojoj studiji usporedili su resekciju EP-a s dva različita uređaja: biopolarnom elektrodom Versapoint i diodnim laserom.[26] Uključili su 102 bolesnice s dijagnosticiranom EP i dobili sljedeće rezultate: intraoperativna bol i vrijeme resekcije polipa bili su slični u obje skupine, veći postotak žena iz Versapoint skupine imao je relaps polipa na drugom pregledu histereoskopije nakon 3 mjeseca, a eliminacija polipa nakon nepotpune resekcije bila je već u laserskoj skupina.[26] Istraživači su zaključili da je polipektomija s diodnim laserom rezultirala manjim brojem recidiva i višom stopom zadovoljstva postupkom u usporedbi s Versapointom.[26] Nappi i sur. procijenili su prednosti upotrebe novog laserskog sustava s dvije valne duljine u liječenju EP-a u izvanbolničkim uvjetima.[28] Utvrdili su da je laserska polipektomija uspješno izvedena u 219 od 225 (97,3%) slučajeva. Nisu prijavili glavne komplikacije tijekom ili neposredno nakon zahvata, a ultrazvučni pregledi 6 i 12 mjeseci kasnije nisu pokazali postojanost ili recidiv polipa. Zaključili su da je laserska histeroskopska polipektomija endometrija siguran i učinkovit postupak. Nadalje, Nappi i suradnici u drugoj nedavno objavljenoj studiji procijenili su dobrobiti upotrebe novog laserskog sustava s dvije valne duljine u liječenju EP-a u izvanbolničkom okruženju.[29] Utvrdili su da je laserska polipektomija uspješno izvedena u 219 od 225 (97,3%) slučajeva. Nisu prijavili glavne komplikacije tijekom ili neposredno nakon zahvata, a ultrazvučni pregledi 6 i 12 mjeseci kasnije nisu pokazali postojanost ili recidiv polipa. Zaključili su da je laserska histeroskopska polipektomija endometrija siguran i učinkovit postupak.

Diodni laser u histeroskopskom liječenju malformacija maternice: individualizirani pristup

Histeroskopsku metroplastiku dismorfne maternice u obliku slova T ili Y pomoću diodnog lasera opisali su Bilgory i sur. u njihovoj retrospektivnoj, jednocentričnoj pilot studiji s prospektivnim praćenjem.[15] Histeroskopska metroplastika diodnim laserom učinjena je u ambulantnim uvjetima. U ovoj studiji glavne mjere ishoda uključivale su operativno vrijeme, komplikacije, histeroskopski izgled šupljine u naknadnoj histeroskopiji i reproduktivne ishode u smislu trudnoće i živorođenja. Ukupno 25 neplodnih žena podvrgnuto je histeroskopskoj metroplastici. Stopa porođaja i trudnoća u tijeku bila je 78%.[15] Histeroskopska metroplastika s diodnim laserom siguran je, jednostavan i učinkovit postupak, poboljšava reproduktivne rezultate u slučajevima dismorfne maternice u obliku slova T ili Y, ali potrebno nam je dulje praćenje i veća kontrolirana ispitivanja koja uspoređuju metroplastiku s nikakvim zahvatom, kako bismo potvrdili učinak na reproduktivne ishode. Diodni laser omogućuje vaporizaciju septuma maternice pokazujući ekstremnu preciznost rezanja, preciznu kontrolu vaporizacije tkiva, kontroliranu snagu penetracije, visok kapacitet hemostaze, visoku sigurnost i dobru suradljivost bolesnica zbog ordinacijskog okruženja bez potrebe za dilatacijom cerviksa.[16,29] Vaporizacija septuma ordinacijskom histeroskopijom s diodnim laserom mogla bi smanjiti stvaranje priraslica i posljedično smanjiti pojavu perzistencije septuma.[30] Vaporizacija tkiva i koagulacija diodnim laserom omogućuju brzo uklanjanje septuma maternice bez utjecaja na miometrij koji leži ispod.[16] Nappi i suradnici u svojoj pilot studiji procijenili su učinkovitost diodnog lasera histeroskopske metroplastike za povećanje volumena endometrija u žena sa septiranom maternicom.[29] Prospektivno su uključili 10 uzastopnih bolesnica sa septiranom maternicom, podvrgnutih ordinacijskoj histeroskopskoj metroplastici diodnim laserom. Kirurški zahvat bio je nekompliciran u svih bolesnica, volumen endometrija povećao se na pregledu nakon tri mjeseca, a tijekom kontrolne histeroskopije došlo je do potpunog uklanjanja septuma bez intrauterinih sinehija.[29] Ordinacijska histeroskopska metroplastika septirane maternice diodnim laserom izvediv je i siguran zahvat i preliminarno je pokazano da povećava volumen endometrija. Manchado i sur. proveli su prospektivnu kohortnu studiju koja je uključivala 41 nuliparu s dijagnozom septirane maternice i poviješću neplodnosti, što je najveća serija histeroskopske metroplastike za potpunu

septiranu maternicu izvedenu u ordinacijskom okruženju s diodnim laserom.[16] Zahvat je većina bolesnica podnijela dobro i bez kirurških komplikacija. Što se tiče učinkovitosti resekcije septuma, postupak je bio 100% učinkovit bez zaostalog septuma identificiranog u svih bolesnica potvrđenih drugom histeroskopijom u ordinaciji.[16] Izvijestili su o reproduktivnim ishodima nakon dvije godine u stopi trudnoće od 78,9% s kumulativnim živorođenjem od 63,2%. Nije bilo slučajeva postporođajnog krvarenja ili rupture maternice među 58% žena koje su imale vaginalni porod.[16] Također su zaključili da se ordinacijska histeroskopska metroplastika septirane maternice uz korištenje diodnog lasera čini izvedivom i sigurnom alternativom drugim tehnikama i ima dovoljnu učinkovitost u smislu reproduktivnih ishoda da se razmotri za daljnja ispitivanja.

Daljnji klinički potencijali

Posljednjih godina tehnološki napredak i poboljšanja razvijaju se brže nego ikada i povećavaju broj postupaka u minimalno invazivnoj ginekologiji koji mogu iskoristiti lasersku tehnologiju.[12] Uz nove i manje kirurške uređaje, napreduje se u razvoju minijaturiziranih mehaničkih instrumenata (npr. škare, pincete, tenakuli i namjenske hvataljke) veće preciznosti i učinkovitosti, posebno za uklanjanje izrezanog tkiva iz šupljine maternice, koje je obično veće od unutarnjeg cervikalnog otvora.[9]

Trenutno je moguće izvesti ablaciju endometrija bez potrebe za općom anestezijom ili operacijskom dvoranom.[9] Još jedna velika prednost histeroskopije danas je ta što kirurg može donijeti histeroskop bilo gdje zahvaljujući potpuno novoj vrsti integriranih sustava koji se mogu natjecati s različitim vrstama kamera i LED zaslona.[9] Dodatno, to omogućuje ginekolozima obavljanje dijagnostičkih i operativnih zahvata putem kamera koje su izravno spojene na prijenosno ili osobno računalo.

Nadalje, važno je primijetiti da je posljednjih godina na tržište ušlo nekoliko pouzdanih setova za histeroskopiju koji su znatno jeftiniji, a izvrsne su kvalitete.[4] Ovi uređaji bore se s najistaknutijim nedostatkom upotrebe lasera u histeroskopiji, a to je cijena. Sa sve raširenijom upotrebom i sustavima za vježbanje virtualne stvarnosti, histeroskopija postaje vrlo dostupna i starijim i mlađim ginekolozima i povećati će učinkovitost liječenja gotovo svih intrauterinih patologija za mnoge žene u ordinacijskom okruženju.[31-33] Posljednji korak biti će smanjenje potrebu za anestezijom, te učiniti ambulantnu histeroskopsku operaciju dostupnom svakoj bolesnici. Svakako je važno napomenuti da upotreba lasera u ginekologiji, za razliku od monopolarnih i bipolarnih uređaja, ostvaruje bolju koagulaciju, uz istovremeno rezanje tkiva. Glavni nedostatak upotrebe laserske tehnologije je cijena jednokratnih sondi zbog kojih još uvijek nije u svakodnevnoj upotrebi.

Upotreba lasera zasigurno je dobila svoje mjesto u ginekologiji razvojem ambulantne histeroskopije, što se manifestira sve većim brojem publikacija i sve širim spektrom indikacija za izvođenje ove metode. Daljnje studije potrebne su kako bi se u potpunosti analizirao ishod liječenja upotrebom lasera.

Literatura

1. Vitale SG, Carugno J, D'Alterio MN, Mikuš M., Patrizio P., Angioni S. A New Methodology to Assess Fallopian Tubes Microbiota and Its Impact on Female Fertility. Diagnostics 2022;12:1375.
2. Angioni S, Loddo A, Milano F, Piras B, Minerba L, Melis GB. Detection of benign intracavitary lesions in postmenopausal women with abnormal uterine bleeding: a prospective comparative study on outpatient hysteroscopy and blind biopsy. J Minim Invasive Gynecol 2008;15:87–91.
3. Vitale SG, Laganà AS, Török P, et al. Virtual sonographic hysteroscopy in assisted reproduction: A retrospective cost-effectiveness analysis. Int J Gynaecol Obstet 2022;156:112–118.
4. Török P, Molnár S, Herman T, et al. Fallopian tubal obstruction is associated with increased pain experienced during office hysteroscopy: a retrospective study. Updates Surg 2020;72:213–218.
5. Luerti M, Vitagliano A, Di Spiezio Sardo A, Angioni S, Garuti G, De Angelis C. Effectiveness of Hysteroscopic Techniques for Endometrial Polyp Removal: The Italian Multicenter Trial. J Minim Invasive Gynecol 2019;26:1169–1176.
6. Okohue JE. Overview of Hysteroscopy. West Afr J Med 2020;37:178–182.
7. Salazar CA, Isaacson KB. Office Operative Hysteroscopy: An Update. J Minim Invasive Gynecol 2018;25:199–208.
8. Vitale SG. The Biopsy Snake Grasper Sec. VITALE: A New Tool for Office Hysteroscopy. J Minim Invasive Gynecol 2020;27:1414–1416.
9. Vitale SG, Haimovich S, Riemma G, et al. Innovations in hysteroscopic surgery: expanding the meaning of "in-office." Minim Invasive Ther Allied Technol 2021;30:125–132.
10. Chiofalo B, Palmara V, Vilos GA, et al. Reproductive outcomes of infertile women undergoing "see and treat" office hysteroscopy: a retrospective observational study. Minim Invasive Ther Allied Technol 2021;30:147–153.
11. Riemma G, Vitale SG, Manchanda R, et al. The role of hysteroscopy in reproductive surgery: Today and tomorrow. J Gynecol Obstet Hum Reprod 2022;51:102350.

12. ESGE Special Interest Group 'Innovations' Working Group. Lasers in gynaecology - Are they still obsolete? Review of past, present and future applications. Facts Views Vis Obgyn 2020;12:63–66.
13. Nappi L, Sorrentino F, Angioni S, Pontis A, Greco P. The use of laser in hysteroscopic surgery. Minerva Ginecol 2016;68:722–726.
14. Law KSK, Abbott JA, Lyons SD. Energy Sources for Gynecologic Laparoscopic Surgery: A Review of the Literature. Obstet Gynecol Surv 2014;69:763–776.
15. Bilgory A, Shalom-Paz E, Atzmon Y, et al. Diode Laser Hysteroscopic Metroplasty for Dysmorphic Uterus: a Pilot Study. Reprod Sci 2022;29:506–512.
16. Esteban Manchado B, Lopez-Yarto M, Fernandez-Parra J, et al. Office hysteroscopic metroplasty with diode laser for septate uterus: a multicenter cohort study. Minim Invasive Ther Allied Technol 2022;31:441–447.
17. Angioni S, Nappi L, Sorrentino F, et al. Laparoscopic treatment of deep endometriosis with a diode laser: our experience. Arch Gynecol Obstet 2021;304:1221–1231.
18. Nappi L, Angioni S, Sorrentino F, Cinnella G, Lombardi M, Greco P. Anti-Mullerian hormone trend evaluation after laparoscopic surgery of monolateral endometrioma using a new dual wavelengths laser system (DWLS) for hemostasis. Gynecol Endocrinol 2016;32:34–37.
19. Chen C-H, Lee W-L, Wang I-T, et al. Hysteroscopic myomectomy using a two-micron continuous wave laser (RevoLix). Gynecol Minim Invasive Ther 2013;2:89–92.
20. Sorrentino F, De Feo V, Stabile G, et al. Cesarean Scar Pregnancy Treated by Artery Embolization Combined with Diode Laser: A Novel Approach for a Rare Disease. Medicina (Kaunas) 2021;57:411.
21. Haimovich S, López-Yarto M, Urresta Ávila J, Tascon AS, Hernandez JL, Carreras Colledo R. Office Hysteroscopic Laser Enucleation of Submucous Myomas without Mass Extraction: A Case Series Study. Biomed Res Int 2015;2015:905204.
22. D'Alterio MN, Scicchitano F, Fanni D, et al. Ex vivo myolysis with dual wavelengths diode laser system: macroscopic and histopathological examination. Clin Exp Obstet Gynecol 2021;48:875-882.
23. De La Cruz MSD, Buchanan EM. Uterine Fibroids: Diagnosis and Treatment. Am Fam Physician 2017;95:100–107.
24. Raz N, Feinmesser L, Moore O, Haimovich S. Endometrial polyps: diagnosis and treatment options – a review of literature. Minim Invasive Ther Allied Technol 2021;30:278–287.
25. Vitale SG, Riemma G, Haimovich S, et al. Risk of endometrial cancer in asymptomatic postmenopausal women in relation to ultrasonographic endometrial thickness: systematic review and diagnostic test accuracy meta-analysis. Am J Obstet Gynecol. 2022;228:22-35.
26. Lara-Domínguez MD, Arjona-Berral JE, Dios-Palomares R, Castelo-Branco C. Outpatient hysteroscopic polypectomy: bipolar energy system (Versapoint®) versus diode laser – randomized clinical trial. Gynecol Endocrinol 2016;32:196–200.
27. Vitale SG, Laganà AS, Caruso S, et al. Comparison of three biopsy forceps for hysteroscopic endometrial biopsy in postmenopausal patients (HYGREB-1): A multicenter, single-blind randomized clinical trial. Int J Gynaecol Obstet 2021;155:425–432.
28. Nappi L, Sorrentino F, Angioni S, Pontis A, Litta P, Greco P. Feasibility of hysteroscopic endometrial polypectomy using a new dual wavelengths laser system (DWLS): preliminary results of a pilot study. Arch Gynecol Obstet 2017;295:3–7.
29. Nappi L, Falagario M, Angioni S, DeFeo V, Ballino M, Sorrentino F. The use of hysteroscopic metroplasty with diode laser to increase endometrial volume in women with septate uterus: preliminary results. Gynecol Surg 2021;18:11.
30. Nappi L, Pontis A, Sorrentino F, Greco P, Angioni S. Hysteroscopic metroplasty for the septate uterus with diode laser: a pilot study. Eur J Obstet Gynecol Reprod Biol 2016;206:32–35.
31. Vitale SG, Di Spiezio Sardo A, Riemma G, De Francis P, Alonso Pacheco L, Carugno J. In-office hysteroscopic removal of retained or fragmented intrauterine device without anesthesia: a cross-sectional analysis of an international survey. Updates Surg 2022;74:1079–1085.
32. Vitale SG, Riemma G, Carugno J, et al. Postsurgical barrier strategies to avoid the recurrence of intrauterine adhesion formation after hysteroscopic adhesiolysis: a network meta-analysis of randomized controlled trials. Am J Obstet Gynecol 2022;226:487-498.e8.
33. Vitale SG, Caruso S, Vitagliano A, et al. The value of virtual reality simulators in hysteroscopy and training capacity: a systematic review. Minim Invasive Ther Allied Technol 2020;29:185–193.

Pregledni članak
Review

ISSN 0351-0093
Coden: MEJAD 53 (2023) 4

Barotrauma of the ear and paranasal sinuses

Barotrauma uha i paranazalnih šupljina

Dražen Shejbal, Tajana Gudlin Sbull, Davor Vagić*

Summary

With the increasing popularity of amateur scuba diving and the availability of commercial airplane flights, otorhinolaryngologists will increasingly encounter patients suffering from the effects of barotrauma. Barotrauma occurs according to the principles of Boyle's law, more precisely, due to the inability to equalize pressures within the body cavities. The pathophysiology of barotrauma of the ear and paranasal cavities is reviewed, as well as therapeutic options for prevention and treatment.

Key words: barotrauma, ear, paranasal sinuses

Sažetak

Porastom popularnosti amaterskog ronjenja i dostupnošću komercijalnih avionskih letova, otorinolaringolozi će se sve više susretati s bolesnicima koji boluju od posljedica barotraume. Barotrauma nastaje po principima Boyleovog zakona, preciznije, zbog nemogućnosti izjednačavanja tlakova unutar tjelesnih šupljina.

Prikazana je patolofiziologija barotraume uha i paranazalnih šupljina, te terapeutske opcije prevencije i liječenja.

Ključne riječi: barotrauma, uho, paranazalni sinusi

Med Jad 2023;53(4):257-262

Introduction

Barotrauma is any tissue damage caused by the pressure difference between the environment and the body cavities.

Pathology of barotrauma in otorhinolaryngology used to be related to the narrow field of military and occupational medicine. The widespread popularity of amateur scuba diving, the commercial accessibility of airplane flights, and the increasing amount of indications for hyperbaric chamber treatment, have increased the incidence of paranasal sinuses and ear injuries. Modern otorhinolaryngology is not only focused on the treatment and prevention of barotrauma, but also tries to make amateur scuba diving and commercial flying accessible to individuals with, until recently, absolute contraindications for these activities.

Pathophysiology

The occurrence of barotrauma takes place according to the principles of Boyle's law; the volume of gas changes depending on the pressure if temperature is held constant. The air pressure at sea level is 101.3 kPa, and is altered by diving or take-off. If a balloon with a volume of 1 liter is brought to the surface from a depth of 10 meters, its volume will

*Poliklinika Sveti Nikola, Varaždin (Tajana Gudlin Sbull, dr.med.); KBC Sestre milosrdnice, Klinika za otorinolaringologiju i kirurgiju glave i vrata (prof.dr.sc. Davor Vagić, dr.med.); Opća bolnica Varaždin, Odjel za otorinolaringologiju (prim.dr.sc. Dražen Shejbal, dr.med.)

Corresponding address/*Adresa za dopisivanje*: Dražen Shejbal, Opća bolnica Varaždin, Odjel za otorinolaringologiju, Ivana Meštrovića 1, 42 000 Varaždin E-mail: dr.azen@vip.hr

Received/*Primljeno* 2023-04-11; Revised/Ispravljeno 2023-11-18; Accepted/*Prihvaćeno* 2023-11-20

increase to 2 liters, and in order to increase its volume by another liter, it would have to be raised to a height of approximately 5,500 meters. From the example above it is clear that barotrauma occurs more easily when diving, or precisely, each dive is accompanied by a smaller or larger barotrauma.[1]

Barotrauma of the outer ear

The outer ear is normally exposed to the outside atmosphere and pressure. Damage occurs if there is an obstruction of the external auditory canal, in this case the equalization of external pressure and pressure behind the obstruction is not possible. The cause of the obstruction may be cerumen, stenosis, atresia, exostoses, foreign bodies, inserts, cotton wool and the like. When diving, a pressure difference of 150 mmHg is critical.[2,3]

Clinical features

The leading symptoms are pain and pressure in the ear. When atresia is unilateral, dizziness can occur due to caloric stimulation, especially if the lateral semicircular canal is placed in a vertical plane. Various degrees of damage to the eardrum, petechial hemorrhages, bulla, and edema of the auditory canal are seen with the otoscope.[3]

Treatment

Cleaning of the external auditory canal and treatment of the eardrum injury.

Prevention

Prohibition of diving and flying for individuals with the obstruction of the external auditory canal, insertsfor the auditory canal,unless they have a specialone-way valvula, must be removed.[2,3]

Barotrauma of the middle ear

The Eustachian tube is an anatomical structure and when it is open it keeps the pressure in the middle ear constant. During diving out or taking-off, its task is to equalize the increased pressure in the middle ear with the smaller atmospheric pressure.

The pressure gradient is from the ear to the pharynx, and the pressure equalization is generally carried out successfully because the tube is physiologically more adapted to this task (Figure 1).

On landing or immersion, when the pressure in the nasopharynx is higher than the pressure in the middle ear, the mouth of the tube protrudes like a beak into the nasopharynx and becomes strangled by the increased nasopharynx pressure, which can result in middle ear barotrauma (Figure 2).

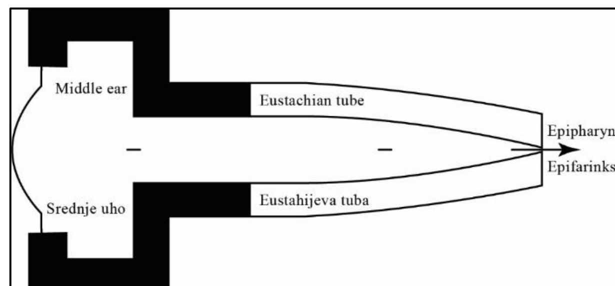


Figure 1 Drawing of the pressure gradient through Eustachian tube during take-off (modified according to Šercer)
Slika 1. Prikaz gradijenta tlaka Eustahijeve tube prilikom uzlijetanja (modificirano prema Šerceru)

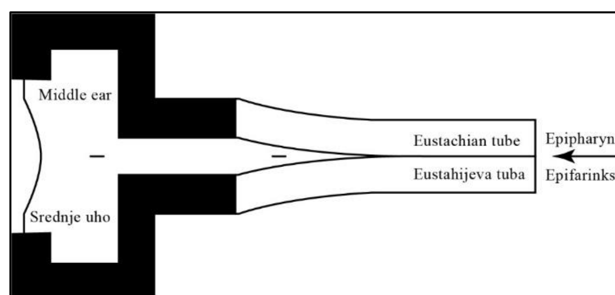


Figure 2 Drawing of the pressure gradient through Eustachian tube during landing (modified according to Šercer)
Slika 2. Prikaz Eustahijeve tube prilikom slijetanja (modificirano prema Šerceru)

In this case barotrauma occurs due to the *ex vacuo* phenomenon in the middle ear, more precisely, the pressure in the middle ear is lower than the pressure in the surrounding structures, and the walls of the middle ear tend to get closer in order to reduce the volume of the middle ear. Negative pressure in the middle ear draws fluid from the middle ear, and the damage to the structures can go as far as the rupture of the blood vessels and mucous membrane of the middle ear.[4] Factors that potentiate the closure of the tube may be congenital, anatomical, or acquired such as inflammatory edema, vegetation, or tumors.[5]

The next important factor in the flow of air and pressure through the middle ear is the mastoid. The volume of the middle ear is about 2 cm^3, and the size of the mastoid is on average 12 cm^2, with variations from 3 to 25 cm^2. In commercial flights, despite the design efforts to keep the pressure inside the aircraft cabin constant, the pressure changes by 20% in the half hour of the aircraft landing. The normal air flow through the middle ear during this time at sea level

would be 10 mcL. For the ear with a small mastoid it increases to 200 mcL during landing, and for the ear with a medium mastoid to 2000 mcL, which is an increase of 20 to 200 times. Loads when diving at depths over 10 meters are even greater. From the above follows that the barotrauma from the anatomical point of view is potentiated by the dysfunction of the Eustachian tube and the size of the mastoid because the mastoid "produces volume" that the Eustachian tube must transport.[6]

Interestingly, provided studies on mastoid volume have opened discussions about established otological dogma: frequent ear infections lead to chronic ear infection, thereby reducing mastoid volume. However, recent research has shown that a congenitally small mastoid during life creates chronic ear infection and related conditions (secretory otitis media syndrome, atelectasis, retraction pocket, cholesteatoma). Simply put, the middle ear, like its "big brother", that is, the lungs, has a system of baroreceptors and stretch receptors that hold the air flow in the mastoid within physiological limits. A small mastoid also means underdeveloped physiological mechanisms, leading to the simple conclusion: a well-pneumatized mastoid will never be associated with a chronically ill ear. On the other hand, a chronically ill ear will have a small mastoid and thus will not be burdened with volume traffic, so in a chronically ill ear (secretory otitis media syndrome, atelectasis, retraction pocket, cholesteatoma) there is no contraindication for airplane flight.[6,7]

In children up to puberty, barotrauma is extremely rare, especially on commercial flights. The reasons are not quite clear, but the three most plausible explanations are: first, by the onset of discomfort in the ear, children become restless and cry, thereby probably equalizing the pressure in the middle ear (by opening the tube)[7], second, they have a relatively smaller mastoid, which makes the load on the ear due to pressure changes lesser[6], and third, the Ostmann's pad of fatty tissue, located along the pharyngeal mouth of the tube, develops with aging, and its relative deficiency in children makes the epipharyngeal mouth larger.[8]

Negative pressure, that is, an ex vaccuo phenomenon, can damage any structure of the middle ear. Most often it occurs when landing an aircraft or during immersion. The eardrum retracts medially which can result in hemorrhage or rupture. By transudation from the mucous membrane, the ear can fill with the fluid, the end result being bursting of blood vessels and hematotympanum. Due to compaction forces auditory ossicles can dislocate, the dislocation of the stapes is particularly dangerous, and the very transfer of force to the labyrinth can damage the structures of the inner ear, which will be discussed later.[2,3]

Clinical features

A pressure difference of 90 mm Hg will strangled the pharyngeal mouth of the tube, and this is the limit when an increased risk of the serious damage to the eardrum occurs, especially in the ear with impaired ventilation mechanisms. It should be emphasized that such a pressure difference occurs when diving at a depth of 1.40 m of water!

