UDK 616 – 053.2
CODEN PCROE6
ISSN 1846-405X
Vol. 68 No 3 2024

PAEDIATRIA CROATICA

Izdavač
Klinika za dječje bolesti Zagreb, 10000 Zagreb, Klaićeva 16

Izdavač / Publisher

KLINIKA ZA DJEČJE BOLESTI ZAGREB, KLAIĆEVA 16, ZAGREB

Indeksiranost / Indexing

• Embase/ExcerptaMedica, Amsterdam; • Index Copernicus; • Abstracts Journal, All-Russian Institute for Scientific and Technical Information (VINITI); • Scopus; • ScientificCommons; • EBSCO host; • Hrčak; • Electornic Journals Online Library (EJOL); • Geneva Foundation for Medical Education and Research; • Google Scholar; • CrossRef; • ResearchGate; • CiteFactor; • DRJI (Directory of Research Journals Indexing)

Časopis izlazi četiri puta na godinu.

Časopis je namijenjen općim pedijatrima, subspecijalistima različitih grana pedijatrije, neonatolozima, obiteljskim liječnicima i ostalim zdravstvenim djelatnicima koji brinu o djeci.

Časopis je *open-access*.

OPEN ACCESS

UDK 616 – 053.2
CODEN PCROE6
ISSN 1846 – 405X

PAEDIATRIA CROATICA

Vol. 68 • Srpanj-Rujan/*July-September* 2024. • Broj/*No* 3

SADRŽAJ / *CONTENT*

IZVORNI ZNANSTVENI RADOVI / *ORIGINAL SCIENTIFIC PAPERS*

Alisha Akhani, Jaishree Ganjiwale, Bhadra Trivedi, Somashekhar Nimbalkar
Safety of pediatric cardiac catheterisation procedures performed in rural India in a catheterisation lab setup for adult work
Sigurnost kateterizacije srca u pedijatrijskoj populaciji izvođenih u ruralnoj indiji u kateterizacijskom laboratoriju za odrasle 123

Sunitha Bhagavathi Mysore, Dragana Djuric, Adam Zeghan, Areen Oudeh, Belal Al Qerem, Abdulla Al Humaidan, Amina Hussain Salem Alyafei, Muhammed Al Jarrah
Rehabilitation services for children with disabilities during the COVID-19 pandemic in the United Arab Emirates: Experiences of parents
Usluge rehabilitacije za djecu s teškoćama u razvoju tijekom COVID-19 pandemije u Ujedinjenim Arapskim Emiratima: iskustva roditelja 128

Dominik Vuletić
Excessive pharmaceutical pricing and repercussions on paediatric health services
Prekomjerno visoke cijene lijekova i njihov utjecaj na pružanje zdravstvenih usluga u pedijatriji 137

Prasad Muley, Dave Hemal, Dave Hardik, Sargam Bhatt, Vaibhavi Mithaiwala
Effect of treatment on quality of life of rural asthmatic children
Utjecaj liječenja na kvalitetu života djece astmatičara u ruralnim sredinama 143

PREGLEDI / *REVIEWS*

Blaženka Kljaić Bukvić, Radenka Kuzmanić Šamija, Silvije Šegulja
Primjena ibuprofena u pedijatrijskoj populaciji
Use of ibuprofen in pediatric population 148

Rok Kralj, Danijel Cvetko, Ana Tripalo Batoš, Tomislav Baudoin, Elvira Kereković, Nada Rajačić, Jasminka Stepan Giljević, Stjepan Višnjić
Limfatičke malformacije
Lymphatic malformations