Symptoms are pain, discomfort, crackling in the ear, sometimes accompanied by dizziness, murmuring, disturbances or hearing loss.

The damage to the eardrum is divided into 6 degrees. 0 - any symptom with a normal eardrum, 1 - injected eardrum, 2 - injected eardrum with areas of hemorrhage, 3 - hemorrhagic eardrum, 4 - hematotympanum, 5 - ruptured eardrum.[2]

Treatment

Treatment is symptomatic, including cleansing of the external auditory canal. Antibiotics are not given routinely, but only if the incident happened in contaminated water.

Return to diving or flying needs to be individually evaluated based on the appearance of the eardrum, pneumatic otoscopy and audiometry.[9]

Prevention

Individuals with a cold should take nasal decongestants before flight or postpone the flight. If the risk of barotrauma is high due to a positive medical history or an acute respiratory infection, especially with a large mastoid, a preventive myringotomy or insertion of ventilation tubes should be performed.[10] There are silicone inserts with a ceramic valvula which, when placed in the external auditory canal, equalize the pressure in people with an insufficient Eustachian tube function and thus protect the eardrum from damage.

When diving, pressure equalization can be performed by several techniques, with an important note: Valsalva maneuver can cause serious damage to the inner ear. Other methods are Frenzel maneuver, Toynbee maneuver, Lowry technique and Edmonds technique. The most successful but most difficult technique to train is Voluntary Tubal Opening (Beance Tubaire Volontaire, BTV). About 50 percent of divers can successfully master this technique. For divers with poorly ventilated ear, a slow immersion is

required, using one of the recommended maneuvers for each breathing cycle, up to a depth of about 6 meters, and then diving head-first towards the bottom. Similar to the aforementioned commercial flight aid, an insert for the external auditory canal of divers was developed.

Patients with perforation of the eardrum, inserted ventilation tubes, a condition behind the mastoidectomy, are forbidden to dive without specially designed diving masks that leave the ear dry; otherwise the risk of caloric stimulation and infection is unacceptable.

It is important to emphasize that the ear inserts in the external auditory canal prevent the barotrauma of the middle ear, but not of the outer ear, therefore they are acceptable for shallow water immersions.[5,9]

Individuals who had undergone stapedectomy or ossicular reconstructions do not have an increased risk of damage to the inner ear when diving, to the extent it has been understood so far, but they dive at their own risk. It is necessary to assess whether sudden changes in body position represent a risk for newly established architectonics of ossicles and implants, and the risk of a liquor fistula in the stapes area is extremely difficult to assess. If diving, immersion to the greater depths is not recommended.[10,11]

One historical interesting thing: during the Second World War, Luftwaffe pilots were periodically subjected to a preventive myringotomy, and shortly after the war, nasopharynx of the Allied pilots was irradiated so that post-radiation scarring would make the tube constantly open.[12]

Barotrauma of the inner ear

The ossicular chain transfers energy generated by the pressure changes in the middle ear to the inner ear. Hemorrhage, labyrinthine membrane rupture, ischemic damage by restriction in blood supply to a. spiralis modioli, and perilymphatic fistulas by a round or oval window rupture may occur. The mechanism of fistula formation has been proven on an animal model, and can be explosive and implosive. The explosive mechanism ruptures the round window membrane if a diver performs a Valsalva maneuver, without successful opening of the Eustachian tube at the same time. Increased pressure of the cerebrospinal fluid is transmitted to the cochlea via the cochlear aqueduct and the internal auditory canal, and it ruptures, by explosion toward the middle ear, through the Scarpa's membrane (Figure 3).[13,14]

The implosion also occurs during the Valsalva maneuver, if the Eustachian tube abruptly opens. The pressure in the middle ear is then increased by approximately 250 mmHg and it moves the stapes plate, which until then was imprinted by an ex vacuo mechanism toward the inner ear, in its normal position. This produces an implosion wave that can dislocate the stapes or rupture the Scarpa's membrane by implosion, or more simplified, toward the inner ear (Figure 4).[15,16]

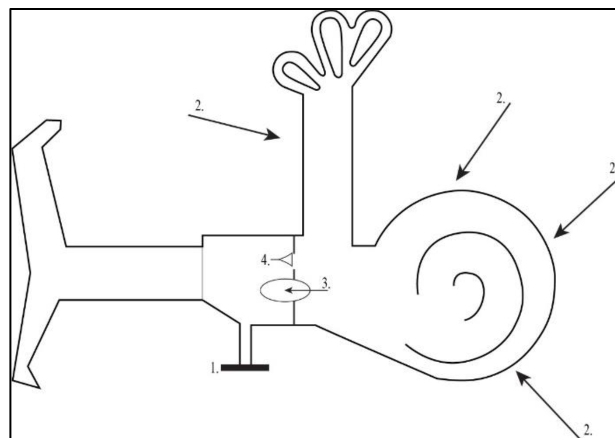


Figure 3 Explosive mechanism of the inner ear injury. 1. Eustachian tube is blocked, shown with thick line. 2. thick arrows show an increased pressure of a cerebrospinal fluid.3. the encircled thin arrow shows an explosive rupture of the Scarpa's membrane. 4. stapes

Slika 3. Eksplozivni mehanizam ozljede uha. 1. debela crta prikazuje blokiranu Eustahijevu tubu. 2. debele strelice prikazuju povećani tlak cerebrospinalne tekućine. 3. zaokružena tanka strelica prikazuje eksplozivnu rupturu membrane Scarpe.4. stapes.

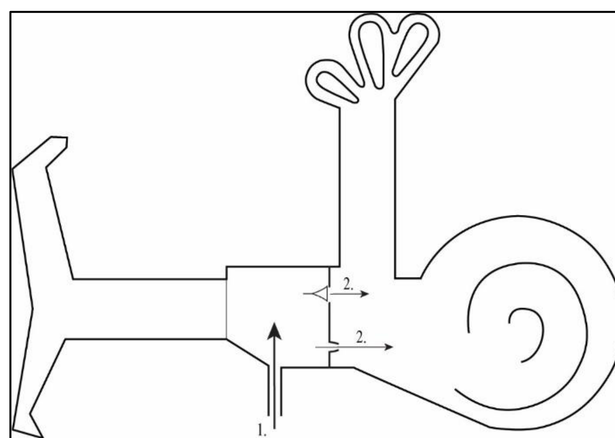


Figure 4 Implosive mechanism of inner ear damage caused by abrupt opening of the tube. 1. vertical arrow: tube opening. 2. horizontal arrows show pressure forces between middle and inner ear mediated by Scarpa´s and stapes.

Slika 4. Implozivni mehanizam ozljede unutarnjeg uha uzrokovan iznenadnim otvaranjem Eustahijeve tube. 1. uspravna strelica prikazuje otvorenu tubu 2. vodoravne

strelice prikazuju sile tlaka između srednjeg uha i unutrašnjeg uha, preko membrane Scarpe i stapesa.

Clinical features

Hearing loss, tinnitus and dizziness are the leading symptoms. Hearing loss is sensorineural, and if the eardrum or middle ear structures are also damaged, the hearing impairment is mixed. Nystagmus may also occur.

If a window rupture occurs, the labyrinthine fistula test is positive in about 30% of cases, a Hennebert's sign may occur, and a reasonable suspicion is raised if hearing fluctuates, with a sudden onset of dizziness, nausea or vomiting.[14,16]

Treatment

Damages to the ear without a window rupture are treated in hospital with bed rest and corticosteroids. Corticosteroids should not be given for more than two weeks, with a gradual decrease in dosage when most mild and moderate hearing impairments are satisfactorily recovering. Severe damages take 6 to 7 weeks to recover, while complete recovery occurs in 50% of patients.[17,18]If labyrinthine fistula is suspected, patients must be hospitalized, with strict bed rest and with the head inclined by 30 to 40 degrees, 7 to 10 days, with sedation if necessary. Heavy physical activity is not recommended for 4 weeks after release from hospital. Nose blowing is forbidden, and the patient must sneeze through open mouth. To minimize the Valsalva effect and the pressure increase of the cerebrospinal fluid, the use of laxatives is recommended as well. If the signs of liquor fistula persist, the ear must be surgically explored.[14,19]

Paparella proved on an animal model that complete healing of the Scarpa's membrane occurs in 90% of cases for a maximum of 9 days.[16] Surgical exploration performed too early risks the surgeon's entry into the non-transparent operative field caused by exudate, edema, and bleeding due to barotrauma. After identification of the round window, the patient should be placed in Trendeleburg position, an anesthesiologist insufflates the lungs for 30 seconds, and the surgeon inspects the eventual appearance of cerebrospinal fluid. The area around the stapes is also inspected. The fistula closes with a fibroadipose autologous tissue piece after careful cleaning of the surrounding from adhesions and mucosa.[14,19]

Barotrauma of the paranasal sinuses

Barotrauma of the paranasal sinuses occurs if their mouths are impenetrable. They are most commonly injured when diving, or landing, when negative pressure is maintained inside the sinus. Obstruction occurs due to anatomical anomalies, polyps, inflammatory edema of the mucosa, or a deformed nasal septum.[2,3]

Clinical features

The most common symptom is pain in the frontal sinuses, then in the ethmoid, and maxillary sinuses. The next symptom by frequency is epistaxis, which is generally neither serious nor long lasting. Cases of blindness, pneumocephalus, trigeminal nerve injury, and meningitis have been sporadically reported as a consequence of barotrauma of the sinuses.[1]

The diagnosis is made on the basis of clinical features and a radiograph. Sinus mucosal edema mimics cystic formation. The aeroliquid level can also be seen. Interestingly, although pain in the frontal sinuses is most common, radiological changes are most commonly seen in the maxillary sinuses.[2,3]

Treatment

Decongestants are sufficient (enough), the routine use of antibiotics is not recommended. It is necessary to diagnose predisposing factors by diagnostic, computerized tomography or endoscopy and to eliminate ostium obstruction by surgical methods.[20,21]

After barotrauma, it is advisable to make an initial RTG imaging of the sinuses, as diving is allowed after 6 weeks if the radiological pathological finding has regressed.[2]

Prevention

If there is a pain in the sinuses, a dive up to 6 m deep must be slowed.down Unless the pain regresses, diving must not be continued. Diagnostic processing and treatment are required, then repeat the dive, preferably in a swimming pool under controlled conditions.[20,22]

Conclusion

A modern man is increasingly diving, flying, professionally and even more for recreation (diving is the fastest growing recreational sport in the USA). Barotrauma of the ears and sinuses is becoming a more frequent diagnose in the pathology of tourism medicine. Therefore, the incidence of such injuries is expected to increase in Croatia as well.

References

1. Becker GD, Parell GJ. Barotrauma of the ears and sinuses after scuba diving. Eur Arch Otorhinolaryngol 2001;258: 159-163
2. Mallen JR, Roberts DS. SCUBA Medicine for otolaryngologists: Part I. Diving into SCUBA physiology and injury prevention. Laryngoscope 2020;130: 52-58.
3. Neblett ML. Otolaryngology and sport scuba diving. Ann Otol Rhinol Laryngol 1985; 94 (suppl 115):1-12.
4. Rišavi A. Avijacijska i astronautska otorinolaringologija. U: Šercer A. Otorinolaringologija II, Zagreb: Jugoslavenski leksikografski zavod, 1965;713-715.
5. Stieler O, Loba W, Gawęcki W.et al. The impact of regular diving on the condition of the middle ear. Int J Occup Med Environ Health 2021;34:779-788.
6. Sade J, Amos A, Fuchs C. Barotrauma vis-a-vis the «Chronic otitis media syndrome»: two condition with middle ear gas deficiency. Ann Otol Rhinol Laryngol 2003;112:230-235.
7. Weiss MH, Frost OJ. May children with otitis media with effusion safely fly? Clin Pediatr (Phila) 1987;26:567-568.
8. Orita Y, Sando I, Hasebe S, Miura M. Postnatal change on the location of Ostmann s fatty tissue in the region lateral to Eustachian tube. Int J Pediatr Otorhinolaryngol 2003;67:1105-1112.
9. Klingmann C, Praetorius M, Baumann I, Plinkert PK. Otorhinolaryngologic disorders and diving accidents: an analysisi of 306 divers. Eur Arch Otorhinolaryngol 2007;264:1243-1251.
10. Lasak JM, Van Ess M, Kryzer TC, Cummings RJ. Middle ear injury through the external auditory canal: a review of 44 cases. Ear Nose Throat J 2006;85:722,724-8.
11. Hüttenbrink KB. Biomechanics of stapesplasty: a review. Otol Neurotol 2003;24:548-557.
12. Pelausa EO. The history of otolaryngology in the Canadian military: from first to last. J Otolaryngol 1997;26:345-350.
13. Thompson JN, Kohut KI. Perilymph fistulae: variability of symptoms and results of surgery. Otolaryngol Head Neck Surg 1979;87:898-903.
14. Scarpa A, Ralli M, De Luca P. et al. Inner Ear Disorders in SCUBA Divers: A Review. J Int Adv Otol 2021;17:260-264
15. Antonelli PJ, Parell GJ, Becker GD, Paparella MM. Temporal bone pathology in scuba diving deaths. Otolaryngol Head Neck Surg 1993;109:514-521.
16. Paparella MM, Schachern PA, Choo YB. The round window membrane: otological observations. Ann Otol Rhinol Laryngol 1983;92:629-634.
17. Singleton GT, Post KN, Karlan MS, Bock DG. Perilymph fistulas. Diagnostic criteria and therapy. Ann Otol Rhinol Laryngol 1978;87:797-803.
18. Parell GJ, Becker GD. Conservative management of inner ear barotrauma resulting from scuba diving. Otolaryngol Head Neck Surg 1985;93:393-397.
19. Pullen FW 2nd. Perilymphatic fistula induced by barotrauma. Am J Otol 1992;13:270-272.
20. Lynch JH, Deaton TG. Barotrauma with extreme pressures in sport: from scuba to skydiving. Curr Sports Med Rep 2014;13:107-112
21. Murrison AW, Smith DJ, Francis TJ, Counter RT. Maxillary sinus barotrauma with fifth cranial nerve involvement. J Laryngol Otol 1991;105:217-219.
22. Parell GJ, Becker GD. Neurological consequences of scuba diving with chronic sinusitis. Laryngoscope 2000;110:1358-1360.

Professional paper
Stručni članak

ISSN 0351-0093
Coden: MEJAD 53 (2023) 4

The impact of early caloric intake on growth parameters in extremely preterm neonates

Utjecaj ranog kalorijskog unosa na parametre rasta u izrazito nezrele nedonoščadi

Tihana Nađ, Nora Pušeljić, Krešimir Šantić, Lea Arambašić, Darjan Kardum*

Summary

Introduction: Even though adequate caloric intake is essential for the promotion of growth in extremely premature infants, this is rarely achieved. We investigated how total caloric intake in the first week of life and other events during the hospitalization impact head circumference and weight at 36 weeks of corrected age in extremely preterm infants.

Patients and methods: The study sample consisted of extremely preterm infants treated at Osijek University Hospital Centre, born between January 2018 and December 2020. Records were collected regarding nutritional data, sex, gestational age, birth weight and head circumference, invasive respiratory support, bacterial infection, necrotizing enterocolitis, postnatal steroids, need for supplemental oxygen at 36 weeks gestation, day of introduction of enteral nutrition, duration of parenteral nutrition, length of stay, hemodynamically significant patent ductus arteriosus, cystic periventricular leukomalacia and retinopathy of prematurity.

Results*:* The study cohort included 30 infants. At 36 weeks gestation for weight, median Z scores were -1.63 (IQR -2.34 to -1.15; 95% CI -2.09 to -1.52), and for head circumference were -1.32 (IQR 2.37 to -0.81; 95% CI -1.75 to -0.91). Median energy intake on the first day of life was 33.42 kcal/kg, and 80.78 kcal/kg on day 7. Early caloric intake was not correlated with changes in Z scores for head circumference and weight at 36 weeks of gestation. Other factors influenced changes in head circumference and weight Z scores, namely: gestational age, respiratory support during the first week, need for additional O_2 at 36 weeks, and retinopathy of prematurity requiring intervention.

Conclusion: In our cohort of premature infants at 36 weeks corrected age other factors, not primarily total caloric intake influenced growth parameters.

Key words: Premature Birth, Extremely Premature Infant, Energy Intake, Growth

Sažetak

Uvod: Iako je adekvatan unos kalorija neophodan za poticanje rasta ekstremno nezrele nedonoščadi, on se rijetko postiže. Istraživali smo kako ukupni kalorijski unos u prvom tjednu života, kao i drugi događaji tijekom hospitalizacije utječu na promjenu opsega glave i težine u 36. tjednu korigirane dobi u izrazito nezrele nedonoščadi.

Bolesnici i metode: Uzorak istraživanja činila je izrazito nezrela nedonoščad koja je liječena u Kliničkom bolničkom centru Osijek, a rođena su od siječnja 2018. do prosinca 2020.godine. Prikupljeni su podaci o kalorijskom unosu, spolu, gestacijskoj dobi, porođajnoj težini, opsegu glave, invazivnoj respiratornoj potpori, bakterijskim infekcijama, nekrotizirajućem enterokolitisu, primjeni postnatalnih steroida, potrebi za dodatnim kisikom u 36. tjednu gestacije, vremenu vođenja enteralne prehrane, trajanju

[*] **Osijek University Hospital Centre, Department of Pediatrics** (Tihana Nađ,MD; Nora Pušeljić, MD); **University J.J. Strossmayer Osijek, Faculty of Medicine**(Tihana Nađ,MD; Lea Arambašić, studentica medicine; Krešimir Šantić,MD; Darjan Kardum, MD,PhD); **Zadar General Hospital, Department of Neonatology** (Darjan Kardum,MD, PhD)

Corresponding address / *Adresa za dopisivanje:* Darjan Kardum, MD, PhD, General Hospital Zadar, Department of neonatology, B.Peričića 5, 23000 Zadar; University J.J. Strossmayer Osijek, J. Huttlera 4, 31000 Osijek E-mail: darjankardum@gmail.com

Received/*Primljeno* 2023-10-09; Revised/*Ispravljeno* 2023-10-25; Accepted/*Prihvaćeno* 2023-11-16

parenteralne prehrane, duljini boravka, postojanju hemodinamski značajanog ductus arteriosus-a, cističnoj periventrikularnoj leukomalaciji i retinopatiji nedonoščadi.

Rezultati: Studijska kohorta uključivala je 30 izrazito nezrele nedonoščadi. U 36. tjednu trudnoće za težinu, medijan Z skora je bio -1,63 (IQR -2,34 do -1,15; 95% CI -2,09 do -1,52), a za opseg glave bio je -1,32 (IQR 2,37 do -0,81; 95% CI -1,75 do -0,91). Medijan energetskog unosa prvog dana života iznosio je 33,42 kcal/kg, a 7. dana 80,78 kcal/kg. Rani unos kalorija nije bio u korelaciji s promjenama u Z rezultatima za opseg glave i težinu u 36. tjednu gestacije. Na promjene u Z rezultatima opsega glave i težine utjecalis u drugi čimbenici: gestacijska dob, respiratorna podrška tijekom prvog tjedna, potreba za dodatnim O_2 u 36. tjednu i retinopatija nedonoščadi koja zahtijeva intervenciju.

Zaključak: U kohorti izrazito nezrele nedonoščadi, u korigiranoj dobi od 36 tjedana, drugi čimbenici, a ne primarno ukupni kalorijski unos, utjecali su na parametre rasta.

Ključne riječi: Prijevremeni porod, izrazito nezrela nedonoščad, energetski unos, rast

Med Jad 2023;53(4):263-270

Introduction

Head circumference and weight are routinely measured during the course of treatment of premature infants. Weight is usually measured every 24 or 12 hours and head circumference is usually measured on a weekly basis. This data provides valuable short term insights into the premature infants' clinical condition and has been used as a predictor of total cerebral volume and neurological outcomes.[1]

Weight gain changes[2] and head circumference trajectory during the initial neonatal intensive care unit (NICU) hospitalization, independently of each other have shown to reflect neurodevelopmental outcomes.[3] Even though adequate caloric intake is essential for promotion of growth in extremely premature infants, this is rarely achieved due to a variety of reasons (overall poor state of the neonate, abdominal distension due to CPAP administration, hyperglycemia, gut ischemia, hyperlipidemia, high blood urea concentration).[4]

The stated goal in providing adequate caloric and micronutrient intake in extremely premature infants is to meet the growth rate of the healthy fetus of the same gestational age.[5] However, in most cases of extreme prematurity it takes up to 17 days for the preterm infant to regain birth weight.[6]

At the corrected age of 36 weeks gestation, approximately 90% of extremely preterm infants suffer from growth restriction.[7] Better growth until discharge in very preterm infants is associated with reduced incidence of bronchopulmonary dysplasia (BPD)[8], reduced risk for severe retinopathy of prematurity (ROP)[9], better brain growth[10] and better neurodevelopmental and growth outcomes.[11]

The purpose of our study was to investigate how total caloric intake in the first week of life and other conditions during the hospitalization impact head circumference and weight at 36 weeks of corrected age.

Patients and methods

This study included all extremely low gestational age (<28 gestational weeks) infants treated and discharged from the Osijek University Hospital Centre, born between January 2018 and December 2020 (n = 30). Only inborn infants were included in the study. The exclusion criteria for the study included death before 36 weeks gestation, hypertensive hydrocephalus, and severe congenital malformation. The final sample consisted of 30 extremely preterm infants. Data regarding nutrition was gathered from the patient's records.

Daily nutritional data was collected from the first incomplete day (on an hourly basis) and after then for the next 6-24 hour days. The estimation of nutrient composition in human milk was as follows: 1.5 g/100 mL for protein, 2.6 g/100 mL for lipids, and 6.2 mg/100 mL for carbohydrates, as per Cormack et al.[12] For infants who were given preterm formula within the first week of life, energy and nutritional calculations were determined based on the disclaimers provided by the manufacturer of the preterm formula.

For parenteral nutrition, the energy content was calculated using the recommended values provided by Cormack et al.[12]: 4 kcal/g for parenteral protein, 10 kcal/g for lipids, and 3.4 kcal/g for carbohydrates. In previous studies, breast milk was estimated to contain 65 kcal/100 ml.[7]

Supplementary data were obtained from the patient records, encompassing information such as the date and time of birth, gender, gestational age, birth weight, head circumference with Z scores, instances of invasive respiratory support within the first week of life, and the presence of early bacterial infection, necrotizing enterocolitis requiring surgery, postnatal steroids for prevention of BPD, need for supplemental oxygen at 36 weeks gestation, day of introduction of enteral nutrition, total duration of

parenteral nutrition, length of hospital stay, hemodynamically significant patent ductus arteriosus (PDA), presence of cystic periventricular leukomalacia and retinopathy of prematurity requiring intervention.

The study outcomes comprised the weight and head circumference, along with their respective Z scores, measured at 36 weeks gestation. These Z scores were calculated using the Fenton growth charts specifically designed for preterm infants.[13]

Investigation of this data set was approved as a part of doctoral dissertation by Osijek University Hospital Centre and Faculty of Medicine, University J. J. Strossmayer Osijek Ethics Committee No. 2158-61-07-19-51. Research carried out is in compliance with Helsinki Declaration.

Statistical analysis

Descriptive statistical methods were employed to describe the data. The association between variables that did not follow a normal distribution was assessed using the Spearman's rho test. Linear regression was utilized to identify significant predictors in predicting Z-score Weight and head circumference. A significance level of 0.05 (Alpha) was set. The statistical analysis was conducted using MedCalc® Statistical Software version 22.006 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023).

Results

The final cohort consisted of 30 extremely preterm neonates. The clinical characteristics of the study population are shown in Table 1.

The median energy intake on the first day of life (DOL) was 33.42 kcal/kg, which progressively increased to 80.78 kcal/kg by DOL 7. The average energy intake during the first week of life is presented in Table 2.

At birth, the median Z scores for weight were 0.13 (IQR -0.31 to 0.86; 95% CI -0.20 to 0.46) and for head circumference were -0.14 (IQR -0.94 to 0.50; 95% CI -0.43 to 0.34). At 36 weeks gestation for weight, median Z scores were -1.63 (IQR -2.34 to -1.15; 95% CI -2.09 to -1.52), and for head circumference were -1.32 (IQR 2.37 to -0.81; 95% CI -1.75 to -0.91). This is shown in Figure 1.

We analyzed the correlation of different factors and changes in head circumference and weight Z scores at 36 weeks gestation. For weight changes the only significant correlation was with gestational age, while for changes in head circumference Z scores were correlated with gestational age, any respiratory support during the first week, the need for additional O_2 at 36 weeks, and retinopathy of prematurity requiring intervention. This is shown in Table 3.

A linear regression (bivariate regression) analysis was done to determine the impact of each of the factors examined on the variation in Z scores in head circumference and weight at 36 weeks gestation. The sole factor influencing changes in weight at 36 weeks gestation was gestational age, while regarding changes in Z scores in head circumference were gestational age, need for supplemental oxygen, birth weight, invasive respiratory support during the first week of life and NEC requiring surgery. No significant correlation was observed between energy intake during the first week of life and changes in Z scores, as indicated in Table 4.

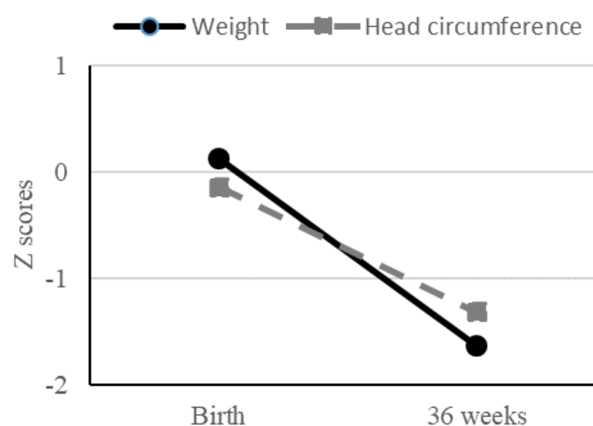


Figure 1 Changes in weight and head circumference from birth to 36 weeks gestation corrected age

Slika 1. Promjene u težini i opsegu glave od rođenja do 36 tjedana korigirane dobi

Discussion

The objective of this study was to examine the potential significance of early caloric intake during the first week of life in extremely premature infants on growth parameters at 36 weeks of corrected gestational age. Additionally, the study aimed to analyze the influence of other factors and their impact on these growth parameters.

Meeting the optimal caloric intake during the initial weeks of life for extremely premature infants is often challenging.[14] This difficulty arises from the fact that nutritional support for these infants, until they can establish full enteral feeds, relies on parenteral nutrition.[15] According to published guidelines, it is recommended to achieve full enteral feeds within 7 days for infants weighing between 1–1.5 kg and within 14 days for infants weighing less than 1 kg.[16] However, in this study population, the infants did not receive the recommended energy

amounts during the first week of life, as suggested by the guidelines (Table 2). These findings align with similar results reported in other studies.[7]

Table 1 Clinical characteristics of the study population
Tablica 1. Kliničke karakteristike ispitivane populacije

Clinical characteristics/*Kliničke karakteristike*	
Sex, female (n %) *Spol, žensko*	14 (47)
Completed gestational age (Median (IQR*) *Završena gestacijska dob*	26 (25 – 27)
Birth weight (g) (Median IQR*) *Težina pri porodu*	0.872 (0.704 – 0.992)
Any invasive respiratory support during the first week (n (%) *Bilo koja invazivna respiratorna podrška tijekom prvog tjedna*	22 (73)
Early bacterial infection (n (%)) *Rana bakterijska infekcija*	11 (37)
NEC† requiring surgery (n (%) NEC†*koje traži kirurški zahvat*	4 (13)
Postnatal steroids (n (%) *Postanatalni steroidi*	9 (30)
O_2 at 36 weeks gestation (n (%) *O_2 u 36. tjednu trudnoće*	6 (20)
Day enteral nutrition started (Median (IQR*) *Započela dnevna enteralna prehrana*	2 (2 – 3)
The total duration of parenteral nutrition, days (Median (IQR*) *Ukupno trajanje parenteralne prehrane, dana*	30 (20 – 43)
Length of stay, days (Median (IQR*) *Duljina trajnja, dani*	77 (68 – 103)
Hemodynamically significant PDA (n (%) *Hemodinamski značajan PDA*	7 (23)
cPVL‡ (n (%))	2 (7)
ROP§ requiring intervention (n (%) ROP§ *koji zahtjeva intervenciju*	15 (50)

*IQR, interquartile range/*interkvartilni raspon*; †necrotizing enterocolitis/ *nekrotizirajući enterokolitis*, ‡cystic periventricular leucomalatia/ *cistična periventrikularna leukomalacija*; §ROP, retinopathy of prematurity/ *retinopatija nedonoščadi*

Table 2 Daily average energy intake during the first week
Tablica 2. Dnevni prosječni energetski unos tijekom prvog tjedna

Day of life/*dan života*	**Energy/*energija*, kcal/kg (Median (IQR*))**
1	33.42 (27.33 - 41.46)
2	57.68 (51.02 - 65.04)
3	65.54 (57.61 - 75.31)
4	70 (61.08 - 80.01)
5	73.71 (63.4 - 88.1)
6	79.08 (63.97 - 92.68)
7	80.78 (70.49 - 103.66)
Total per day, median (IQR*) *Sveukupno po danu*	67.25 (59.22 – 75.21)

*IQR, interquartile range/*interkvartilni raspon*

Table 3 Correlation of different factors and changes in head circumference and weight Z scores at 36 weeks gestation
Tablica 3. Korelacija različitih čimbenika i promjena u Z vrijednostima opsega glave i težine u 36. tjednu korigirane dobi

	Spearman Rho (P value) / *P vrijednost*	
Factor	**Change in head circumference Z score at 36 weeks** ***Promjena u Z rezultatu opsega glave u 36. tjednu***	**Change in weight Z score at 36 weeks** ***Promjena Z rezultata u težini nakon 36 tjedana***
Sex, female *Spol, žensko*	-0.278 (0.14)	0.139 (0.46)
Completed gestational age *Završena gestacijska dob*	0.526 (0.003)	0.383 (0.04)
Any invasive respiratory support during the first week *Bilo koja invazivna respiratorna podrška tijekom prvog tjedna*	-0.435 (0.02)	-0.209 (0.27)
Early bacterial infection *Rana bakterijska infekcija*	0.040 (0.83)	0.188 (0.32)
NEC* requiring surgery *NEC* koji zahtijeva kirurški zahvat*	-0.329 (0.08)	-0.136 (0.47)
Postnatal steroids *Postnatalni steroidi*	-0.332 (0.07)	0.130 (0.49)
O_2 at 36 weeks gestation *O_2 u 36. tjednu trudnoće*	-0.568 (0.001)	0.067 (0.72)
Day enteral nutrition started *Dan početka dnevne enteralne prehrane*	-0.177 (0.35)	0.090 (0.64)
PDA†	-0.219 (0.25)	-0.105 (0.58)
cPVL‡	-0.108 (0.57)	-0.232 (0.22)
ROP§ requiring therapy *ROP§ koji zahtijeva intervenciju*	-0.431 (0.02)	-0.089 (0.64)
Energy (kcal/kg) in the first 7 days *Energija kcal/kg kod prvih 7 dana*	0.291 (0.12)	0.154 (0.42)

*NEC, necrotizing enterocolitis, †PDA, patent ductus arteriosus, ‡cPVL, cystic periventricular leucomalatia; §ROP, retinopathy of prematurity
NEC, nekrotizirajući enterokolitis, †PDA, otvoreni ductus arteriosus, ‡cPVL, cistična periventrikularna leukomalacija; §ROP, retinopatija nedonoščadi

Table 4 Linear regression analysis of factors influencing changes in head circumference and weight Z scores
Tablica 4. Linearna regresijska analiza čimbenika koji utječu na promjene u Z vrijednostima opsega glave i težine

Risk Factor/*Faktor rizika*	**ß**	**95% CI**	**R2**	**P value**
Weight Z score changes / *Promjene u Z rezultatu težine*				
Sex, female /*spol, žensko*	0.18	-0.36 to 0.71	0.016	0.5
Completed gestational age *Završena gestacijska dob*	0.22	0.01 to 0.43	0.143	0.04
Any invasive respiratory support during the first week *Bilo koja invazivna respiratorna podrška tijekom prvog tjedna*	-0.31	-0.91 to 0.29	0.038	0.3
Early bacterial infection *Rana bakterijska infekcija*	0.31	-0.24 to 0.85	0.045	0.26
NEC* requiring surgery *NEC* koji zahtijeva kirurški zahvat*	-0.24	-1.03 to 0.55	0.014	0.54
Postnatal steroids *Postnatalni steroidi*	0.23	-0.35 to 0.81	0.023	0.42

Risk Factor/*Faktor rizika*	**ß**	**95% CI**	**R2**	**P value**
O_2 at 36 weeks gestation *O2 u 36. tjednu trudnoće*	0.12	-0.55 to 0.79	0.005	0.71
Day enteral nutrition started *Dan početka dnevne enteralne prehrane*	0.07	-0.13 to 0.27	0.017	0.49
Hemodynamically significant PDA† *Hemodinamski značajan PDA†*	-0.17	-0.81 to 0.46	0.011	0.58
cPVL‡	-0.63	-1.69 to 0.42	0.051	0.23
ROP§ requiring intervention *ROP§ koji zahtijeva intervenciju*	-0.09	-0.64 to 0.44	0.005	0.71
Energy kcal/kg (sum 7 days) *Energija kcal/kg (zbroj 7 dana)*	0.001	-0.002 to 0.005	0.017	0.49
Head circumference Z score changes / *Opseg glave Z rezultat se mijenja*				
Sex, female /*spol, žensko*	-0,55	-1.26 to 0.16	0.082	0.13
Completed gestational age *Završena gestacijska dob*		0.22 to 0.72	0.348	<0.001
Any invasive respiratory support during the first week *Bilo koja invazivna respiratorna podrška tijekom prvog tjedna*		-1.63 to -0.09	0.158	0.03
Early bacterial infection *Rana bakterijska infekcija*		-0.57 to 0.96	0.010	0.6
Birth weight *Težina pri porodu*	2,78	1.16 to 4.42	0.304	0.002
NEC* requiring surgery *NEC* koji zahtijeva kirurški zahvat*	-1,07	-2.08 to -0.06	0.145	0.04
Postnatal steroids *Postnatalni steroidi*	-0,64	-1.41 to 0.13	0.093	0.1
O_2 at 36 weeks gestation *O2 u 36. tjednu trudnoće*	-1,35	-2.11 to -0.58	0.316	0.001
Day enteral nutrition started *Dan početka dnevne enteralne prehrane*	-0,18	-0.46 to 0.09	0.064	0.18
Hemodynamically significant PDA† *Hemodinamski značajan PDA†*	-0,61	-1.45 to 0.24	0.072	0.15
cPVL‡	-0,25	-1.74 to 1.23	0.004	0.73
ROP§ requiring intervention *ROP§ koji zahtijeva intervenciju*	-0,78	-1.46 to -0.09	0.165	0.03
Energy kcal/kg (sum 7 days) *Energija kcal/kg (zbroj 7 dana)*	0,004	-0.001 to 0.01	0.102	0.09

*NEC, necrotizing enterocolitis, †PDA, patent ductus arteriosus, ‡cPVL, cystic periventricular leucomalatia; §ROP, retinopathy of prematurity
NEC, nekrotizirajući enterokolitis, †PDA, otvoreni ductus arteriosus, ‡cPVL, cistična periventrikularna leukomalacija; §ROP, retinopatija nedonoščadi

Recently, the traditional belief that extremely premature neonates should exhibit growth patterns similar to those of fetuses has been challenged. Despite implementing optimal clinical practices, a majority of extremely premature infants still experience extrauterine growth retardation. It is important to recognize that attaining fetal growth rates may not be realistic or appropriate for these infants, and that individualized growth trajectories should be considered to optimize their overall health and development.[17]

All 30 extremely premature infants in our cohort exhibited negative changes in Z scores for head circumference and weight at 36 weeks gestation (Figure 1). The observation that extremely premature infants experience extrauterine growth retardation is a recognized phenomenon supported by previous studies.[7,18] However, it is important to note that this initial growth delay is often followed by a period of catch-up growth. Catch-up growth typically begins in early infancy and typically concludes around 2-3 years of age, although in certain cases, it may extend into adolescence.[19]. During this catch-up growth phase, the premature infants show an accelerated growth rate, aiming to bridge the gap between their current growth status and the growth trajectory expected for their age. Monitoring and promoting appropriate catch-up growth are crucial for

optimizing the long-term health and development of extremely premature infants.

Subsequently, we conducted an analysis to examine the correlation between early caloric intake during the first weeks of life and other factors that could potentially influence the growth parameters in our cohort of extremely premature infants (Table 3). Interestingly, we did not find a significant correlation between total caloric intake during the first week of life and changes in Z scores for head circumference and weight at 36 weeks of gestation.

It is worth noting that other studies have examined growth patterns over longer periods, including until discharge or follow-ups of 1 to 3 years.[7,20-23] While our study did not specifically evaluate early caloric intake as a potential risk factor for long term postnatal growth, these other studies have considered various factors associated with achieving adequate caloric intake, and they have shown positive correlations with postnatal growth outcomes.

For instance, Lee et al found that the duration of total parenteral nutrition and the number of days required to reach enteral nutrition above 100 cc/kg were significantly associated with postnatal growth retardation.[20] Additionally, Kavurt et al identified that the time taken to regain birth weight was a risk factor for postnatal growth restriction in preterm infants.[23] A study by Hiltunen et al found a positive. association between energy intake during the first 7 days of life and weight, length, and head circumference from birth until the corrected age of 2 years.[7]

While our study did not observe a direct correlation between early caloric intake and growth parameters at 36 weeks of gestation, it is essential to consider that achieving adequate caloric intake and other related factors may still play a role in postnatal growth outcomes in the longer term.

For changes in weight Z scores at 36 weeks the only significant positive correlation was found for completed gestational age (p = 0.04), while for changes in head circumference Z scores a significant positive correlation was found for completed gestational age (p = 0.003), while a negative correlation was found in infants that received any invasive respiratory support during the first week (p = 0.02), and in those which had a need for additional O_2 at 36 weeks (p = 0.001) and those which developed retinopathy of prematurity requiring intervention (p = 0.02). These findings are reported by other researchers, they found that the severity of respiratory disease has a high impact on postnatal growth failure.[20-24]

In the linear regression analysis of factors influencing changes in head circumference Z scores additional factors were found to be significant, namely NEC requiring surgery (p = 0.04) and ROP requiring intervention (p = 0.03). This is also a finding reported earlier.[19,20]

Our study has several limitations. First, we analyze a relatively small number of patients. Second, we focused only on the impact on growth measurements until 36 weeks of corrected age. Several previous studies with long-term follow-up provide similar results, but only a small number of them provided some results regarding growth until term equivalent age.[7]

In conclusion, in our cohort of extremely premature infants, at 36 weeks corrected age, other factors, not primarily total caloric intake, influenced growth parameters, especially head circumference growth. However, this conclusion is not straightforward since respiratory problems, the infant's more severe general condition, and complications during hospitalization contributed to increased caloric requirements in extremely immature premature infants.

References

1. Georgieff MK, Mills MM, Zempel CE, Chang PN. Catch-up growth, muscle and fat accretion, and body proportionality of infants one year after newborn intensive care. J Pediatr 1989;114:288-92.
2. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006;117:1253-61.
3. Cho H, Kim EK, Song IG, Heo JS, Shin SH, Kim HS. Head growth during neonatal intensive care unit stay is related to the neurodevelopmental outcomes of preterm small for gestational age infants. Pediatr Neonatol 2021;62:606-611.
4. Ho MY, Yen YH. Trend of Nutritional Support in Preterm Infants. Pediatr Neonatol 2016;57:365-370.
5. American Academy of Pediatrics. Committee on Nutrition:Nutritional needs of low-birth-weight infants. Pediatrics 1985;75:976–986.
6. Hay WW Jr. Aggressive Nutrition of the Preterm Infant. Curr Pediatr Rep 2013;1:10.1007/s40124-013-0026-4.
7. Hiltunen H, Löyttyniemi E, Isolauri E, Rautava S. Early Nutrition and Growth until the Corrected Age of 2 Years in Extremely Preterm Infants. Neonatology 2018;113:100-107.
8. Uberos J, Jimenez-Montilla S, Molina-Oya M, García-Serrano JL. Early energy restriction in premature infants and bronchopulmonary dysplasia: a cohort study. Br J Nutr2 020;123:1024-1031.
9. Stoltz Sjöström E, Lundgren P, Öhlund I, Holmström G, Hellström A, Domellöf M. Low energy intake during the first 4 weeks of life increases the risk for severe retinopathy of prematurity in extremely preterm infants. Arch Dis Child Fetal Neonatal Ed

2016;101:F108-13.
10. Schneider J, Fischer Fumeaux CJ, Duerden EG et al. Nutrient Intake in the First Two Weeks of Life and Brain Growth in Preterm Neonates. Pediatrics 2018;141:e20172169.
11. Cleminson JS, Zalewski SP, Embleton ND. Nutrition in the preterm infant: what's new? Curr Opin Clin Nutr Metab Care 2016;19:220-5.
12. Cormack BE, Embleton ND, van Goudoever JB, Hay WW Jr, Bloomfield FH. Comparing apples with apples: it is time for standardized reporting of neonatal nutrition and growth studies. Pediatr Res 2016;79:810-20.
13. Fenton TR., Kim, JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.
14. Hay WW Jr. Optimizing nutrition of the preterm infant.Zhongguo Dang Dai Er Ke Za Zhi 2017;19:1-21.
15. Denne SC. Early nutritional support for extremely premature infants: what amino acid amount should be given? Am J Clin Nutr 2016;103:1383-4.
16. Dutta S, Singh B, Chessell L et al. Guidelines for feeding very low birth weight infants. Nutrients 2015;7:423-42.
17. Villar J, Giuliani F, Barros F et al. Monitoring the Postnatal Growth of Preterm Infants: A Paradigm Change. Pediatrics 2018;141:e20172467.
18. Cho H, Kim EK, Song IG, Heo JS, Shin SH, Kim HS. Head growth during neonatal intensive care unit stay is related to the neurodevelopmental outcomes of preterm small for gestational age infants. Pediatr Neonatol 2021;62:606-611.
19. Euser AM, de Wit CC, Finken MJJ, Rijken M, Wit JM. Growth of preterm born children. Horm Res 2008;70:319-28.
20. Lee SM, Kim N, Namgung R, Park M, Park K, Jeon J. Prediction of Postnatal Growth Failure among Very Low Birth Weight Infants. Sci Rep 2018;8:3729.
21. Lim J, Yoon SJ, Shin JE et al. Growth failure of very low birth weight infants during the first 3 years: A Korean neonatal network. PLoS One 2021;16:e0259080.
22. Liao WL, Lin MC, Wang TM, Chen CH; Taiwan Premature Infant Follow-up Network. Risk factors for postdischarge growth retardation among very-low-birth-weight infants: A nationwide registry study in Taiwan. Pediatr Neonatol 2019;60:641-647.
23. Kavurt S, Celik K. Incidence and risk factors of postnatal growth restriction in preterm infants. J Matern Fetal Neonatal Med 2018;31:1105-1107
24. Wang L, Lin XZ, Shen W et al. Chinese Multicenter EUGR Collaborative Group. Risk factors of extrauterine growth restriction in very preterm infants with bronchopulmonary dysplasia: a multi-center study in China. BMC Pediatr 2022;22:363.

Stručni članak
Professional paper

ISSN 0351-0093
Coden: MEJAD 53 (2023) 4

Utjecaj bolesti uzrokovane koronavirusom na primarnu i tercijarnu razinu zdravstvene zaštite iz perspektive otorinolaringologa

The impact of coronavirus disease on primary and tertiary health care levels from an otorhinolaryngological perspective

Mirta Pećek, Siniša Stevanović, Marijana Pećek Vidaković, Andro Košec*

Sažetak

Cilj istraživanja: Pandemija koronavirusa ima značajan utjecaj na društvo i zdravstveni sustav. Cilj ovoga rada je usporediti podatke o broju i strukturi dijagnoza i obavljenih pregleda iz područja otorinolaringologije i kirurgije glave i vrata na razini primarne (PZZ) i tercijarne zdravstvene zaštite, u razdoblju od godinu dana prije i godinu dana nakon proglašenja pandemije koronavirusa.

Bolesnici i metode: Podaci su prikupljani retrospektivno, za razdoblja od 20.3.2019. do 19.3.2020. i od 20.3.2020. do 20.3.2021. Uzorak je prigodan, prikupljen iz jedne ustanove na razini primarne i jedne ustanove na razini tercijarne zdravstvene zaštite. Iz dobivenih podataka isključene su one dijagnoze koje se ne odnose na stanja i bolesti iz otorinolaringologije i kirurgije glave i vrata.

Rezultati: Tijekom promatranog razdoblja 20.3.2020.-20.3.2021. došlo je do značajnog pada broja pregleda u objema ustanovama u odnosu na razdoblje 20.3.2019.-19.3.2020. Na razini PZZ bilo je ukupno 533 pregleda, što predstavlja 50,5% pregleda obavljenih u istom razdoblju 2019.godine, dok je na razini specijalističko-konzilijarne zdravstvene zaštite (SKZZ) obavljeno 1672 pregleda, odnosno 56,4% pregleda obavljenih 2019. godine. Do najvećeg pada broja pregleda na razini PZZ došlo je među dijagnozama: zloćudni melanom kože, gripa, akutni bronhitis i bronhiolitis, akutne infekcije gornjeg dišnog sustava i bronhitis, emfizem, astma i druge kronične opstruktivne bolesti. Analizirajući preglede obavljene u SKZZ, najveći pad broja pregleda zabilježen je za dijagnoze: pneumonija, bronhitis, emfizem, astma i druge kronične opstruktivne bolesti, oštećenje sluha, zloćudni melanom kože i ostale bolesti dišnog sustava.

Zaključci: Smanjeni broj pregleda i hospitalizacija u odnosu na vrijeme prije početka pandemije kao posljedicu mogu imati povećani broj bolesnika s novim dijagnozama, među kojima i karcinoma otkrivenih u kasnijim stadijima bolesti, što će u konačnici rezultirati kasnijim početkom liječenja i lošijim ishodom bolesti, ali i povećanim opterećenjem zdravstvenog sustava i povećanim troškovima liječenja.

Ključne riječi: COVID-19, primarna zdravstvena zaštita, tercijarna zdravstvena zaštita, organizacija zdravstvene skrbi, otorinolaringologija

Summary

Introduction: The SARS-CoV-2 pandemic has a profound impact on our society and health system. This paper aims to report the impact of the COVID-19 pandemic on patients referred to tertiary health care, as well as primary health care practice settings.

Patients and methods: The number of patient referrals to a University Hospital Center Otorhinolaryngology and Head and Neck Surgery department and a primary care office requiring patient consultations regarding otorhinolaryngologic conditions between March 20th, 2019 and March 19th, 2020, and March 20th, 2020 and March 20th, 2021, was retrospectively collected. Diagnoses that do not relate to

[*]**Medicinski fakultet Sveučilišta u Zagrebu** (Mirta Pećek, studentica medicine); **Klinički bolnički centar „Sestre milosrdnice“, Klinika za otorinolaringologiju i kirurgiju glave i vrata** (prim.dr.sc. Siniša Stevanović, dr.med.,dr.sc. Andro Košec, dr.med.); **Specijalistička ordinacija obiteljske medicine Marijana Pećek Vidaković, Orahovica** (Marijana Pećek Vidaković, dr.med.)

Adresa za dopisivanje / *Corresponding address:* Mirta Pećek, studentica medicine, Medicinski fakultet Sveučilišta u Zagrebu, Šalata 3, 10000 Zagreb E-mail: mirta.pec@gmail.com

Primljeno/*Received* 2022-09-17; Ispravljeno/*Revised* 2023-05-22; Prihvaćeno/*Accepted* 2022-11-17

conditions related to otorhinolaryngology and head and neck surgery, or those that were not found in both health care settings, were excluded.

Results: A significant reduction in the total number of consultations during the pandemic was observed, at both levels of health care. In primary care, 533 consultations were performed (50.5% of the total number in 2019), and at the tertiary level, 1672 consultations were performed (56.4% consultations performed in 2019). When analyzing the conditions treated in primary care, the most relevant reduction regarded skin melanoma, influenza, acute bronchitis and bronchiolitis, acute upper respiratory infections, bronchitis, emphysema, asthma, and other chronic obstructive pulmonary diseases. When analyzing the conditions treated at the ENT department, the most relevant reduction regarded pneumonia, bronchitis, emphysema, asthma, other chronic obstructive pulmonary diseases, hearing impairment, skin melanoma, and other respiratory tract diseases.

Conclusions: A reduced number of consultations and hospitalizations compared to pre-pandemic time may result in an increased number of patients with new diagnoses, including cancer detected in later stages of the disease, which will lead to later treatment and worse disease outcome, and also higher burden of treatment costs.

Keywords: COVID-19, primary health care, tertiary health care, health care organization, otorhinolaryngology

Med Jad 2023;53(4):271-278

Uvod

Pandemija koronavirusa ima značajan utjecaj na društvo i zdravstveni sustav, kojem je teško analizirati aktualni doseg, a posebice predvidjeti utjecaj na budućnost.[1] Tijekom prva četiri mjeseca 2020. godine, brzina transmisije SARS-CoV-2 bila je izrazito velika, te su stoga brojne vlade bile prisiljene uvesti stroge mjere zatvaranja (eng. *lockdown).*[2] Prvi slučaj koronavirusa u Hrvatskoj zabilježen je 25.veljače 2020. godine. Nakon što je Svjetska zdravstvena organizacija 11.ožujka 2020. proglasila pandemiju koronavirusa, sredinom je ožujka i u Hrvatskoj uveden *lockdown,* koji je u značajnoj mjeri promijenio opseg i vrstu postupaka u svim razinama sustava zdravstva. Cilj je ovoga rada usporediti podatke o broju i strukturi dijagnoza i obavljenih pregleda iz područja otorinolaringologije i kirurgije glave i vrata na razini primarne i tercijarne zdravstvene zaštite, u razdoblju od godinu dana prije i godinu dana nakon proglašenja pandemije koronavirusa.

Bolesnici i metode

Podaci su prikupljani retrospektivno za razdoblja od 20.3.2019. do 19.3.2020. i od 20.3.2020. do 20.3.2021. Prikupljani su podaci iz jedne ustanove na razini primarne (Specijalistička ordinacija obiteljske medicine Marijana Peček Vidaković, Orahovica; PZZ) i jedne ustanove na razini tercijarne zdravstvene zaštite (Klinika za otorinolaringologiju i kirurgiju glave i vrata Kliničkog bolničkog centra Sestre milosrdnice, specijalističko-konzilijarna zdravstvena zaštita, SKZZ). Podaci su prikupljeni iz medicinskih informacijskih sustava (Medicus.net i Bolnički informatički sustav - BIS). Dobiveni su podaci o svim posjetama i pregledima prema dijagnozama (prema Međunarodnoj klasifikaciji bolesti) u navedenim ustanovama za ranije definirana razdoblja, te oni čine prigodni uzorak. Iz dobivenih podataka isključene su one dijagnoze koje se ne odnose na stanja i bolesti iz otorinolaringologije i kirurgije glave i vrata i one koje nisu zajedničke objema razinama zdravstvene zaštite. Iz skupine „Ostale bolesti dišnog sustava“ isključene su sljedeće dijagnoze: J00-J06 (akutne infekcije gornjeg dišnog sustava), J10-J11 (gripa), J12-J18 (pneumonija), J20-J21 (akutni bronhitis i bronhiolitis), J40-J44, J47 (bronhitis, emfizem, astma i druge kronične opstruktivne bolesti) i J60-J70 (plućne bolesti uzrokovane vanjskim agensima, pneumokonioze), a iz skupine ostale bolesti uha i mastoidnog nastavka: H65-H75 (upala srednjeg uha i druge bolesti srednjeg uha i mastoida) i H90-H91 (oštećenje sluha), jer su u analizi incidencije pregleda po dijagnozama obrađene kao zasebne kategorije. Uključni kriteriji bili su: svi bolesnici koji su imali dostupne potpune podatke o datumu i razlogu pregleda, te MKB šifru koja odgovara ORL području. Na razini SKZZ iz istraživanja je isključeno 19,2% bolesnika za razdoblje od 20.3.2019. do 19.3.2020. i 13% bolesnika za razdoblje od 20.3.2020. do 20.3.2021. Istraživanje je provedeno po STROBE smjernicama i sukladno etičkim načelima Deklaracije iz Helsinkija iz 2000. godine i njezinim dopunama iz 2002. i 2004. godine. Zbog retrospektivne prirode istraživanja nije bilo potrebno tražiti etičko odobrenje od ustanova u kojima je provedeno istraživanje.

Rezultati

Tijekom promatranog razdoblja 20.3.2020.-20.3.2021.došlo je do značajnog pada broja pregleda u objema ustanovama u odnosu na razdoblje 20.3.2019.-19.3.2020. Na razini PZZ bilo je ukupno 533 pregleda, što predstavlja 50,5% pregleda obavljenih u istom razdoblju 2019.godine (1055), dok

je na razini SKZZ obavljeno 1672 pregleda, odnosno 56,4% pregleda obavljenih 2019. godine (2962). Do najvećeg pada broja pregleda na razini PZZ došlo je među dijagnozama: zloćudni melanom kože (-100%), gripa (-100%), akutni bronhitis i bronhiolitis (-82,4%), akutne infekcije gornjeg dišnog sustava (-75%) i bronhitis, emfizem, astma i druge kronične opstruktivne bolesti (-59,4%). Povećan broj pregleda obavljen je za dijagnoze zloćudna novotvorina dušnika, dušnice i pluća (+100%), pneumonija (+100%) i ostale bolesti uha i mastoidnog nastavka (+19,3%) (Tablica 1.).

Broj upućivanja na specijalističke preglede u navedenom razdoblju smanjio se za 36,6% (s 3692 na 2340 upućivanja s razine PZZ).

Nakon pojave SARS-CoV-2 zabilježen je pad broja pregleda u hitnim otorinolaringološkim ambulantama diljem svijeta.[3] Analizirajući preglede obavljene u SKZZ, najveći pad broja pregleda zabilježen je za dijagnoze: pneumonija (-100%), bronhitis, emfizem, astma i druge kronične opstruktivne bolesti (-100%), oštećenje sluha (-74,6%), zloćudni melanom kože (-73,7%) i ostale bolesti dišnog sustava (-57,8%). Unutar skupine „Ostale bolesti dišnog sustava“ do najvećeg pada broja pregleda došlo je među dijagnozama devijacija nazalnog septuma (-41,1%) i hipertrofija tonzila s hipertrofijom adenoida (-96,1%). Povećan broj pregleda zabilježen je u skupini dijagnoza objedinjenih pod „Ostali vanjski uzroci slučajnih ozljeda“ (+44,4%), koji obuhvaćaju dijagnoze S01-S09 (Tablica 2.).

Tablica 1. Incidencija pregleda po dijagnozama u PZZ
Table 1 *Incidence of examinations by diagnoses in primary health care*

Dijagnoza *Diagnosis*	PZZ 2019. *Primary health care 2019*	PZZ 2020. *Primary health care 2020*
Zloćudna novotvorina dušnika (traheje), dušnice (bronha) i pluća *Carcinoma of trachea, bronchus and lungs*	2	4
Zloćudni melanom kože *Skin melanoma*	2	0
Ostale zloćudne novotvorine *Other carcinomas*	30	25
Novotvorine in situ i dobroćudne novotvorine nepoznate prirode *In situ neoplasm and tumors of undefined neoplastic nature*	59	38
Poremećaji štitnjače *Thyroid diseases*	40	33
Upala srednjeg uha i druge bolesti srednjeg uha i mastoida *Otitis media and other middle ear and mastoid process diseases*	55	31
Oštećenje sluha *Hearing impairment*	2	1
Ostale bolesti uha i mastoidnog nastavka *Other ear and mastoid process diseases*	62	74
Akutne infekcije gornjeg dišnog sustava *Acute upper respiratory infections*	453	115
Gripa *Influenza*	14	0
Pneumonija *Pneumonia*	3	6
Akutni bronhitis i akutni bronhiolitis *Acute bronchitis and bronchiolitis*	17	3
Bronhitis, emfizem, astma i druge kronične opstruktivne bolesti pluća *Bronchitis, emphysema, asthma, and other chronic obstructive pulmonary diseases*	32	13
Ostale bolesti dišnog sustava *Other respiratory tract diseases*	96	80
Bolesti usne šupljine, žlijezda slinovnica i čeljusti *Oral cavity, salivary glands and jaw diseases*	7	5
Ostali vanjski uzroci slučajnih ozljeda *Other external causes of accidental injuries*	181	105

Tablica 2. Incidencija pregleda po dijagnozama u SKZZ
Table 2 Incidence of examinations by diagnoses in specialist - consultative healthcare

Dijagnoza *Diagnosis*	SKZZ 2019. / *Specialist - con sultative healthcare 2019*	SKZZ 2020. / *Specialist - con sultative healthcare 2020*
Zloćudna novotvorina dušnika (traheje), dušnice (bronha) i pluća *Carcinoma of trachea, bronchus and lungs*	4	42
Zloćudni melanom kože *Skin melanoma*	19	5
Ostale zloćudne novotvorine *Other carcinomas*	628	489
Novotvorine in situ i dobroćudne novotvorine nepoznate prirode *In situ neoplasm and tumors of undefined neoplastic nature*	272	167
Poremećaji štitnjače *Thyroid diseases*	285	178
Upala srednjeg uha i druge bolesti srednjeg uha i mastoida *Otitis media and other middle ear and mastoid process diseases*	252	148
Oštećenje sluha *Hearing impairment*	67	17
Ostale bolesti uha i mastoidnog nastavka *Other ear and mastoid process diseases*	146	92
Akutne infekcije gornjeg dišnog sustava *Acute upper respiratory infections*	15	15
Gripa *Influenza*	0	0
Pneumonija *Pneumonia*	2	0
Akutni bronhitis i akutni bronhiolitis *Acute bronchitis and bronchiolitis*	0	0
Bronhitis, emfizem, astma i druge kronične opstruktivne bolesti pluća *Bronchitis, emphysema, asthma, and other chronic obstructive pulmonary diseases*	1	0
Ostale bolesti dišnog sustava *Other respiratory tract diseases*	1242	524
Bolesti usne šupljine, žlijezda slinovnica i čeljusti *Oral cavity, salivary glands and jaw diseases*	11	7
Ostali vanjski uzroci slučajnih ozljed *Other external causes of accidental injuries*	18	26

Rasprava

Kako bi se izbjegla preopterećenost zdravstvenog sustava, bilo je nužno prilagoditi javni zdravstveni sustav epidemiološkoj situaciji, reorganizirati bolnički sustav i primarnu zdravstvenu zaštitu, ograničiti kirurške zahvate na one najhitnije, te optimizirati raspodjelu zdravstvenih resursa (ljudskih i materijalnih).[4-7] S obzirom na sve veći broj zaraženih SARS-CoV-2 bolesnika, skrb i liječenje tih bolesnika postalo je fokusom većine zdravstvenih sustava.[8-11]

Na razini PZZ u razdoblju 20.3.2020.-20.3.2021. ostvareno je 23 217 posjeta, što predstavlja 94,8% posjeta ostvarenih u razdoblju 20.3.2019-19.3.2020. (24 501). Broj posjeta povezanih sa stanjima i bolestima iz područja ORL i KGV smanjen je za gotovo 50% u odnosu na razdoblje prije proglašenja pandemije (s 1055 na 533). Na razini SKZZ u razdoblju 20.3.2020.-20.3.2021. ostvareno je 1922 posjeta, što predstavlja 52,5% posjeta ostvarenih u razdoblju 20.3.2019-19.3.2020. (3664). Na smanjenje dostupnosti svih razina zdravstvene zaštite u Zagrebu, utjecaj je imao i razoran potres koji je pogodio grad u ožujku 2020.godine, što je dovelo do reorganizacije, kako prostornih, tako i ljudskih resursa.

Prema Godišnjem izvješću o radu stacionarnih zdravstvenih ustanova, na stacionarnim odjelima hrvatskih bolnica bilo je 581 093 otpusta osoba liječenih po pojedinim bolničkim djelatnostima tijekom 2020. godine (u 2019. godini bilo ih je 715 639), uključujući boravke u bolnici zbog poroda,

pobačaja i bolničke rehabilitacije. Od toga, 530 117 otpusta za osobe koje su liječene u akutnim bolničkim djelatnostima, a 50 976 u kroničnim bolničkim djelatnostima.[12] S obzirom na navedeni pad broja posjeta u PZZ i SKZZ, posljedično je vidljiv i pad broja hospitalizacija za 18,8%.

U 2019. godini broj umrlih iznosio je 51 794. Najviše osoba umrlo je od ishemijske bolesti srca (7 965) i cerebrovaskularnih bolesti (5 180). Slijede šećerna bolest (4 017) i hipertenzija (3 789), rak bronha i pluća (2 874) na petom mjestu, te rak debelog crijeva (2 095) na šestom mjestu. Na sedmom mjestu je kronični bronhitis, emfizem i astma (1 908), na osmom se pojavljuje ateroskleroza (1 180), na devetom kronične bolesti jetre (967), a na desetom rak prostate (807).[13] Prema podacima Državnog zavoda za statistiku u 2020. godini zabilježen je porast broja umrlih osoba u odnosu na 2019. godinu, tj. umrlo je 5 229 osoba više, ukupno 57 023. Najviše osoba umrlo je od ishemijske bolesti srca (7 589) i cerebrovaskularnih bolesti (4 950). Slijede šećerna bolest (4 697) na trećem i hipertenzija (4 487) na četvrtom mjestu, bolest uzrokovana koronavirusom (eng.coronavirus disease 2019, COVID-19) (4 478) na petom mjestu, rak bronha i pluća (2 819) na šestom, te rak debelog crijeva (2 079) na sedmom mjestu. Na osmom mjestu ove godine je kronični bronhitis, emfizem i astma (1 696), na devetom je ateroskleroza (1 569), a na desetom insuficijencija srca (865).[14] U 2019.godini od bolesti dišnog sustava (J00-J99) preminulo je 2 313 osoba, a 2020. njih 2 224.[13,14]

Dostupnost zdravstvene zaštite odnosi se na dobivanje adekvatne zdravstvene skrbi onda kada je ona potrebna.[15] Ekonomske, socijalne i organizacijske prepreke mogu utjecati na dostupnost zdravstvene zaštite.[16] Širenje SARS-CoV-2 imalo je globalni utjecaj na ekonomiju, dostupnost zdravstvene zaštite, a do izražaja su došle i brojne socioekonomske nejednakosti.[17] S obzirom na to da se mnogi zdravstveni sustavi nisu adekvatno prilagođavali organizacijskim izazovima pandemije, rasla je zabrinutost oko dostupnosti i pravilnog pružanja zdravstvene skrbi.[18] Već su na početku pandemije izdane preporuke o mobilizaciji i preraspodjeli zdravstvenog osoblja, prvenstveno zbog njihovog nedostatka u bolničkim sustavima.[19] U nekim je ustanovama došlo do podjele zdravstvenog osoblja na one koji rade na COVID-odjelima i na one koji rade na ostalim odjelima.[20] Neke su bolnice, s ciljem povećanja sigurnosti bolesnika i osoblja, odgađale sve preglede koji nisu bili hitni.[21] Starija životna dob, strah od suočavanja s obolijevanjem od COVID-19, anksioznost, izbjegavanje mjesta s mnogo ljudi, češće pranje ruku i nošenje zaštitne maske, bili su značajni čimbenici koji su utjecali na otkazivanje pregleda tijekom pandemije.[22]

Izravan kontakt s oboljelima od COVID-19 zahtijeva odgovarajuću zaštitu medicinskog osoblja, a posebno otorinolaringologa, anesteziologa i liječnika u jedinicama intenzivne njege.[23]

Pandemija koronavirusa uzrokovala je smanjenu dostupnost zdravstvene zaštite diljem svijeta, neovisno o tome radi li se o razvijenim zemljama ili o zemljama u razvoju. U Njemačkoj i Italiji uočen je smanjen broj prijama u hitnu službu među pedijatrijskom populacijom.[15] Iako su djeca i odrasli izloženi različitim respiratornim virusima tijekom cijele godine, tijekom pandemije koronavirusa, zbog uvođenja *lockdowna,* ograničenja putovanja i preporuke nošenja zaštitne maske, stopa transmisije ovih virusa bila je niža nego inače.[24] Tome u prilog govore i naši podaci u kojima je vidljivo da tijekom razdoblja od 20.3.2020. do 20.3.2021. nije zabilježen nijedan slučaj gripe, a na razini primarne zdravstvene zaštite došlo je do pada broja pregleda zbog akutnih infekcija gornjeg dišnog sustava za gotovo 75%. Zbog smanjenog izlaganja respiratornim virusima tijekom zimskih mjeseci, stvorena je posebno ranjiva skupina djece mlađe od 5 godina, bez prethodno stečenog imuniteta.[25] Posljedice toga bile su vidljive već 2021. godine na Novom Zelandu, gdje je zabilježen povećan broj oboljele i hospitalizirane djece zbog respiratornih infekcija, a među njima i mnogi oboljeli od respiratornog sincicijskog virusa.[26]

U Danskoj je zabilježen smanjen broj prvih pregleda povezanih uz nesreće, maligne bolesti i bolesti vezivnog tkiva.[27] Uvođenje *lockdowna* rezultiralo je i smanjenim brojem pregleda povezanih s anksioznim poremećajima u Švicarskoj i Španjolskoj, smanjenim brojem hospitalizacija na odjelima kardiologije u Italiji, a u Njemačkoj je zabilježen i pad broja pregleda vezanih uz neurološka stanja, među kojima je najveći zabilježeni pad povezan uz tumore mozga. U Južnoj Koreji zabilježen je smanjeni broj hospitalizacija povezanih s kroničnim opstruktivnim bolestima i astmom.[28] I u našim je podacima zabilježen smanjen broj pregleda za dijagnoze bronhitis, astma, emfizem i ostale kronične opstruktivne bolesti za 60% na razini PZZ i za 100% na razini SKZZ. Smanjeni broj hospitalizacija i operacija za bolesnike s ortopedskim ozljedama zabilježen je u Hong Kongu.[29] U Rumunjskoj je za vrijeme pandemije koronavirusa smanjen broj hospitalizacija za bolesti kardiovaskularnog, probavnog i dišnog sustava, kao i za stanja povezana s mentalnim poremećajima i poremećajima ponašanja.[30]

Slični podaci dobiveni su i u istraživanju provedenom u Općoj bolnici Zadar, gdje su 2020.

godine zabilježene 51 152 hospitalizacije, što je 10% manje nego 2019. godine.[31]

Ispitivanja provedena na otorinolaringološkim bolesnicima u RH pokazala su znatan pad broja pregledanih i operiranih bolesnika u razdoblju COVID-19 pandemije.[32,33]

Za očekivati je da će smanjena dostupnost zdravstvene zaštite za vrijeme pandemije kao posljedicu imati kasnije dijagnosticiranje bolesti, odgođeni početak liječenja i lošiji ishod bolesti. U prilog tomu govori i istraživanje provedeno u Kanadi, gdje je došlo do drastičnog pada broja obavljenih biopsija kožnih promjena.[34] I prema našim podacima došlo je do drastičnog pada pregleda bolesnika oboljelih od melanoma kože, za 100% na razini PZZ i za 74% na razini SKZZ.

Smanjenje broja pregleda na razini PZZ za posljedicu ima izostanak preventivnih pregleda i kontinuiranog praćenja kroničnih bolesnika, a koji za cilj imaju pravovremeno otkrivanje i liječenje bolesti, dok se smanjenje broja pregleda na razini SKZZ očituje u odgođenom dijagnosticiranju i specifičnom liječenju bolesti.

S obzirom na nepovoljnu epidemiološku situaciju, neizvjesnost i strah od moguće zaraze, ali i reorganizaciju zdravstvenog sustava, smanjenje broja pregleda bilo je očekivano na obje razine zdravstvene zaštite. Međutim, smanjeni broj pregleda, hospitalizacija i povećana smrtnost u odnosu na vrijeme prije početka pandemije, otvaraju pitanje dugoročnih posljedica ove situacije. Stoga je za očekivati povećani broj bolesnika s novim dijagnozama, a među kojima i karcinoma otkrivenih u kasnijim stadijima bolesti, što će u konačnici rezultirati kasnijim početkom liječenja i lošijim ishodom bolesti, ali i povećanim opterećenjem zdravstvenog sustava, kao i povećanim troškovima liječenja.

Literatura

1. Kruizinga MD, Peeters D, van Veen M et al. The impact of lockdown on pediatric ED visits and hospital admissions during the COVID19 pandemic: a multicenter analysis and review of the literature. Eur J Pediatr. 2021;180:2271-2279.
2. Alfano V, Ercolano S. The efficacy of lockdown against COVID-19: a cross-country panel analysis. Appl Health Econ Health Policy. 2020;18:509–517.
3. Ralli M, Greco A, de Vincentiis M. The effects of the COVID-19/SARS-CoV-2 pandemic outbreak on otolaryngology activity in Italy. Ear Nose Throat J. 2020;99:565–566.
4. Coimbra R, Edwards S, Kurihara H.et al. European Society of Trauma and Emergency Surgery (ESTES) recommendations for trauma and emergency surgery preparation during times of COVID-19 infection. Eur J Trauma Emerg Surg. 2020;46:505–510.
5. Finley C, Prashad A, Camuso N, Daly C, Aprikian A, Ball CG. Guidance for management of cancer surgery during the COVID-19 pandemic. Can J Surg. 2020;63:S2–S4.
6. Mayo-Yánez M, Calvo-Henríquez C, Lechien JR, Fakhry N, Ayad T, Chiesa-Estomba CM. Is the ultrasonic scalpel recommended in head and neck surgery during the COVID-19 pandemic? State-of-the-art review Head Neck 2020; 42:1657-1663.
7. Zhao C, Viana A, Wang Y, Wei HQ, Yan AH, Capasso R. Otolaryngology during COVID-19: preventive care and precautionary measures. Am J Otolaryngol. 2020;41(4):102508.
8. Gelardi M, Iannuzzi L, Trecca EMC, Kim B, Quaranta NAA, Cassano M. COVID-19: what happened to all of the otolaryngology emergencies? Eur Arch Otorhinolaryngol 2020;277:3231-3232.
9. Elli F, Turri-Zanoni M, Arosio AD, Karligkiotis A, Battaglia P, Castelnuovo P. Changes in the use of otorhinolaryngology emergency department during the COVID-19 pandemic: report from Lombardy, Italy Eur Arch Otorhinolaryngol 2020;277:3525-3528.
10. Slagman A, Behringer W, Greiner F. Et al. Medical emergencies during the COVID-19 pandemic. Dtsch Arztebl Int. 2020;117:545–552.
11. Smith AC, Thomas E, Snoswell CL et al. Telehealth for global emergencies: implications for coronavirus disease 2019 (COVID-19). J Telemed Telecare. 2020;26:309–313.
12. Hrvatski zavod za javno zdravstvo. Rad bolnica u Hrvatskoj 2020.godine. [Internet] Zagreb: Hrvatski zavod za javno zdravstvo; 2021 [pristupljeno 6.2.2022.]. Dostupno na: https://www.hzjz.hr/wp-content/uploads/2021/07/Rad-bolnica-u-2020.pdf
13. Hrvatski zavod za javno zdravstvo. Izvješće o umrlim osobama u Hrvatskoj 2019.godine. [Internet] Zagreb: Hrvatski zavod za javno zdravstvo; 2020 [pristupljeno 6.2.2022.]. Dostupno na: https://www.hzjz.hr/wp-content/uploads/2020/09/Bilten__Umrli-_2019-1-2.pdf
14. Hrvatski zavod za javno zdravstvo. Izvješće o umrlim osobama u Hrvatskoj 2020.godine. [Internet] Zagreb: Hrvatski zavod za javno zdravstvo; 2021 [pristupljeno 6.2.2022.]. Dostupno na: https://www.hzjz.hr/wp-content/uploads/2021/10/Bilten_Umrli-_2020.pdf
15. Tuczynska M, Matthews-Kozanecka M, Baum E. Accessibility to Non-COVID Health Services in the World During the COVID-19 Pandemic: Review. Front Public Health 2021;9:760795.
16. Gulliford M, Figueroa-Munoz J, Morgan M et al. What does 'access to health care' mean? J Health Serv Res Policy 2002;7:186-188.
17. Kaye AD, Okeagu CN, Pham AD et al. Economic impact of COVID-19 pandemic on healthcare facilities and systems: international perspectives. Best Pract Res Clin Anaesthesiol 2020;35:293–306.
18. Kc A, Gurung R, Kinney MV et al. Effect of the COVID-19 pandemic response on intrapartum care,

stillbirth, and neonatal mortality outcomes in Nepal: a prospective observational study. Lancet Glob Health 2020;8:e1273-e1281.

19. Ross SW, Lauer CW, Miles WS et al. Maximizing the calm before the storm: tiered surgical response plan for novel coronavirus (COVID-19). J Am Coll Surg 2020;230:1080– 1091.
20. Mari GM, Crippa J, Casciaro F, Maggioni D. A 10-step guide to convert a surgical unit into a COVID-19 unit during the COVID-19 pandemic. Int J Surg 2020;78:113-114.
21. Vagal A, Mahoney M, Allen B et al. Rescheduling nonurgent care in radiology: implementation during the coronavirus disease 2019 (COVID-19) pandemic. J Am Coll Radiol 2020;17:882–889.
22. Hsieh YP, Yen CF, Wu CF, Wang PW. Nonattendance at scheduled appointments in outpatient clinics due to COVID-19 and related factors in Taiwan: a health belief model approach. Int J Environ Res Public Health 2021;18:4445.
23. Skitarelić N, Dželalija B, Skitarelić N. Covid-19 pandemija: kratki pregled dosadašnjih spoznaja. Med Jad 2020;50:5-8.
24. Tempia S, Walaza S, Bhiman JN et al. Decline of influenza and respiratory syncytial virus detection in facility-based surveillance during the COVID-19 pandemic, South Africa, January to October 2020. Euro Surveill 2021;26:2001600.
25. Mahase E. Winter pressure: RSV, flu, and covid-19 could push NHS to breaking point, report warns. BMJ 2021;374:1802.
26. Institute of Environmental Science and Research (ESR). ESR data highlights surge of respiratory syncytial virus (RSV). [Internet] Novi Zeland: ESR; 2021. [pristupljeno 6.2.2022.] Dostupno na: https://www.esr.cri.nz/home/about-esr/media-releases/esr-data-highlights-surge-of-respiratory-syncytial-virus-rsv-new-news-page/
27. Bodilsen J, Nielsen PB, Søgaard M et al. Hospital admission and mortality rates for noncovid diseases in Denmark during covid-19 pandemic: nationwide population based cohort study. BMJ. 2021;373:1135.
28. Huh K, Kim YE, Ji W et al. Decrease in hospital admissions for respiratory diseases during the COVID-19 pandemic: a nationwide claims study. Thorax 2021; 76:939-941.
29. Wong JSH, Cheung KMC. Impact of COVID-19 on orthopaedic and trauma service: an epidemiological study. J Bone Joint Surg Am 2020;102:e80.
30. Cucu AM, Dima C, Georgescu D, Bratu EC. Access to tertiary mental health care services during the Covid-19 pandemic in Romania. Acta Medica Transilvanica 2021;26:14–16.
31. Balorda A, Balorda Lj. Što je bilo drugačije u prvoj godini COVID-19 pandemije? Razlike u hospitalizacijama u 2019. i 2020. godini u Općoj bolnici Zadar. Med Jad 2021;51:301-310.
32. Veršić M, Grgec Dragičević M, Skitarelić N. Pregled rada rinološke ambulante tijekom Covid -19 pandemije u Općoj bolnici Zadar. Med Jad 2022;52(Supl 1):44.
33. Obrovac A, Naletilić N, Baudoin T. Istraživanje incidencije miringotomije i implantacije ventilacijskih cjevčica u razdoblju prije, za vrijeme i nakon COVID-19 pandemije na Klinici za ORL i kirurgiju glave i vrata KBC Sestre milosrdnice. Med Jad 2023;53(Supl 1):57.
34. Asai Y, Nguyen P, Hanna TP. Impact of the COVID-19 pandemic on skin cancer diagnosis: A population-based study. PLoS One 2021;16:e0248492.

Stručni članak
Professional paper

ISSN 0351-0093
Coden: MEJAD 53 (2023) 4

Učinak terapijskog ultrazvuka kod simptoma sindroma karpalnog tunela

Effect of therapeutic ultrasound in symptoms of carpal tunnel syndrome

Sonja Iža, Ines Ivanković, Marija Crnković Knežević*

Sažetak

Sindrom karpalnog tunela (Carpal tunnel syndrome CTS) jedna je od najčešćih neuropatija, te nastaje posljedično kao kompresija na *nervus medianus* u karpalnom kanalu. Klinička slika se očituje parestezijama i utrnulošću prva tri prsta ili cijele šake, te prisutnom boli. Cilj je analizirati kakav je učinak terapijskog ultrazvuka (UZV) kod simptoma sindroma karpalnog kanala. Analizom radova iz online bibliografske baze Pubmed izabrano je 11 radova koji odgovaraju temi. Zaključno, iako postoji određena doza efikasnosti u primjeni ultrazvuka (UZV) kod sindroma karpalnog kanala, većina dostupnih rezultata istraživanja fokusira se na kombinaciju različitih terapijskih metoda. Ovaj trenutni nedostatak jasnoće ukazuje na potrebu za novim istraživanjima. Stoga, precizan zaključak o efikasnosti samog ultrazvuka kao pojedinačne metode ostaje neodređen i zahtijeva daljnje proučavanje kako bi se dobili konkretniji rezultati.

Ključne riječi: sindrom karpalnog kanala, *nervus medianus*, terapijski ultrazvuk

Summary

The carpal tunnel syndrome (CTS) is one of the most common neuropathies, resulting from compression on the median nerve within the carpal tunnel. The clinical presentation manifests with paresthesias and numbness in the first three fingers or the entire hand, accompanied by pain. The aim is to analyze the impact of therapeutic ultrasound (US) on the symptoms of the carpal tunnel syndrome. Through the analysis of articles from the online bibliographic database PubMed, 11 relevant studies were selected. In conclusion, while there is a certain degree of effectiveness in the application of ultrasound therapy (US) for the carpal tunnel syndrome, the majority of available research results focus on the combination of different therapeutic methods. This current lack of clarity indicates the need for new research. Therefore, a precise conclusion regarding the effectiveness of ultrasound itself as a standalone method remains inconclusive and requires further investigation to obtain more concrete results.

Key words: carpal tunnel syndrome, median nerve, therapeutic ultrasound

Med Jad 2023;53(4):279-284

Uvod

Sindrom karpalnog tunela (CTS) smatra se jednim od najčešćih neuropatija gornjih ekstremiteta, te nastaje kao posljedica kompresije *nervusa medianusa* u karpalnom kanalu.[1] CTS pogađa više žene nego muškarce. Čimbenici rizika su fibroza i upala tetiva, trauma kao što su prijelomi zapešća, a ostali rizici vezani su za spol, dob, dijabetes, trudnoću, genetiku i pretilost.[2] Etiologija je najčešće idiopatska, a ne sekundarna.[3] Klinička slika manifestira se prvenstveno s boli, parestezijom, slabosti u zapešću i šaci, te senzornim smetnjama.[4] Osim ovih simptoma javlja se i utrnulost prva tri prsta ili cijele šake.[5]

***Kineziološki fakultet Sveučilišta Josip Juraj Strossmayer u Osijeku** (Sonja Iža, mag. med. physioth.); **Opća bolnica Šibenik** (Ines Ivanković, mag.physioth.); **Veleučilište Lavoslav Ružićka, Vukovar** (Marija Crnković Knežević, mag.physioth.)

Adresa za dopisivanje/*Correspondence address:* Sonja Iža, J.J.Strossmayer 151, 31 000 Osijek E-mail: sonja.iza@gmail.com

Primljeno/*Received* 2023-02-22; Ispravljeno/*Revised* 2023-10-05; Prihvaćeno/*Accepted* 2023-10-20

Dijagnoza CTS-a postavlja se na temelju prisutnih simptoma koji su otkriveni tijekom kliničkog pregleda.[6] Klinički pregled za postavljanje dijagnoze CTS-a uključuje Tinelovtest, Phalenov test i/ili elektrofiziološko mjerenje.[7] Preporučuje se konzervativno liječenje za kontrolu simptoma i kod gubitka funkcionalnosti blagog i umjerenog CTS.[8] Blagi i umjereni CTS se odnose na različite razine ozbiljnosti ovog medicinskog stanja. Blagi CTS obično uključuje rane simptome i manju ometenost. Bolesnici s blagim CTS-om mogu iskusiti povremene parestezije (trnjenje, utrnulost) i blage bolove u prstima, posebno u prva tri prsta. Funkcionalnost ruke i šake obično nije značajno narušena i bolesnici često mogu obavljati svoje svakodnevne aktivnosti.[8] Kod umjerenog CTS-a simptomi postaju izraženiji i mogu ometati svakodnevne aktivnosti. Bolesnici s umjerenim CTS-om mogu iskusiti izraženije parestezije i bolove, što može utjecati na sposobnost držanja i korištenja ruke. Može se javiti slabost mišića i gubitak fine motoričke koordinacije, što može utjecati na sposobnost obavljanja preciznih radnji.[8] Operativno liječenje daje dugotrajnije olakšanje simptoma, no većina ljudi s umjerenom i blagom kliničkom slikom liječi se konzervativno. Konzervativno liječenje podrazumijeva nošenje ortoze, kinesiotaping metodu, UZV i neurodinamičke tehnike, laser,ekstrakorporalnu terapiju udarnim valom, te injekcije kortikosteroida i plazme bogate trombocitima.Ultrazvuk povećava temperaturu u dubini tkiva dovodeći tamo energiju. Na taj način se može poboljšati regeneraciju živca medianusa koji je pod kompresijom. Ova metoda može kratkoročno modificirati simptome, ali trenutno nema jasnih i dostupnih kvalitetnih ispitivanja na tu temu.[9]

Cilj

Analizom postojećih istraživanja utvrditi postoji li i kakav je učinak terapijskog UZV kod simptoma sindroma karpalnog kanala.

Metode

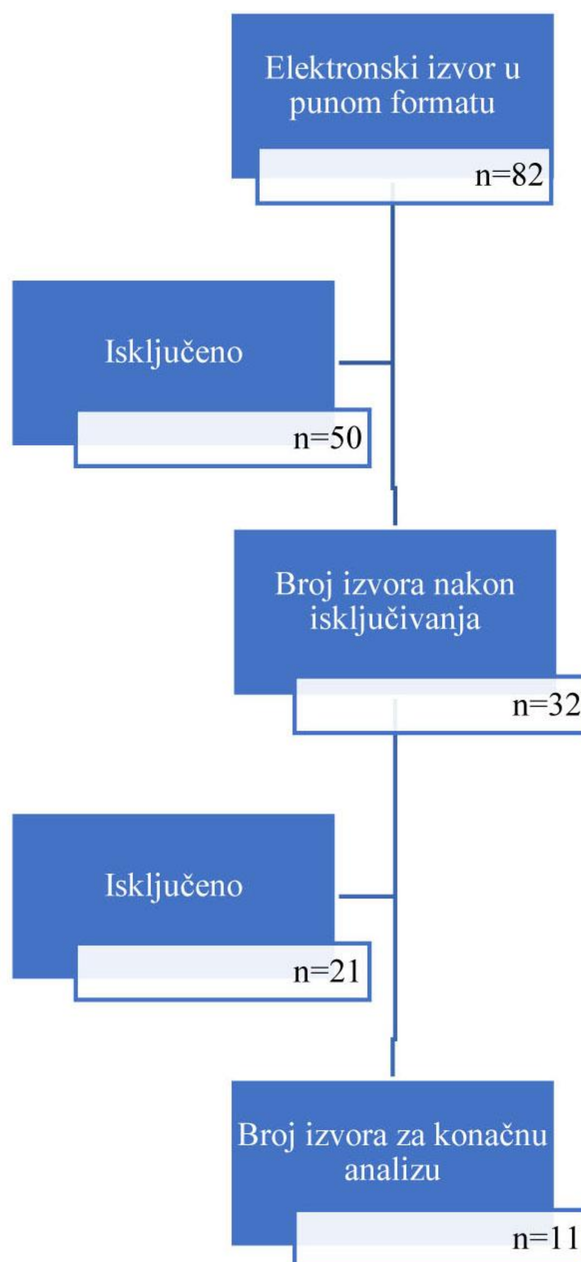
Odabir studija uključenih u analizu obavljen je elektronskim pretraživanjem literature.

U analizu su uključeni cjeloviti besplatni radovi prospektivnih ili retrospektivnih istraživanja. Kao kriterij uključivanja postavljeni su: radovi od 2000-2022, clinical trial, meta-analysis, randomized controlled trial.

Detaljnom analizom cjelovitih tekstova radova izabrali smo one koji su najviše odgovarali temi koju istražujemo.

Za konačnu analizu iz bibliografske baze Pubmed izabrano je 11 izvora koji su odgovarali istraživačkoj temi.

Bibliografska baza	Pubmed
Ključne riječi	Ultrasound, therapy, carpal tunnel syndrome
Broj izvora	82
Broj izabranih izvora za konačnu analizu	11



Rezultati

Tablica 1. Popis radova koji su odgovarali istraživačkoj temi i njihova analiza
Table 1 List of works corresponding to the research team and ther analysis

Autori	Naslov rada	Godina objave	Vrsta istraživanja	Broj ispitanika	Zaključak autora
Krisna Piravej, Jariya Boonhong	Effect of ultrasound thermotherapy in mild to moderate carpal tunnel syndrome.	2004.		18	Terapijska učinkovitost UZV niskog intenziteta bila je pozitivna za blagi do umjereni karpalni sindrom. Elektrofiziološke promjene nakon tretmana UZV zahtijevaju dodatna istraživanja.[10]
Yi-Wei Chang, Shih-Fu Hsieh, Yu-ShiowHorng, Hui-Ling Chen, Kun-Chang Leeand, Yi-Shiung Horng	Comparative effectiveness of ultrasound and paraffin therapy in patients with carpal tunnel syndrome: a randomized trial	2014.	Randomizirano ispitivanje	47	Kombinacija ultrazvučne terapije s ortozom za zglob može biti učinkovitija od parafinske terapije s ortozom za zglob.[11]
Ozlem Baysal, Zühal Altay, COzcan, Kadir Ertem, S Yologlu, A Kayhan	Comparison of three conservative treatment protocols in carpal tunnel syndrome	2006.		28	Rezultati sugeriraju da je kombinacija udlage, tjelesne aktivnosti i ultrazvučne terapije poželjna i učinkovita konzervativna metoda liječenja u sindromu karpalnog kanala.[12]
Umit Dincer, Engin Cakar, Mehmet Zeki Kiralp, Hilmi Kilacand Hasan Dursun	The Effectiveness of Conservative Treatments of Carpal Tunnel Syndrome: Splinting, Ultrasound, and Low-Level Laser Therapies	2009.		50	Nakon tri mjeseca praćenja, svaka od skupina imala je poboljšanja. Čini se da su kombinacije UZ ili lasera niske razine, terapije s ugradnjom udlage učinkovitije u liječenju od same udlage, no međutim, terapija laserom uz udlagu bila je korisnija od UZ terapije uz postavljanje udlaga.[13]
Onur Armagan, Fulya Bakilan, Merih Ozgen, Ozlem Mehmetoglu i Setenay Oner	Effects of placebo-controlled continuous and pulsed ultrasound treatments on carpal tunnel syndrome: a randomized trial	2014.	Kontrolirana studija	46	Rezultati ove studije pokazuju da su bolesnici liječeni kontinuiranim i pulsirajućim UZV pokazali poboljšanje, ali rezultati nisu bili bolji od onih kod placeba.[14]
Nadica Laktašić Žerjavić, Nikolino Žura, Mislav Jezidžić, Iva Žagar i Porin Perić	Kratkoročna učinkovitost ultrazvuka i lasera u liječenju sindroma karpalnog kanala	2016.		40	Kod liječenja sindroma karpalnog kanala terapijski UZV pokazuje kratkoročnu učinkovitost.[15]
Mislav Jezidžić	Učinkovitost ultrazvuka i lasera u liječenju sindroma karpalnog kanala	2016.		40	U kombinaciji s vježbama korištenje UZV i lasera ne pokazuje statistički značajnu razliku, no, sve promatrane varijable pokazale su poboljšanje.Tako je poboljšana gibljivosti, te povećana mišićna snaga i smanjena bol u odnosu na početno stanje.[16]

Autori	**Naslov rada**	**Godina objave**	**Vrsta istraživanja**	**Broj ispitanika**	**Zaključak autora**
Nadica Laktašić-Žerjavić, Nikolino Žura, Ivan Jurak, Mislav Jezidžić, Iva Žagar, Kristina Kovač-Durmiš, Josip Draženović i Porin Perić	Kratkoročna učinkovitost terapijskog ultrazvuka i lasera u liječenju sindroma karpalnog kanala	2017.		60	Ultrazvuk i laser u kombinaciji s vježbama pokazuju bolji kratkoročni učinak na funkcionalni status šake.[17]
Kamalakannan P Jothi, Jeremy D P Bland	Ultrasound therapy adds no benefit to splinting in carpal tunnel syndrome	2019.		40	Nema klinički značajne koristi od UZV tretmana za sindrom karpalnog kanala.[18]
Erol Öten	The efficacy of ultrasound and low-intensity laser therapy in carpal tunnel syndrome	2022.		11	Kada su UZV i laser niskog intenziteta uspoređeni kod bolesnika s blagim i umjerenim sindromom karpalnog tunela, nije pronađena značajna razlika između skupina u pogledu kliničkih i elektrofizioloških parametara no međutim, uočena je statistički značajna razlika u skupini koja je koristila laser u pogledu nekih kliničkih parametara prije i poslije tretmana.[19]

Rasprava

Rezultati istraživanja Piravej, Boonhong.[10] pokazuju kako je terapijska učinkovitost UZV niskog intenziteta pozitivna za blagi do umjereni karpalni sindrom. Elektrofiziološke promjene nakon tretmana UZV zahtijevaju dodatna istraživanja.[10] Nastavno, studija Armagan i sur.[12] pokazuje kako su bolesnici liječeni kontinuiranim i pulsirajućim UZV pokazali elektrofiziološko poboljšanje, no također je bitno istaknuti kako nije bilo razlike u rezultatima kod placebo grupe. Zaključak autora je da terapijski UZV pokazuje kratkoročnu učinkovitost kod liječenja sindroma karpalnog kanala. Laktašić Žerjavić i sur.[15] u svom istraživanju provedenom na 40 ispitanika s ciljem analize kratkoročne učinkovitosti terapijskog UZV na karpalni sindrom došli su do zaključka kako terapijski UZV ima kratkoročnu učinkovitost kod liječenja sindroma karpalnog kanala.

Pojedina istraživanja, osim UZV, u istraživanje su uključila određene kombinacije. Istraživanje Chang i sur.[11] pokazuje kako kombinacija ultrazvučne terapije s ortozom za zglob može biti učinkovitija od parafinske terapije s ortozom za zglob. S navedenim se slažu Dincer i sur.[13] koji ističu kako su kombinacije UZV ili lasera niske razine terapije s ugradnjom udlage učinkovitije od same udlage u liječenju. Međutim, terapija laserom uz udlagu bila je korisnija od UZV terapije uz postavljanje udlaga, dok rezultati istraživanja Baysali sur.[12] sugeriraju kako je kombinacija udlage, tjelesne aktivnosti i UZV terapije poželjna i učinkovita konzervativna metoda liječenja u sindromu karpalnog kanala.

Istraživanje Oten[19] u kojem su UZV i laserska terapije niskog intenziteta uspoređeni kod bolesnika s blagim i umjerenim sindromom karpalnog tunela, nije pokazalo značajnu razliku između skupina u pogledu kliničkih i elektrofizioloških parametara. Međutim, uočena je statistički značajna razlika u skupini terapije laserom u pogledu nekih kliničkih parametara prije i poslije tretmana.Prema istraživanju Jezidžića[16] u kombinaciji s vježbama, korištenje UZV i lasera ne pokazuje statistički značajnu razliku, no sve promatrane varijable pokazale su poboljšanje. Tako je poboljšana gibljivosti, povećana mišićna snaga i smanjena bol u odnosu na početno stanje.. S navedenim se slažu Laktašić i sur.[17] čije istraživanje pokazuje kako se UZV i laser mogu primijeniti u konzervativnom liječenju u kombinaciji s vježbama i uz bolji, ali kratkoročni učinak UZV na funkcionalni status šake.

Istraživanje Kamalakannan i sur.[18] pokazuje kako nema klinički značajne koristi od UZV tretmana za sindrom karpalnog kanala.

Zaključak

Rezultati većine studija analiziranih u ovom radu pokazuju kako postoji određena količina kratkoročne učinkovitosti u korištenju terapijskog UZV kod sindroma karpalnog kanala, no s obzirom na to kako je dosta rezultata usmjereno na kombinaciju nekoliko metoda, potrebne su nove studije usmjerene isključivo na UZV, te provedene na većem broju ispitanika.

Literatura

1. Ibrahim I, Khan WS, Goddard N, Smitham P. Carpal tunnel syndrome: a review of the recent literature. Open Orthop J 2012; 6:69–76.
2. Skuladottir AT, Bjornsdottir G, Ferkingstad E et al. A genome-wide meta-analysis identifies 50 genetic loci associated with carpal tunnel syndrome. Nat Commun 2022; 13:1598.
3. Ng AWH, Griffith JF, Tsoi C et al. Ultrasonography Findings of the Carpal Tunnel after Endoscopic Carpal Tunnel Release for Carpal Tunnel Syndrome. Korean J Radiol 2021; 22:1132-1141.
4. Jiménez-del-Barrio S, Cadellans-Arróniz A, Ceballos-Laita L et al. The effectiveness of manual therapy on pain, physical function, and nerve conduction studies in carpal tunnel syndrome patients: a systematic review and meta-analysis. Int Orthop 2022; 46:301-312.
5. Jiménez del Barrio S, Ceballos-Laita L, Bueno-Gracia E, Rodríguez-Marco S, Haddad-Garay M, Estébanez-de-Miguel E. Effects of Diacutaneous Fibrolysis on Mechanosensitivity, Disability, and Nerve Conduction Studies in Mild to Moderate Carpal Tunnel Syndrome: Secondary Analysis of a Randomized Controlled Trial. Phys Ther 2021; 101:222.
6. Erickson M, Lawrence M, Lucado A. The role of diagnostic ultrasound in the examination of carpal tunnel syndrome: an update and systematic review. J Hand Ther 2022; 35:215-225.
7. Padua L, Coraci D, Erra C et al. Carpal tunnel syndrome: clinical features, diagnosis, and management. Lancet Neurol 2016; 15:1273-1284.
8. Klokkari D, Mamais I. Effectiveness of surgical versus conservative treatment for carpal tunnel syndrome: a systematic review, meta-analysis and qualitative analysis. Hong Kong Physiother J 2018; 38:91–114.
9. Karjalanen T, Raatikainen S, Jaatinen K, Lusa V. Update on Efficacy of Conservative Treatments for Carpal Tunnel Syndrome. J Clin Med 2022; 11:950.
10. Piravej K., Boonhong, J. Effect of ultrasound thermotherapy in mild to moderate carpal tunnel syndrome. J Med Assoc Thai 2004; 87 (Supl 2): S100-6.
11. Chang YW, Hsieh SF, Horng YS, Chen HL, Lee KC, Horng YS. Comparative effectiveness of ultrasound and paraffin therapy in patients with carpal tunnel syndrome: a randomized trial. BMC Musculoskelet Disord 2014; 15:399.

12. Baysal O, Altay Z, Ozcan C, Ertem K, Yologlu S, Kayhan A.Comparison of three conservative treatment protocols in carpal tunnel syndrome. Int J Clin Pract 2006; 60:820-828.
13. Dincer U, Cakar E, Kiralp MZ, Kilac H, Dursun H. The Effectiveness of Conservative Treatments of Carpal Tunnel Syndrome: Splinting, Ultrasound, and Low-Level Laser Therapies. Photomed Laser Surg 2009; 27:119-125.
14. Armagan O, Bakilan F, Ozgen M, Mehmetoglu O, Oner S. Effects of placebo-controlled continuous and pulsed ultrasound treatments on carpal tunnel syndrome: a randomized trial. Clinics 2014; 69:524-528.
15. Laktašić Žerjavić N, Žura N, Jezidžić M, Žagar I, Perić P. Kratkoročna učinkovitost ultrazvuka i lasera u liječenju sindroma karpalnog kanala. Fiz rehabil med 2016; 28:322-323.
16. Jezidžić M. Učinkovitost ultrazvuka i lasera u liječenju sindroma karpalnog kanala [Master's thesis]. Zagreb: University of Applied Health Sciences, 2016.
17. Laktašić-Žerjavić N, Žura N, Jurak I i sur. Kratkoročna učinkovitost terapijskog ultrazvuka i lasera u liječenju sindroma karpalnog kanala. Reumatizam 2017; 64:103-109.
18. Jothi KP, Bland JD. Ultrasound therapy adds no benefit to splinting in carpal tunnel syndrome. Muscle Nerve 2019; 60:538-543.
19. Öten E. The efficacy of ultrasound and low-intensity laser therapy in carpal tunnel syndrome.J Health Sci Med 2014; 5:423-428.

Case report
Prikaz bolesnika

ISSN 0351-0093
Coden: MEJAD 53 (2023) 4

A case report of appendiceal adenoma – a rare entity

Prikaz bolesnice s adenomom apendiksa – rijedak entitet

Fatima Juković Bihorac, Anhel Koluh, Emir Begagić*

Summary

Appendiceal neoplasms are quite uncommon. They are detected in fewer than 0.5 percent of appendectomies and less than 0.5 percent of all gastrointestinal neoplasms. Similar to a colonic adenoma, an appendiceal adenoma is neoplasm with precancerous nature. A rare case of appendiceal adenoma is presented here in a 65-year-old female patient, incidentally discovered at the orifice of the appendix, during the screening analysis. The patient felt well. Abdominal examination and laboratory analysis were regular. Due to the inaccessibility of the lesion by colonoscopy, surgical treatment was recommended. A laparoscopic appendectomy was performed. On pathological examination, diagnosis of tubulovillous adenoma was performed. Endoscopic screening analysis of precancerous appendiceal neoplasm is very important. The method of choice for any appendiceal neoplasm is surgical removal i.e. appendectomy, preferably with a clean caecal margin, which requires stapling of the cecum. Early detection can prevent complications and decrease the risk of consequential appendiceal or colorectal carcinoma.

Key words: adenoma, appendectomy, appendix, appendiceal neoplasms, diagnostic screening programs, dysplastic changes, colonoscopy

Sažetak

Tumori apendiksa prilično su rijetki. Javljaju se u manje od 0,5 % apendektomija i u manje od 0,5 % svih gastrointestinalnih tumora. Slično kao i adenoma kolona, adenoma apendiksa prekancerozne su prirode. Prikazali smo rijedak slučaj adenoma apendiksa, incidentalno otkrivenogna u ušću apendiksa, skrininig metodom. Bolesnica se u vrijeme analize osjećala dobro. Klinički pregled i laboratorijske analize bili su uredni. Bolesnici se preporuči kirurški tretman. Uradi se laparoskopska apendektomija. Patohistološkom analizom postavi se dijagnoza tubuloviloznog adenoma. Endoskopska skrining analiza prekanceroznih neoplazmi apendiksa i kolona od iznimne je važnosti. Za sve tumore apendiksa metoda izbora je kirurška - apendektomija s dobijanjem čistih resekciskih margina, što zahtijeva stapliranje cekuma. Rana detekcija ovih neoplazmi prevenira komplikacije i smanjuje rizik od posljedičnih koloničnih i karcinoma apendiksa.

Ključne riječi: adenoma, apendektomija, apendiks, tumori apendiksa, dijagnostički skrining program, displastične promjene, kolonoskopija

Med Jad 2023;53(4):285-288

Introduction

Appendiceal neoplasms are quite uncommon. They occur in under 0.5% of cases of the total number of GI tumors and in under 1% of appendectomies.[1-3] Neuroendocrine tumors (NETs) and tumors with an epithelial origin comprise most of appendiceal tumors. Other more rare tumors are metastatic

***Cantonal Hospital Zenica, Department of Pathology** (Fatima Juković Bihorac, MD); **Cantonal Hospital Zenica, Department of Surgery** (Assist. Prof. Anhel Koluh, MD, PhD); **University of Zenica, Medicinal faculty, Department of general medicine** (Emir Begagić, student)

Correspondence address/*Adresa za dopisivanje:* Fatima Juković Bihorac, Department of Pathology, Cantoal Hospital Zenica, Crkvice 67, 72000 Zenica, Bosnia and Herzegovina E-mail: fatima.bihorac@live.com

Received/*Primljeno* 2023-06-16; Revised/*Ispravljeno* 2023-25-07; Accepted/*Prihvaćeno* 2023-11-02

tumors, lymphoma, tumors of neural origin, and mesenchymal tumors.[4]

In between 30 and 50 percent of patients, appendiceal neoplastic lesions most frequently mimic or cause acute appendicitis.[5]

About 10% of appendiceal polyps are detected incidentally.[6] They were reported in 0.004 and 0.08% of autopsies.[7]

Rarely, polyps may be concealed inside the appendiceal lumen near the appendiceal orifice and occasionally only become apparent after thoroughly examining the coecum. Only three instances like this have been documented in the literature thus far.[8-10]

Appendectomy is the method of choice for treating appendiceal adenomas, as it leaves a tumor-free resection margin.[3]

Here we report a case of an incidentally discovered appendiceal tubulovillous adenoma.

Case history

The Ethics Committee of Zenica Cantonal Hospital approved this case report and the patient gave us informed consent for the data we used in this article.

A 65-year-old female was accepted to the routine colonoscopy screening which revealed a polypoid lesion at the orifice of the appendix. The patient was asymptomatic. Laboratory results were regular.

The dilated bowel loops precluded the radiologist to find the appendix. At the Surgery Department, a laparoscopic appendectomy was performed (Fig.1). The base of the appendix is secured by a single endoloop. Three days after surgery, after a routine postoperative observation, the patient was released from hospital. The appendix was sent to the Pathology Department for analysis.

Grossly, the appendix was measured 7.5×1.2×1 cm. At the 5 mm of resection margin a polypoid lesion with a diameter of 5 mm was observed. The appendiceal wall was of regular thickness. Microscopic analysis showed tall columnar epithelium with focal stratification and mild dysplastic alterations, predominantly covering a mucosa with tubulous and discreet papillary infoldings (Fig.2). The layers of the wall and residual mucosa were normal. The surgical margin of the appendix was free of tumor. The pathohistological diagnosis was tubulovillous adenoma of the appendix with mild dysplasia.

Discussion

An appendiceal adenoma is an uncommon pathological diagnosis.[11] In most cases, they are asymptomatic and discovered unintentionally. Only cases progressing to acute appendicitis and intusussception are symptomatic, and the symptomatology corresponds to the underlying disease.[3] About 10% of these polyps are unintentionally discovered during laparotomies during unrelated surgeries.[6] Also, these polyps were discovered in 0.004 and 0.08% of autopsies.[7]

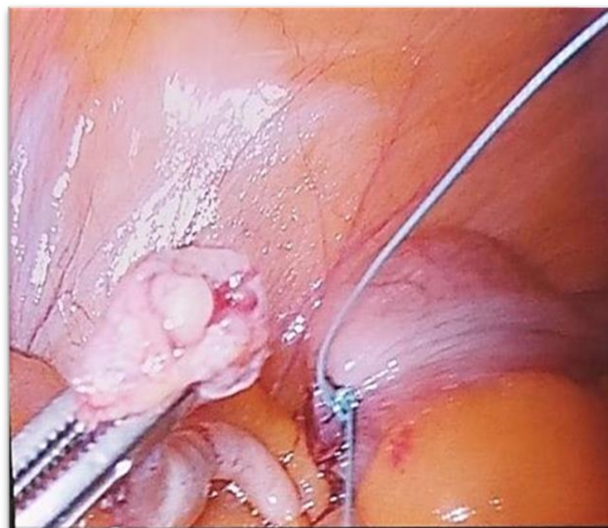


Figure 1 Laparoscopic appendectomy. There is a polypoid lesion at the tip of the sample.
Slika 1 Laparoskopska apendektomija. Na vrhu uzorka prisutna polipoidna lezija.

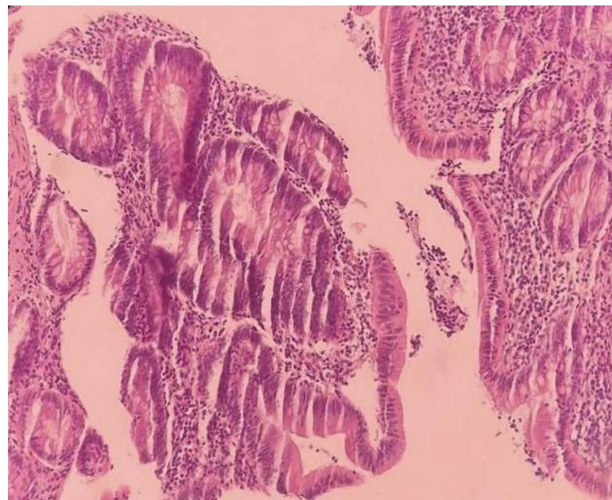


Figure 2 Microscopic appearance of appendiceal adenoma with mild dysplasia, ×20 HE.
Slika 2 Mikroskopski izgled adenoma apendiksa s umjerenom displazijom, ×20 HE.

Like colonic adenoma, appendiceal adenoma is precancerous lesion and can develop into carcinoma.[12] It is thus essential to identify

precancerous appendiceal neoplasm early on for they can be associated with adenoma and adenocarcinoma elsewhere in the gastrointestinal tract, especially in the colon. Once they are diagnosed, the patient needs further analysis and follow-up.[12] Appendiceal adenomas are lesions with tubular, villous, or combined tubulovillous architecture. They originate from the mucosa. A focal serrated pattern may also be seen. In the stratified epithelium, there are dysplastic changes, with crowding, nuclear atypia, and focal mitotic figures.[4] In dependence on the number and size of the adenoma, the patients are categorized into two groups, with low and high risk. The first recommended monitoring colonoscopy for low-risk patients, defined as those with one to two tubular adenomas smaller than 1 cm, should be carried out every five to ten years.[13] The second category consists of those with high-risk adenomas, which are defined as having three or more tubular or adenomatous polyps with a diameter of at least 1 cm or having villous histology or high-grade dysplasia. In this category, the first recommended surveillance colonoscopy should be performed after three years.[14] A prospective cohort research involving 15,935 patients found that, after 13 years of follow-up, patients with high-risk adenomas had a risk of colorectal cancer that was 2.7 times higher than that of patients without adenomas annually.[15] In a recent retrospective study, 38.3% of the 691 individuals with appendiceal polyps identified by colonoscopy were non-neoplastic lesions, and 61.6% were neoplastic lesions, according to histological analysis. Neoplasms comprise 30.4% adenomas, 30.2% tubular lesions, 2.4% tubulo-villous lesions, 0.1% villous lesions, 17.8% sessile serrated lesions/polyps, 8.8% hyperplastic lesions, and 1.1% conventional serrated lesions. In 0.4% of adenomas, high-grade dysplasia was present.[16]

Due to the close relationship between appendiceal adenomas and synchronous or metachronous colorectal adenomas and carcinomas, patients with appendiceal adenomas require careful assessment of the remaining colon.[3]

In cases of most appendiceal neoplasms, the treatment of choice is surgery. The minority of appendiceal adenomas are pedunculated, and just in that case the treatment of choice is endoscopic removal.[17]

Endoscopic screening analysis and early detection of appendiceal adenoma have a crucial role. Endoscopists have to be aware of a hidden adenoma, especially at the orifice of the appendix. Endoscopic or laparoscopic appendectomy has to provide a resection margin free of tumor, and close follow-up is recommended due to the precancerous nature of the adenoma.

References:

1. Mc Cusker ME, Coté TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973-1998. Cancer 2002;94:3307-12.
2. Machado NO, Chopra P, Pande G. Appendiceal tumour--retrospective clinicopathological analysis. Trop Gastroenterol 2004;25:36-9.
3. Søreide K, Gudlaugsson E, Kjellevold KH. Mucinøstcystadenom i appendix [Appendiceal mucinous cystadenoma]. Tidsskr Nor Laegeforen. 2005;12:289-91.
4. Leonards LM, Pahwa A, Patel MK, Petersen J, Nguyen MJ, Jude CM. Neoplasms of the Appendix: Pictorial Review with Clinical and Pathologic Correlation. Radiographics 2017;37:1059-1083.
5. Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. Dis Colon Rectum 1998;41:75-80.
6. Aranha GV, Reyes CV. Primary epithelial tumors of the appendix and a reappraisal of the appendiceal "mucocele". Dis Colon Rectum 1979;22:472-6.
7. Cirocco WC, Rusin LC. Factors that predict incomplete colonoscopy. Dis Colon Rectum 1995;38:964-8.
8. Green PH, Perry E, Curry WT. Colonoscopic diagnosis of an appendiceal villous adenoma. Gastrointest Endosc. 1992;38:522-3.
9. Khawaja FI. Colonoscopic removal of an appendiceal polyp. Saudi J Gastroenterol 2002;8:93-5.
10. Ruffolo TA, Daly C. Identifying obscure appendiceal polyps: the “deflated lumen” technique [Commentary]. Gastrointest Endosc 2006;63:704–5.
11. Fernández Blanco CM, Fraguela JA, Gulías A, Sánchez Blas M, Freijoso C. Villous adenoma of the appendix. Diagnostic and therapeutic approach. Rev Esp Enferm Dig 2002;94:537-43.
12. Taylor JV, Thomas MG, Kelly S, Sutton R. Villous adenoma of the distal appendix. Eur J SurgOncol 1997;23:185-6.
13. Winawer SJ, Zauber AG, Fletcher RH et al.; US Multi-Society Task Force on Colorectal Cancer; American Cancer Society. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. Gastroenterology 2006;130:1872–85.
14. Hassan C, Quintero E, Dumonceau JM. et al.; European Society of Gastrointestinal Endoscopy. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2013;45:842–51.
15. Click B, Pinsky PF, Hickey T, Doroudi M, Schoen RE. Association of Colonoscopy Adenoma Findings with

Long-term Colorectal Cancer Incidence. JAMA 2018;319:2021-2031.
16. Hassab TH, Church JM. Appendix orifice polyps: a study of 691 lesions at a single institution. Int J Colorectal Dis 2019;34:711-718.
17. Giday SA., Nidiry J. Anappendiceal adenoma: 678. Am J Gastroenterol 2004; 99:S220.

Case report
Prikaz bolesnice

ISSN 0351-0093
Coden: MEJAD 53 (2023) 4

Multifocal metachronous occurence of different hystologic sinonasal-type papilloma: a case report

Multifokalna metakrona pojava različitih histoloških sinonazalnih papiloma: prikaz bolesnice

Jakov Ajduk, Mirta Peček, Marija Pierobon, Iva Mažić, Tomislav Gregurić, Andro Košec*

Summary

Introduction: Sinonasal-type papilloma is a very rare tumor, most commonly connected with the sinonasal space, and very rarely with the middle ear. Primary tumors of the temporal bone are extremely rare and only 28 cases have been described in literature, with additional 29 cases of tumor spreading from the sinonasal tract to the temporal bone.

Case presentation: We discuss the case of a 49-year-old woman who had a primary right-sided exophytic form of the sinonasal papilloma of the middle ear, which led to right-sided hearing loss, aural fullness, and otorrhea. During postoperative CT and MRI follow-up one year after surgery, a sinonasal oncocytic-type papilloma was discovered in the sphenoid sinus. To our knowledge, this is the first described case of histologically two different primary sinonasal-types of papilloma in a patient. Common presenting symptoms associated with sinonasal papilloma of the middle ear can be easily misdiagnosed with chronic otitis media or Eustachian tube dysfunction. Although primarily benign, sinonasal papillomas are locally aggressive and pose a risk of recurrence and malignant transformation. Therefore, surgery remains the treatment of choice with necessary long-term follow-up, to detect relapse or even a completely new tumor in that area.

Key words: exophytic type; middle ear; papilloma; sinonasal papilloma; sphenoid sinus; temporal bone

Sažetak

Uvod: Sinonazalni tip papiloma vrlo je rijedak tumor, najčešće vezan uz sinonazalni prostor, a vrlo rijetko za srednje uho. Primarni tumori temporalne kosti izuzetno su rijetki, a u literaturi je opisano samo 28 slučajeva, uz dodatnih 29 slučajeva širenja tumora iz sinonazalnog trakta u temporalnu kost.

Prikaz bolesnice: Prikazana je 49-godišnja žena koja je imala primarni desnostrani egzofitični oblik sinonazalnog papiloma srednjeg uha, koji je doveo do desnostranog gubitka sluha, osjećaja punoće u uhu i otoreje. Tijekom postoperativnog CT i MRI praćenja godinu dana nakon operacije, sinonazalni onkocitni tip papiloma otkriven je u sfenoidalnom sinusu. Prema našim saznanjima ovo je prvi opisani slučaj dvaju histološki različitih primarnih sinonazalnih tipova papiloma u jednog bolesnika. Uobičajeni simptomi povezani sa sinonazalnim papilomom srednjeg uha mogu se lako zamijeniti s kroničnom upalom srednjeg uha ili disfunkcijom Eustahijeve cijevi. Iako primarno benigni, sinonazalni papilomi su lokalno agresivni i predstavljaju opasnost od recidiva i maligne transformacije. Stoga operacija ostaje liječenje izbora, uz potrebno dugotrajno praćenje, kako bi se otkrio recidiv ili čak potpuno novi tumor na tom području.

Ključne riječi: egzofitični tip; srednje uho; papilom; sinonazalni papilom; sfenoidni sinus; temporalna kost

Med Jad 2023;53(4):289-292

***KBC Sestre milosrdnice, Klinika za otorinolaringologiju i kirurgiju glave i vrata** (doc.dr.sc. Jakov Ajduk, dr.med.; dr.sc. Andro Košec, dr.med.); **Medicinski fakultet Sveučilišta u Zagrebu** (doc.dr.sc. Jakov Ajduk, dr.med.; Mirta Peček, studentica medicine; Marija Pierobon, studentica medicine; Iva Mažić, studentica medicine; dr.sc. Andro Košec, dr.med.); **KBC Sestre milosrdnice, Klinički zavod za dijagnostičku i intervencijsku radiologiju** (dr.sc. Tomislav Gregurić, dr.med.)

Correspondence address/*Adresa za dopisivanje:* Mirta Peček, studentica medicine, Medicinski fakultet Sveučilišta u Zagrebu, Šalata 2, 10 000 Zagreb E-mail: mirta.pec@gmail.com

Received/*Primljeno* 2023-07-05; Revised/*Ispravljeno* 2023-11-17; Accepted/*Prihvaćeno* 2023-11-20

Introduction

A rare tumor formed from the Schneiderian membrane, which lines the nasal cavity and paranasal sinuses, called sinonasal-type papilloma (formerly known as Schneiderian papilloma), most frequently develops in the sinonasal tract.[1] Although it has the same histological characteristics, it is extremely uncommon in the middle ear, mastoid[1–5], lacrimal sac, or nasopharynx.[6] Sinonasal papillomas are divided into three histological types: exophytic (ESP), oncocytic (OSP), and inverted (ISP)[3], which is the most common (60%).[6-10] While it is considered benign, it is locally aggressive and tends to invade adjacent structures. Disease incidence cannot be accurately calculated due to scarce reports in literature. Etiology remains unknown, with two hypotheses proposed: direct extension from the sinonasal cavity through the Eustachian tube or primary involvement of the middle ear due to the metaplastic changes in the middle ear mucosa.[4] Symptoms most commonly include otorrhea, aural fullness, hypoacusis, tinnitus, and otalgia.[5] It has been noted that sinonasal papillomas of the temporal bone have a higher recurrence and malignant transformation rate compared to papillomas in the sinonasal tract.[1,7] We describe a case of a 49-year-old female with a primary ESP located in the middle ear and mastoid with another primary OSP located in the sphenoid sinus, discovered on regular CT and MRI follow-up one year after the surgery.

Case presentation

A 49-year-old female presented to the ENT clinic with a complaint of aural fullness, otorrhoea, and pulsating tinnitus of the right ear. Patient history was significant for hearing difficulties and intermittent tinnitus lasting for 4 years. An otoscopic examination of the right ear showed a slightly extruded and hyperemic eardrum covered with a small polyp in posterior-inferior parts. Endoscopic rhinoscopy found no pathological changes in the mucosa. Pure tone audiometry showed conductive hearing loss with an air-bone gap of 55 to 75 db across middle and high frequencies on the right side. CT and MRI (Figures 1,2) of the temporal bones showed a process in the right cavum tympani with postcontrast imbibition extending towards the apex of the pyramid, foramen lacerum, and dura. There was no pathology in the nose and the paranasal sinuses. Due to the afore mentioned findings, a right-sided tympano-mastoidectomy was performed. Intraoperatively, the mastoid antrum was filled by tumorous tissue. The tumor filled the tympanic cavity and encapsulated the auditory ossicles.

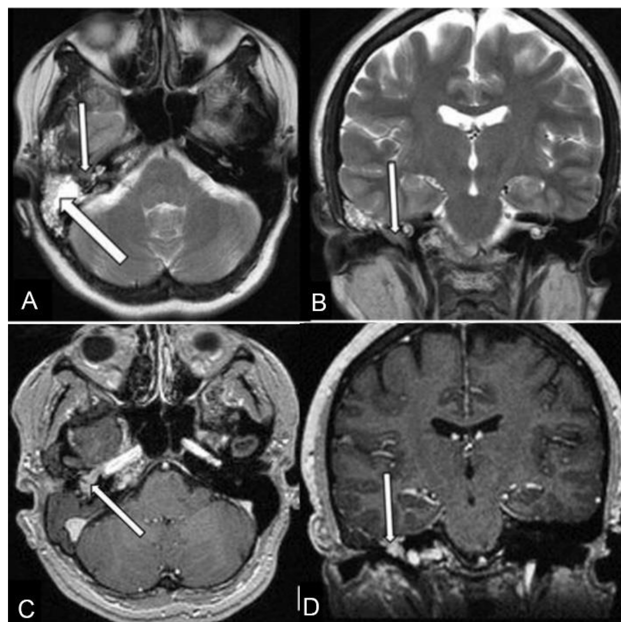


Figure 1 MRI of temporal bones, T2 images (A, B): A soft tissue formation in the right tympanum exhibiting a low signal (narrow arrow) and liquid content in the antrum and pneumatic cells of the right mastoid process exhibiting a high signal (wide arrow). In T1contrast enhanced images (C, D), a formation in the right tympanum can be seen, intensively imbibed with contrast (narrow arrow). The liquid content in the antrum and pneumatized mastoid cells does not show imbibition.

Slika 1. MRI sljepoočnih kostiju, T2 slike (A, B): formacija mekog tkiva u desnom bubnjištu s niskim signalom (uska strelica) i sadržaj tekućine u antrumu i pneumatskim stanicama desnog mastoidnog nastavka s visokim signalom (široka strelica). Na T1 prikazima s kontrastom (C, D) vidi se tvorba u desnom bubnjištu, intenzivno imbibirana kontrastom (uska strelica). Tekući sadržaj u antrumu i pneumatiziranim mastoidnim stanicama nije imbibiran.

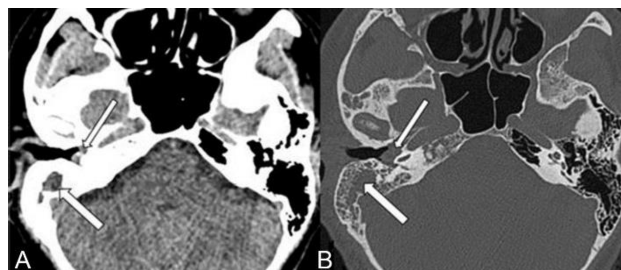


Figure 2 CT of the right temporal bone showing liquid content in the pneumatized right mastoid process and in the antrum. Imaging protocol for showing soft tissue structures (A) and imaging protocol for showing bone structures (B) was used. The right tympanum shows soft tissue content (narrow arrow).

Slika 2. CT desne sljepoočne kosti prikazuje tekući sadržaj u pneumatiziranom desnom mastoidnom nastavku i u antrumu. Korišten je protokol za prikaz struktura mekog tkiva (A) i slikovni protokol za prikaz koštanih struktura (B). Desno bubnjište prikazuje sadržaj mekog tkiva (uska strelica).

The incus and malleus were infiltrated by the tumor and were removed. The facial nerve canal and the Eustachian tube were not affected. Canal-wall-down tympanomastoidectomy was performed to facilitate complete disease removal from cavum tympani and epitympanum, safer follow-up and possible recurrence identification. Also, the tumor was removed from the foramen lacerum. The histopathology finding described an ESP. Immunohistochemical analysis was performed due to possible human papillomavirus (HPV) association and was HPV16 negative (Figure 3). One year after surgery, a control MRI and CT were performed and showed a new papilloma, located on the posterior part of the roof of the sphenoid sinus (Figure 4). Functional endoscopic sinus surgery (FESS) was performed and a small tumor was removed. The histopathology finding was the HPV16 positive OSP (Figure 3). Six months after the FESS, MRI showed no signs of recurrence. This case presentation has been assembled with informed consent from our patient, and IRB approval has been waived.

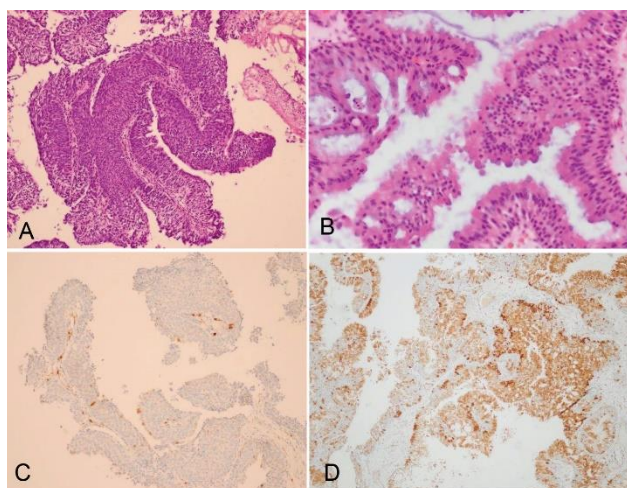


Figure 3 a) Exophytic papillary tissue consisting from villi, whose fibrovascular stroma was covered in reactive transitional, "Schneiderian" epithelium. According to WHO 2017 classification, it corresponds to an exophytic subtype papilloma (hematoxylin-eosin staining, 400× magnification). b) Exophytic papillary tissue consisting from villi, whose fibrovascularstroma was covered in oncocytic transitional, "Schneiderian" epithelium. According to WHO 2017 classification, it corresponds to an oncocytic subtype papilloma (hematoxylin-eosin staining, 400× magnification). c) Immuno-histochemical analysis was negative for possible human papilloma virus (HPV) association (p16 immunostaining, 200× magnification) d) Immunohistochemical analysis was positive on human papilloma virus (HPV) association (p16 immunostaining, 200× magnification).

Slika 3. a) Egzofitično papilarno tkivo koje se sastoji od resica, čija je fibrovaskularna stroma bila prekrivena reaktivnim prijelaznim, "Schneiderian" epitelom. Prema klasifikaciji WHO-a iz 2017. odgovara egzofitičnom podtipu papiloma (bojenje hematoksilin-eozinom, povećanje 400×). b) Egzofitično papilarno tkivo koje se sastoji od resica, čija je fibrovaskularna stroma prekrivena onkocitnim prijelaznim, "Schneiderian" epitelom. Prema klasifikaciji WHO-a iz 2017. odgovara onkocitnom podtipu papiloma (bojenje hematoksilin-eozinom, povećanje 400×). c) Imunohistokemijska analiza bila je negativna na moguću povezanost humanog papiloma virusa (HPV) (p16 imunološko bojenje, povećanje 200×) d) Imunohistokemijska analiza bila je pozitivna na povezanost humanog papiloma virusa (HPV) (p16 imunobojenje, povećanje 200×).

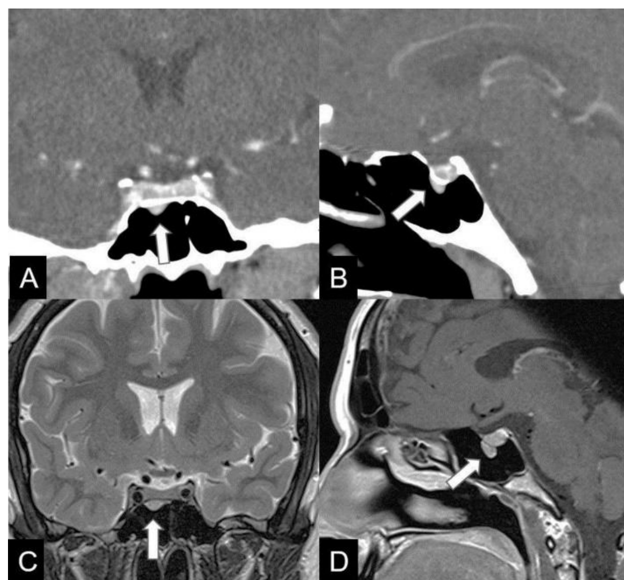


Figure 4 Coronal and sagittal CT images (A, B) demonstrate a well-defined solid mass (arrows) with homogeneous enhancement in the sphenoid sinus roof without defect of bony contour of sphenoid sinus. Coronal T2WI (C) and sagittal contrast-enhanced T1WI (D) MRI images show marked enhancement of the tumor in the sphenoid sinus roof (arrows).

Slika 4. Koronalne i sagitalne CT slike (A, B) pokazuju dobro definiranu čvrstu masu (strelice) s homogenim pojačanjem u krovu sfenoidnog sinusa, bez defekta koštane konture sfenoidnog sinusa. Koronalne T2WI (C) i sagitalne T1WI (D) MRI slike pokazuju značajno povećanje tumora u krovu sfenoidnog sinusa (strelice).

Discussion

So far, only 29 cases of the primary sinonasal papilloma affecting the temporal bone have been

reported. Recurrence, according to the majority of authors, indicates an insufficient resection and frequently occurs at the initial site within two years following surgery. The multifocal appearance of the same type of sinonasal papilloma has been described.[6] To our knowledge, this is the first described case of different types of sinonasal-type papilloma (exophytic and oncocytic) in two different locations (middle ear and sphenoid sinus) in a patient. The ESP in the middle ear, which was identified in our case is very rare and only four cases described to date. In our case, direct extension from the sinonasal tract can be excluded since the tumor was localized in the mastoid and middle ear space, while an extension to the Eustachian tube was not present. Clinical presentation mostly resembles chronic otitis media with polyp formation in the posterior tympanic membrane segments, but a glomus tympanicum should also be considered, especially if there is brisk bleeding present upon manipulation[6], as well as Eustachian tube dysfunction.[7,8] The etiology is probably multifactorial – no cases so far have been unequivocally linked with HPV infection, including ours, yet its contribution cannot be ruled out completely.[6] Histological features are similar to sinonasal localized Schneiderian-type papillomas. The characteristic features of ESP - fibrovascular stroma covered in the reactive transitional epithelium were found in our case. Microcysts, muciphages, goblets cells, and an inflammatory infiltration may also be present in Schneiderian-type papillomas.[9] A recent report showed that ESP does not show malignant transformation, but its biological behavior in the middle ear is difficult to predict.[3] Recurrence was reported at 100% in all previously reported cases treated only with tympanoplasty and simple excision compared to 39% following radical surgery (mastoidectomy or temporal bone resection).[7,8] These results can be compared with recurrence rates of ISP when treated with a similar extent of surgery.[1] The treatment of choice is surgery–radical tympanomastoidectomy, with other approaches proving inefficient in disease control.[1] If the diagnosis of the tumor is done very early, like the second tumor in this case, then more preservative surgery can be performed. The tumor in the sphenoid sinus was still asymptomatic and was diagnosed only due to regular MRI follow-ups. Since it was a small tumor, it was easy to remove it using FESS. Sinonasal-type papillomas are very prone to recurrence but the occurrence of different histological types is not common. The diagnosis is usually obtained with CT, MRI, and radical surgery, due to the advanced stage of the tumor being the treatment of choice. Strict postoperative follow-up is necessary and should include routine otoscopy, nasendoscopy, and imaging due to the high possibility of recurrence, unknown malignant potential, and the lack of accurate prognostic indicators.

References

1. Thompson LDR. Middle Ear and Temporal Bone Papilloma: A Clinicopathologic Study and Comprehensive Literature Review of 57 Cases. Head Neck Pathol 2021; 15:1212-1220.
2. Wenig BM. Schneiderian-type mucosal papillomas of the middle ear and mastoid. Ann Otol Rhinol Laryngol 1996;105:226-33.
3. Vorasubin N, Vira D, Suh JD, Bhuta S, Wang MB. Schneiderian papillomas: comparative review of exophytic, oncocytic, and inverted types. Am J Rhinol Allergy 2013;27:287-292.
4. Jones ME, Wackym PA, Said-Al-Naief N. et al.Clinical and molecular pathology of aggressive Schneiderian papilloma involving the temporal bone. Head Neck 1998;20:83-8.
5. Nudell J, Chiosea S, Thompson LD. Carcinoma ex-Schneiderian papilloma (malignanttransformation): a clinicopathologic and immunophenotypic study of 20 cases combined witha comprehensive review of the literature. Head Neck Pathol 2014;8:269-86.
6. Shen J, Baik F, Mafee MF, Peterson M, Nguyen QT. Inverting papilloma of the temporalbone: case report and meta-analysis of risk factors. Otol Neurotol 2011;32:1124-33.
7. De Filippis C, Marioni G, Tregnaghi A, Marino F, Gaio E, Staffieri A. Primary inverted papilloma of the middle ear and mastoid. Otol Neurotol 2002;23:555-9.
8. Santos Torres S de M, Castro TW, Bento RF, Lessa HA. Middle ear papilloma. Braz J Otorhinolaryngol 2007;73:431.
9. Schaefer N, Chong J, Griffin A, Little A, Gochee P, Dixon N. Schneiderian-Type Papilloma of the Middle Ear: A Review of the Literature. Int Surg 2015;100:989-93.
10. Nath J, Das B. Primary Inverted Papilloma of Middle Ear and Mastoid: A Rare Case Report. J Clin Diagn Res 2016;10:XD01-XD03.

Case report
Prikaz bolesnice

ISSN 0351-0093
Coden: MEJAD 53 (2023) 4

Long lasting atrophic glossitis due to autoimmune atrophic gastritis

Atrofični glositis kao prvi znak autoimunog atrofičnog gastritisa

Filip Miletić, Vladimir Bauer, Andro Košec, Sonja Radić*

Summary

Autoimmune gastritis is a primary chronic inflammatory disease of the stomach mucosa caused by a pathologic autoimmune response directed against H/K -ATPase. Gastric lesions lead to sideropenic anemia due to iron malabsorption, megaloblastic anemia arising from vitamin B12 deficiency and atrophic glossitis, which may be the first and only clinical symptom. In everyday practice, tongue diseases are often misdiagnosed. A holistic approach, detailed history and examination may reveal underlying and interconnected diseases which are the main cause of the symptoms, presenting a significant challenge for the otorhinolaryngologist. The paper presents a 53- years old patient who was misdiagnosed with burning mouth mucosa syndrome

Key words: atrophic glossitis, autoimmune gastritis, megaloblastic anemia, holistic approach

Sažetak

Autoimuni gastritis je primarna kronična upalna bolest želučane sluznice uzrokovana patološkim odgovorom usmjerenim protiv H/K –ATP-aze. Želučane lezije dovode do razvoja sideropenične anemije uslijed malapsorpcije željeza, te megaloblastične anemije zbog deficijencije vitamina B12. Atrofični glositis može biti prvi i jedini znak bolesti. U svakodnevnoj kliničkoj praksi bolesti jezika često su pogrešno dijagnosticirane i predstavljaju izazov za otorinolaringologe. Sveobuhvatni pristup, detaljna anamneza i fizikalni pregled mogu razotkriti podležeće bolesti koje su međusobno ovisne i pravi uzrok tegoba. U radu je prikazana 53- godišnja bolesnica kod koje je pogrešno dijagnosticiran sindrom žarenja sluznice usta.

Ključne riječi: atrofični glositis, autoimuni gastritis, megaloblastična anemija, sveobuhvatni pristup

Med Jad 2023;53(3):293-298

Introduction

Oral status is often underestimated or misdiagnosed and inflammatory diseases of the oral cavity with different pathogenesis are treated by unwarranted antibiotic or symptomatic therapy. On the other hand, there are many oral manifestations of systemic diseases, in early and advanced stages. There are also many systemic manifestations including hematologic, gastroenterological, neurologic and psychiatric aspects of the same disease.[1] In that sense, a holistic diagnostic and therapeutic approach leads to success in making the right decision in cases presenting with complex differential diagnoses.

Every clinician should carefully examine the head and neck status, especially oral mucosa for potentially important findings. We present a case of a silent, slowly progressive and unrecognized disease where only one clinical sign revealed an interesting cascade

***Karlovac General Hospital, Department of Otorhinolaryngology** (Filip Miletić, MD; Vladimir Bauer, MD); **University Hospital Center Sestre milosrdnice, Department of Otorhinolaryngology and Head and Neck Surgery** (Andro Košec, MD, PhD); **University of Zagreb, School of Medicine** (Andro Košec, MD, PhD); **Karlovac General Hospital, Department of Pathology and Cytology** (Sonja Radić, MD)

Correspondence address/*Adresa za dopisivanje:* Filip Miletić, MD, Department of otorhinolaryngology, General hospital Karlovac, Andrije Štampara 3, 47000 Karlovac E-mail: mileticfilip@gmail.com

Received/*Primljeno* 2023-09-05; Revised/*Ispravljeno* 2023-11-17; Accepted/*Prihvaćeno* 2023-11-20

of interconnected findings leading to a diagnosis of autoimmune atrophic gastritis.

Case report

In 2021, a 53-year-old woman was referred to an otorhinolaryngologist by her family medicine practitioner due to burning mouth syndrome lasting for nine years. Her chief complaint was difficulty in eating certain types of food due to burning sensations and aches in her tongue and mouth. She also suffered paresthesia in the lower extremities, panic attacks, depression episodes and nausea. Her diet included vegetables and fruit shakes, avoiding lemon and cinnamon. For the past 25 years, she complained of sideropenic anemia because of menometrorrhagia, while gynecological disturbances where excluded. Numerous visits to different specialists during the years, ranging from hematologists, gastroenterologists, otorhinolaryngologists to oral pathologists revealed no underlying causes. After a detailed physical examination, we could suspect and trace the underlying disease back for several years.

Clinical examination showed an indurated, red and smoothed tongue with a pronounced central fissure and smoothened and red soft palate mucosa (Figure 1). Her medical history included chronic gastritis, sideropenic anemia due to menometrorrhagia lasting for twenty-five years, panic attacks, depression, previous thyroid surgery due to follicular adenoma. A comprehensive diagnostic approach to atrophic glossitis causes included laboratory tests whichrevealed macrocytosis without anemia, low levels of ferritin and eosinophilia. Microbiological analysis of the tongue swab showed no infections. A megaloblastic anemia due to vitamin B12 deficiency was diagnosed. A gastroenterologist was consulted and the patient underwent esophagogastroduodenoscopy revealing atrophic gastritis of the fundus and corpus of the stomach mucosa (Figure 2). A biopsy performed during endoscopy showed metaplastic epithelium and immunochromatographic detection of Helicobacter pylori presence was negative (Figure 3). To confirm the diagnosis of autoimmune gastritis, a laboratory test for antiparietal cell antibodies was performed and came back positive. Since the diagnosis was established, we did not perform sternal punction seeking potential myelodysplastic syndrome. A neurologist was also consulted due to paresthesia of the lower extremities. Electromyoneurography findings showed a L5-S1 bilateral radiculopathy and axonal sensory polyneuropathy of the lower extremities due to demyelination of the sensory nerves caused by low levels of cyanocobalamin.

After the initial examination, we prescribed a polyvinylpyrrolidone — hyaluronic acid gel as a symptomatic relief which the patient used twice daily. She reported immediate improvement of the symptoms after two or three applications. When the diagnosis was established, treatment of atrophic glossitis included parenteral use of 1000 mcg of cyanocobalamin intramuscular injections every other day for the first week, once weekly for two months, and once monthly lifelong, respectively.

The patient showed complete resolution of the symptoms of atrophic glossitis in two weeks. Repeated oral examination showed no signs of glossitis revealing a normal architecture of the tongue and soft palate mucosa three months after the initial treatment (Figure 4). The psychological state of our patient improved successfully without the need for chronic therapy. Regular annually esophago-gastroduodenoscopy will be needed because of the malignant potential of the disease.

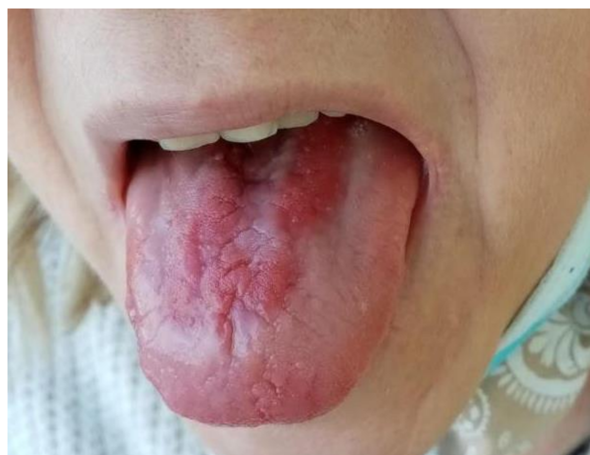


Figure 1 Atrophic glossitis and the absence of filliform and fungiform papillae

Slika 1. Atrofični glositis i odsustvo filiformnih i fungiformnih papilla

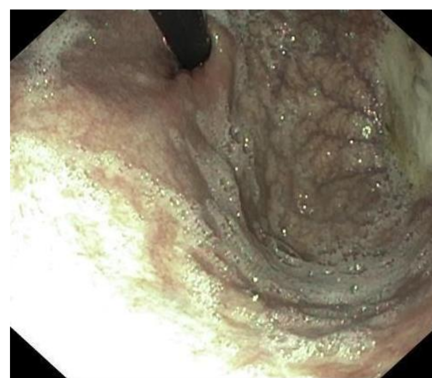


Figure 2 Pale atrophic fundal mucosa with prominent blood vessels

Slika 2. Atrofična sluznica želuca s istaknutim krvnim žilama

Table 1 Patient key laboratory findings
Tablica 1. Ključni laboratorijski nalazi bolesnice

Parameter *Parametar*	Value *Vrijednost*	Unit *Jedinica*	Reference interval/ *Referentni interval*
Red blood cells/*Eritrociti*	**3.80** L	10^{12}/L	3.86 - 5.08
Haemoglobin/*Hemoglobin*	137	g/L	119 - 157
Haematocrit/*Hematokrit*	0.414	L/L	0.356 - 0.470
MCV	**108.9** H	fL	83.0 – 97.2
MCH	**36.1** H	pg	27.4 – 33.9
MCHC	331	g/L	320 – 345
RDW	12.1	%	9.0 – 15.0
Platelets count/*Trombociti*	247	10^9/L	158 – 424
MPV	9.6	fL	6.8 – 10.4
White blood cells/*Leukociti*	6.79	10^9/L	3.4 – 9.7
Eosinophils/*Eozinofili*	**8.5** H	rel%	0 – 7
Basophils/*Bazofili*	0.4	rel%	0 – 1
Neutrophils/*Neutrofili*	45.9	rel%	44 – 72
Lymphocites/*Limfociti*	38.1	rel%	20 – 46
Monocites/*Monociti*	7.1	rel%	2 – 12
Glucose/*Glukoza*	5.9	mmol/L	4.4 – 6.4
Creatinine/*Kreatinin*	73	µmol/L	49 – 90
Glomerular filtration/*Glomerularna filtracija*	82	mL/min/1.73m^2	>60
Bilirubin/*Bilirubin*	10	µmol/L	3 – 20
AST	27	U/L	8 – 30
ALT	24	U/L	10 – 36
GGT	24	U/L	9 – 35
ALP	93	U/L	64 – 153
Alpha amylase/*Alfa amilaza*	**97** H	U/L	23 - 91
Fe	18	µmol/L	8 - 30
UIBC	42	µmol/L	26 - 59
TIBC	59	µmol/L	49 - 75
Ferritin/*Feritin*	**6** L	µg/L	9 - 136
Cyanocobalamine/*Cijanokobalamin*	**<109** L	pmol/L	138 - 652
Folic acid/*Folna kiselina*	33.0	nmol/L	7.0 – 46.4
APCA	positive	titer / titar	neg.: < 1 : 40

*Abbreviations/*Kratice:* MCV – mean corpuscular volume/*prosječni volumen eritrocita*; MCH – mean corpuscular *haemoglobin/prosječni hemoglobin u eritrocitu*; MCHC – mean corpuscular haemoglobin concentration/*prosječna koncentracija hemoglobina u eritrocitu*; RDW – red cell distribution width/*širina distribucije volumena eritrocita*; MPV – mean platelet volume/*prosječni volume trombocita*; T. Bilirubin – total bilirubin/*ukupni bilirubin*; AST - aspartate aminotransferase/*aspartat aminotransferaza*; ALT – alanine aminotransferase/a*lanin aminotransferaz*a; GGT – gamma-glutamyl transferase/*gama glutamil transferaza*; ALP – alkaline phosphatase/*alkalna fosfataza*; Fe – ferrum/*željezo*; UIBC - unsaturated iron- binding capacity/*nezasićeni kapacitet vezanja željeza*; TIBC - total iron-binding capacity/*ukupni kapacitet vezanja željeza*; APCA - anti parietal cell antibodies/*antitijela na parijetalne stanice*

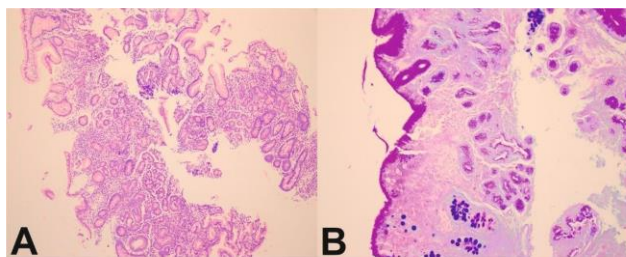


Figure 3 A) Microscopic appearance of gastric mucosa with reduced glandular structures and mononuclear inflammatory cells in lamina propria (HE×100), B) intestinal metaplasia in glandular epithelia (APAS×200).

Slika 3. A) Mikroskopski prikaz želučane sluznice reduciranih žljezdanih struktura i mononuklearnog infiltrata u lamini propriji. (He×100), B intestinalna metaplazija u žljezdanom epitelu (APAS×200).

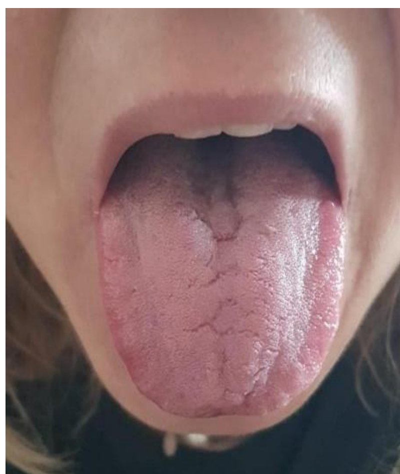


Figure 4 Three months after the beginning of treatment, a normal architecture of the tongue with filliform and fungiform papillae

Slika 4. Tri mjeseca od početka liječenja, normalna arhitektonika jezika s filiformnim i fungiformnim papilama

Discussion

Parietal cells are the largest and most complex cells in the gastric mucosa. They are found mostlywithin the middle third of the gastric glands of the body and fundus of the stomach. These cells are considered to be the source of hydrochloric acid and Castle's intrinsic factor as well as the rather large volume of water that accompanies active gastric secretion.[2] Such distribution and function are important in understanding the localization and nature of autoimmune gastritis which is restricted to body and fundus of the stomach.[3] A combination of host and environmental factors are responsible for the onset of the disease.[4] There is evidence, yet controversial, that Helicobacter pylori could induce autoimmune gastritis through mechanisms of molecular mimicry and/or epitope spreading since Th1 cells cross react to certain peptides expressed both on the wall of Helicobacter pylori bacteria and H/K ATP-ase of parietal cells membranes. The gastric H/K-ATP-ase, a member of the P2-type ATP-ase family**,** is the integral membrane protein responsible for gastric acid secretion. The gastric H/K-ATP-ase is located in the canaliculus of the stimulated state and secretes gastric acid by an electroneutral ATP dependent hydrogen-potassium exchange.[5] The transformation of these cells into antigen presenting cells activates the immunologic cascade reaction leading either to killing or apoptosis of the cells.[6] Clearance of Helicobacter pylori infection with progression of gastritis to corpus atrophy suggests a major underestimation of its association with chronic atrophic gastritis.[7] The associations with other autoimmune diseases led to further investigations and detection of HLA alleles DRB-1*3 and DRB-1*4 with predisposition to development of autoimmune gastritis.[8] The incidence of gastric neoplasm is higher in patients with autoimmune gastritis compared to the general population.[1] Prospective studies have shown that 4-9% of patients with autoimmune gastritis, or its more severe form pernicious anemia, have gastric carcinoid tumors, whose frequency is 13-times higher than that of control subjects. In addition, autoimmune gastritis progression to atrophic gastritis, associated with intestinal metaplasia, may predispose to gastric adenocarcinoma in more than 10% of patients.[9] Since gastric mucosa is atrophic, incompetent in producing an adequate amount of hydrochloric acid and intrinsic factor, there are no mechanisms of binding and transportation of exogenous cyanocobalamin from duodenum to terminal ileum and its absorption into circulation.[10] This results in the lack of cyanocobalamin, a DNA synthesis precursor, leading to damaged erythropoiesis and release of immature macrocytes impotent to bind and transport oxygen to the cells causing manifesting megaloblastic anemia and atrophic glossitis.[11] Iron, which is reducedin the stomach by action of ascorbic acid cannot be absorbed because of atrophic mucosa leading to iron deficiency anemia, the first sign of megaloblastic anemia and autoimmune gastritis.[10]

Our patient had refractory iron deficiency anemia lasting for twenty-five years, caused by menometrorrhagia until menopause which was treated numerous times by parenteral or orally prescribed iron supplements. During that time, a gynecological examination showed no disease. Causes of vulvovaginal, cervical, uterine origin were excluded such as coagulopathies leaving menometrorrhagia, as a cause of chronic blood loss,

unclear. Hematological findings during that period included tongue examination which was described as red without atrophy but no further investigations were conducted. Cyanocobalamin, folic acid or antiparietal cell antibody laboratory tests were not ordered, so we could not exactly trace the time of origin of the disease. It can be assumed that iron deficiency anemia was a first sign of autoimmune atrophic gastritis. Autoimmune gastritis can have psychiatric manifestations due to B12 deficiency, such as psychosis or depression which were present in our patient for around 20 years. In accordance with that, chronic stress, as a manifestation of autoimmune gastritis, may be a cause of menometrorrhagia and iron deficiency anemia, solely, and in combination with poor iron absorption.[12]

Other etiology of atrophic glossitis includes deficiencies of some major nutrients besides B12 such us riboflavin, niacin, pyridoxine, folic acid, iron, zinc and vitamin E. Moreover, protein-calorie malnutrition, candidiasis, Helicobacter pylori colonization, xerostomia and diabetes mellitus are also the etiologies. Thyroglobulin antibody and thyroid microsomal antibodies are positive in patients with autoimmune gastritis connecting it to thyroid autoimmune diseases. Differential diagnosis includes migratory glossitis, rhomboid glossitis, black hairy tongue, candidiasis, lingua geographica and strawberry tongue.[13]

In cases of suspected atrophic glossitis, normal laboratory tests and without anemia should not exclude further investigation of cyanocobalamin or folic acid levels. In cases of normal laboratory findings, we should determine precursors of cyanocobalamin and folic acid — homocysteine and methylmalonic acid. A consultation with a gastroenterologist is necessary due to heightened gastric cancer risk and a hematologist in case of potential myelodysplastic syndrome.

Acknowledgment

This case report was presented online during the 12th congress of the Croatian Society of Otorhinolaryngology, Head and Neck Surgery and was published in Medica Jadertina, Vol.51, No. Supplement, 2021 as an abstract.

References

1. Minalyan A, Benhammou JN, Artashesyan A, Lewis MS, Pisegna JR. Autoimmune atrophic gastritis: current perspectives. Clin Exp Gastroenterol 2017;10:19-27.
2. Rohrer GV. Human gastric mucosa: correlation of structure and function. Am J Clin Nutr1971;24:137-43
3. Kulnigg-Dabsch S. Autoimmune gastritis. Wien Med Wochenschr 2016;166:424-430.
4. Rodriguez-Castro KI, Franceschi M, Miraglia C, et al. Autoimmune diseases in autoimmuneatrophic gastritis. Acta Biomed 2018;89:100-103.
5. Shin JM, Munson K, Vagin O, Sachs G. The gastric HK-ATPase: structure, function, and inhibition. Pflugers Arch 2009;457:609-22.
6. D'Elios MM, Appelmelk BJ, Amedei A, Bergman MP, Del Prete G. Gastric autoimmunity: the role of Helicobacter pylori and molecular mimicry. Trends Mol Med 2004 ;10:316-23
7. Toh BH, Chan J, Kyaw T, Alderuccio F. Cutting edge issues in autoimmune gastritis. Clin Rev Allergy Immunol 2012;42:269-78.
8. Lahner E, Spoletini M, Buzzetti R, et al. HLA-DRB1*03 and DRB1*04 are associated withatrophic gastritis in an Italian population. Dig Liver Dis 2010;42:854-9
9. Bizzaro N, Antico A, Villalta D. Autoimmunity and Gastric Cancer. Int J Mol Sci 2018 ;19:377
10. Atrah HI, Davidson RJ. Iron deficiency in pernicious anaemia: a neglected diagnosis. Postgrad Med J 1988;64:110-111.
11. Das KC, Das M, Mohanty D. et al. Megaloblastosis: from morphos to molecules. Med Princ Pract 2005;14 Suppl 1:2-14
12. Miceli E, Brondino N, Lenti MV. et al. Impaired Quality of Life in Patients with Autoimmune Atrophic Gastritis. Dig Dis Sci 2021;66:3322-3329.
13. Chiang CP, Chang JY, Wang YP, Wu YH, Wu YC, Sun A. Atrophic glossitis: Etiology, serum autoantibodies, anemia, hematinic deficiencies, hyper-homocysteinemia, and management. J Formos Med Assoc 2020;119:774-780

Recenziji podliježu članci koji se prema općim standardima dijele u četiri kategorije:

- izvorni znanstveni članak (Sadrži dotada neobjavljene rezultate znanstvenog istraživanja. Članak mora sadržavati sve detalje nužne radi ponovljivosti opisanog rada.)
- prethodno priopćenje (Sadrži dotad neobjavljene preliminarne rezultate znanstvenog istraživanja koje je poželjno brzo objaviti.)
- pregledni članak (Sažet i kritičan pregled specifičnog istraživačkog područja sa svježim informacijama o trenutačnom stanju razvoja i usmjerenja.)
- stručni članak (Sažet i kritičan pregled odabrane teme, s usmjerenjima i kontroverzama u njoj. Mora biti razumljiv i nespecijalistima tog područja. Od znanstvenoga se razlikuje prvenstveno u tomu što ne donosi originalne rezultate autora istraživanja nego rabi već objavljene rezultate i koje usustavljuje i objašnjava.)

Kategoriju članka predlaže autor, a konačan sud donosi urednik na prijedlog recenzenata rada. Nekategorizirani radovi (recenzije, prikazi i slično) ne podliježu recenzentskom postupku, uredništvo ih prihvaća na temelju vlastitih uvida.

Recenzent je odgovoran za kritičku procjenu kvalitete rada koji je dobio na ocjenu.

Dužnost mu je iznijeti detaljne primjedbe i savjete o istraživanju i formulaciji rezultata kako bi autoru/ima pomogao pri poboljšanju njihova rada. Procjena rada uključuje ocjenu njegove izvornosti i važnosti, njegova metodološkog ustroja te valjanosti zaključaka izvedenih na temelju dobivenih rezultata.

Recenzent je dužan upozoriti uredništvo o mogućim poteškoćama koje bi ga spriječile u objektivnosti pri postupku recenziranja. Također je dužan s dobivenim člankom postupati kao s povjerljivim spisom, tj. ne pokazivati rad bilo kome drugom bez pristanka uredništva, ne koristiti rezultate iz rada koji im je poslan na recenziju za vlastita istraživanja prije objave rada.

Recenzent je dužan recenziju obaviti na vrijeme i zadržati akademsku razinu komunikacije pri pisanju recenzije.

Nakon pročitanog rada, recenzent je dužan dati svoj sud o tome treba li rad objaviti, predložiti kategorizaciju ukoliko je recenzija pozitivna te iznijeti sud o tome treba li se u radu išta popraviti ili doraditi. Ocjena se treba kretati unutar sljedećih smjernica:

- DA – („Prihvaća se“) Bezuvjetno odobrenje za objavu rada.
- DA, POD UVJETOM DA – („Prihvaća se uz doradu“) Odobrenje predviđa izvjesne modifikacije/poboljšanja koja se trebaju izvršiti na radu
- NE, OSIM U SLUČAJU – („Ne prihvaća se“) Nužna temeljita revizija i rekonstrukcija rada.
- NE – („Ne prihvaća se“) Ne postoji niti minimum elemenata koji se mogu iskoristiti.

Recenzije su dvostruko slijepe, tj. recenzent neće znati ime autora niti će autor znati ime recenzenta.

Articles divided into four categories according to general standards are subject to reviews such as:

- Original scientific article (It contains previously unpublished results of scientific research. The article must contain all the details necessary for the reproducibility of the described work.)
- Previous announcement (It contains previously unpublished preliminary results of scientific research, desired to be published quickly)
- Review article (A concise and critical overview of a specific research area with fresh information on the current state of development and direction)
- Expert article (A concise and critical overview with guidelines and controversies in it. It must be understandable to non-specialists of the field. It differs from the scientific article primarily in that it does not bring the original results of the authors of the research, but uses already published results it systematizes and explains.)

The author suggests the article category, while the final judgement is made by the editor at the suggestion of the reviewer of the work. Non-categorized works (reviews, displays and similar) are not subject to review procedure, the editorial board accepts these based on their own insights.

The reviewer is responsible for critically evaluating the quality of the work received for evaluation. It is his duty to provide detailed remarks and advice on research and formulation of results in order to help the author/s in improving his/their work. The evaluation of the paper includes an assessment of its originality and importance, its methodological structure and the validity of the conclusions drawn based on the obtained results.

The reviewer is obliged to warn the editorial board on the possible difficulties that may prevent him in being objective in the review procedure. He is also obliged to treat the received article as a confidential file, i.e. not show the work to anyone without the approval of the editorial board, not use for his own research the work results sent for review prior to the work being published.

The reviewer is obliged to perform the review on time and retain the academic level of communication in writing his review.

Having read the paper, the reviewer is obliged to give his judgment on whether the paper should be published, suggest the categorization if the review is positive, and make a judgment on whether anything in the paper should be corrected or amended.

The evaluation should be within the following guidelines:

- YES – ("Accepted ") Unconditional approval for the publication of the paper.
- YES, UNDER THE CONDITION THAT – ("Accepted with amendments") The approval foresees certain amendments/improvements that are to be performed in the work
- NO, EXCEPT IN THE CASE THAT – ("Not accepted") A thorough revision and reconstruction of the work is necessary.
- NO – ("Not accepted") There is not even a minimum of elements that can be used.

Reviews are double blind, i.e. the reviewer shall not know the name of the author nor shall the author know the name of the reviewer.

Časopis MEDICA JADERTINA objavljuje uvodnike, izvorne znanstvene i stručne radove, prethodna priopćenja, pregledne radove, izlaganja sa znanstvenih skupova i druge priloge iz područja temeljnih i kliničkih medicinskih znanosti. Rukopisi mogu biti napisani na hrvatskom ili na engleskom jeziku.

Uredništvo primljene radove upućuje na obveznu recenziju dvama recenzentima. Izneseni stavovi u radovima predstavljaju mišljenje autora, stoga je svaki autor odgovoran za etičku prihvatljivost svojega rada. Radovi objavljeni u časopisu zaštićeni su autorskim pravom. Tekst i slike iz ovog časopisa mogu se koristiti za osobnu i edukacijsku svrhu uz poštivanje autorskih prava autora i izdavača. Svaka druga uporaba zabranjena je bez izričitog pisanog dopuštenja izdavača, Opće bolnice Zadar. Svi radovi vlasništvo su izdavača časopisa.

Uredništvo radove ne mora objavljivati slijedom kojim pristižu. Tiskani radovi u časopisu, dostupni su u cijelosti na Portalu hrvatskih znanstvenih radova – HRČAK. Radove poslati naslovu na elektroničku adresu: opca-bolnica-zadar@zd.t-com.hr ili poštom na adresu: Uredništvo časopisa MEDICA JADERTINA, Opća bolnica Zadar, Bože Peričića 5, 23000 Zadar, Hrvatska.

Priprema rada

Izvorni znanstveni i pregledni radovi ne smiju biti dulji od 3000 riječi (iznimno 4000 riječi). Preduge radove, osim onih naručenih, Uredništvo neće prihvatiti i vratiti će ih autorima.

Radove treba pisati na računalu u programu MS Word ili sličnom programu s proredom (1,5) u fontu Times New Roman, veličina slova 12. Format stranice mora biti A4, a margine 2,5 cm sa svih strana. Svako poglavlje rada treba započeti na novoj stranici. Svi dijelovi rada uključujući tablice, slike i popis literature moraju biti u jednom elektronskom dokumentu. Uz rukopis je potrebno priložiti izjave o nepostojanju sukoba interesa, financijskog ili bilo kakvog drugog interesa, autorstvu i prijenosu autorskih prava, te izjavu da rad nije već objavljen ili prihvaćen za objavu u nekog drugom časopisu. Obrazac izjave nalazi se na kraju ovog dokumenta.

Naslovna stranica

Naslovna stranica treba sadržavati naslov rada na hrvatskom i engleskom jeziku, puna imena i prezimena svih autora, s njihovim akademskim stupnjevima te specijalnostima, kao i službenim nazivima organizacija u kojima rade. U naslovu rada ne smiju se koristiti kratice. Pri dnu stranice treba navesti ime, prezime, adresu i elektronsku adresu autora za dopisivanje.

Sažetak (Summary)

Sažetak s najviše 300 riječi na hrvatskom i engleskom jeziku treba biti strukturiran, na zasebnoj stranici. Preporučuje se pisati u prvom licu množine, izbjegavati pasivne glagolske oblike i ne koristiti kratice.

Ključne riječi

Na stranici s hrvatskim, odnosno engleskim sažetkom ispod teksta valja napisati tri do šest ključnih riječi karakterističnih za glavnu temu rada i prikladnih za uvrštenje u bibliografska kazala. Ključne riječi moraju biti u skladu s naslovima u Index Medicusu.

Rad

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).

Tablice i slike

Tablice treba izraditi na zasebnoj stranici s rednim brojem i naslovom. Riječi u tablicama ne smiju se kratiti. Naslovi i tekstualni sadržaj tablice moraju biti dvojezični, na hrvatskom i engleskom jeziku. Svaka tablica mora imati redni broj. Naslov i redni broj pišu se iznad tablice. Izbjegavati korištenje vertikalnih linija u tablici. Legende tablica pisati ispod tablice.

Iznimno, na zahtjev recenzenata ili Uredništva časopisa, autori će dostaviti podatke na temelju kojih su izrađeni grafikoni (u formatu .xls). Naslovi slika (crteža, ilustracija, fotografija) moraju biti navedeni dvojezično, na hrvatskom i engleskom jeziku i

označeni rednim brojem. Naslov i redni broj pišu se ispod slike, a umetnuti su na posebnoj stranici na kraju dokumenta. Slike je potrebno dostaviti posebno u .jpeg, .png ili .tiff formatu (min. razlučivosti 300 dpi). Potrebno je označiti gornji dio slike te po potrebi bitna mjesta na slikama označiti strelicom. Za reprodukcije slika i tablica iz drugih izvora treba priložiti dozvolu njihovih izdavača/autora. Fotografije osoba mogu se objavljivati samo uz pismeno dopuštenje osobe na fotografiji. U protivnom osoba na fotografiji mora biti neprepoznatljiva (prekrivene oči). Uredništvo pridržava pravo odbiti slike koje kvalitetom ne zadovoljavaju.

Literatura

Popis literature sadržava radove koji su navedeni u tekstu i to slijedom kako se pojavljuju u tekstu. Popis je potrebno navesti na posebnoj stranici. Pojedine citate na popisu navesti rednim brojem pod kojim se nalaze u tekstu, gdje su označeni superskriptom. Za nazive časopisa koristiti kratice iz Index Medicusa.

Literatura se citira:

a) Periodične publikacije

Članak u časopisu

Navesti sve autore ako ih je šest ili manje, ako ih je sedam ili više, navesti prva tri i dodati: i sur., a u literaturi na engleskom jeziku: et al.

Soter NA, Wasserman SI, Austen KF. Cold urticaria: 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 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

Matić-Glažar Đ. Etičke dileme. Novi list 1985. Prosinac 13;11.

b) Knjige, monografije, zbornici, doktorski ili diplomski radovi

Iza navedenog citata navesti godinu tiska i brojeve stranica poglavlja u knjizi ili zborniku na kojima je naveden citat. Kod doktorskog, diplomskog ili sličnog rada, osim godine tiska treba napisati stranicu na kojoj je naveden citat.

Jedan autor knjige

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.

MEDICA JADERTINA journal releases editorials, original scientific and professional articles, earlier announcements, review articles, presentations from scientific meetings and other supplements from basic and clinical medical fields. The manuscripts can be written in the Croatian or English language. The Editorial Board of the paper submits a mandatory review to two reviewers. The stated articles in the papers represent the opinion of the author, therefore, each author is responsible for the ethical approval of his paper. The papers released in the journal are copyrighted. The text and illustrations from the journal can be used for personal and training purposes respecting the copyright of the author and publisher. Any other use is prohibited without the expressed written permission of the publisher, Zadar General Hospital. All papers are the property of the journal publisher.

The Editorial Board does not have to release the papers in the order of their arrival. The printed papers in the journal are available in full on the Portal of Croatian scientific papers – HRČAK. Papers are to be sent to the above at the electronic address: opca-bolnica-zadar@zd.t-com.hr or by post at the address: MEDICA JADERTINA Editorial Board, Zadar General Hospital, Bože Peričića 5, 23000 Zadar, Croatia.

Preparation of works

Original scientific and review papers may not exceed 3000 words (exceptionally 4000 words). The Editorial Board will not accept too long articles other than those ordered and will return them to the authors.

Papers should be written on a MS Word program or similar line spacing programs (1.5) in Times New Roman font, size 12. The page size should be A4, with 2.5 cm margins on all sides.

Every paper chapter is to start on a new page. All parts of the paper, including tables, illustrations and bibliography list must be in one electronic document. The manuscript must include statements of no conflict of interest, no financial or any other conflict of interest, authorship or transfer of copyright, and a statement that publication has not been published or accepted in another journal. The statement form can be found at the end of this document.

Cover page

The cover page must consist of the paper title in the Croatian and English language, full name and surname of the authors with their academic title and specializations, as well as the official titles of their working organization. The paper title must not consist of abbreviations. The name, surname, address and electronic address for correspondence is to be stated at the bottom of the page.

Summary

A summary of at most 300 words in the Croatian and English language must be structured on a separate page. It is recommended to be written in the first person plural, avoiding the passive voice and the use of abbreviations.

Key words

Three to six key words are to be written on a page in the Croatian language, the English language summary under the text respectively, characteristic of the main theme of the paper and suitable for inclusion in the Bibliographical Index. The key words must be in accordance with the Index Medicus titles.

Articles

When possible, the paper should be divided as follows: introduction, patients (material) and methods, results, discussion, conclusion, summary and the bibliography. The introduction is to state the purpose of the paper and reason for carrying out the research. The patients and methods chapter covers all the important research characteristics. It is necessary to state that the Ethics Committee has given its approval for the examination which has been performed in line with the ethical principles of the Helsinki Declaration. It is to be emphasized that the examinees gave their consent to participate in the examination as well as the submission of their patient's consent to publishing their data in the "Case Presentation". It is necessary to describe the used statistical methods as well as statistical program used for data processing. The significance of the results needs to be statistically substantiated. The measurement units must be expressed according to the SI system. The discussion should emphasize new and important knowledge arising from the research and compare theses with the results from the bibliography. The abbreviations can be used in the text only after the second mention of the entire word in the text. It is possible to use prominent words in italic font in exceptional cases. It is necessary to mark the places where the tables or illustrations are to be placed citing the parenthesis in the text – i.e. (Table 1). All supplements to the paper text are to be reduced to a reasonable number (six tables at most, illustrations/ figures respectively).

Tables and figures

The tables should be prepared on a separate page in ordinal number and titles. The words in the tables must not be abbreviated. The titles and text contents of the tables must be in bilingual, in the Croatian and English language. Each table must have its ordinal number. The title and ordinal number are to be written above the table. Avoid the use of vertical lines in the table. Write the table legend under the table. Exceptionally, and at the request of the reviewer of the journal Editorial

Board, the authors will provide the data on which the graphs were made (.xls format). The titles of the figures (drawings, illustrations, figures) must be bilingual, in Croatian and English and marked in ordinal number. The titles and ordinal numbers are to be written under the figures, and placed on a separate page at the end of the document. The figures need to be sent separately in.jpeg, .png or .tiff format (min. resolution 300 dpi). The upper part of the figures needs to be marked, and, if necessary, the essential parts of the figure marked with an arrow. Permission from publishers/authors should be attached to the reproduced figures and tables from other sources. Photos of persons may only be published with the written permission of the person in the photograph. Otherwise, the person in the photo must be unrecognizable (eyes covered). The Editorial Board reserves the right to reject figures that do not meet the quality requirements.

Bibliography index

The bibliography consists only of papers mentioned in the text and in the order in which they appear in the text. The bibliography index must be written on a separate page. Separate quotes on the list are to be mentioned in the ordinal number under which they are found in the text, where they are marked in superscript. Use Index Medicus for journal titles.

The bibliography is quoted:

a) Periodical publications

Article in journal

Mention all the authors, if there are six or less, if seven or more, then mention the first three and add et al. in the English bibliography.

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

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

Journal Supplement

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

News article

Matić-Glažar Đ. Etičke dileme. Novi list 1985. Dec 13;11.

b) books, monographs, proceedings, doctoral or graduate thesis

State the year of the print and the page numbers of the chapter in the book or proceedings citing the quote after the mentioned quote. In case of a doctoral, diploma or similar thesis, except for the year of printing, the page on which the citation is quoted should be written.

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.

Medica Jadertina

Priznanje autorstva, Izjava o publikaciji, Izjava o sukobu interesa i Ugovor o prijenosu autorskih prava

Medica Jadertina objavit će Vaš rad ("Rad") pod naslovom:

Svi autori moraju značajno doprinijeti izradi rada. Svaki autor preuzima odgovornost za sadržaj rada. Urednici mogu tražiti od autora da obrazlože svoj doprinos radu, što može biti i objavljeno.

Autor za dopisivanje u ime svih autora prenosi na *Medicu Jadertinu* vlasništvo nad autorskim pravima rada i pravima vezanima uz rad, u svim oblicima i svim medijima. Navedeni autor jamči da je rad izvoran, da nije u razmatranju za objavljivanje u drugom časopisu i da nije prethodno objavljen. Također, autor za dopisivanje potvrđuje da su svi navedeni autori rada upoznati sa sadržajem rada, te su suglasni s objavljivanjem rada u obliku u kojem je upućen Uredništvu časopisa.

Autori su dužni navesti eventualni financijski ili bilo koji drugi sukob interesa, vezan uz navedeni rad, kao i eventualnu financijsku potporu radu.

Ovu izjavu potpisuje autor za dopisivanje.

Ime i prezime autora za dopisivanje **Potpis** **Datum**

Medica Jadertina
Acknowledgement of Authorship, Publication Statement, Conflict of Interest Statement, and Transfer of Copyright Agreement

The Medica Jadertina will publish your article ("the Work") entitled:

____

____

All persons designated as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content. Editors may ask authors to describe what each one contributed; this information may be published.

The undersigned corresponding author, on behalf of all authors, transfers all copyright ownership in and relating to the Work, in all forms and media, to Medica Jadertina. The corresponding author warrants that the Work is original, that it is not under consideration by another journal, and has not been previously published. Also, the undersigned corresponding author confirms that all designated authors are familiar with the content of the work, and agree to publish the paper in the form in which it has been sent to the Editorial Board.

When authors submit the Work, whether an article or a letter, they are responsible for recognizing and disclosing financial and other conflicts of interest that might bias their work. They should acknowledge in the manuscript all financial support for the Work and other financial or personal connections to the Work.

This agreement must be signed by the corresponding author.

____

Corresponding author's name & signature **Date**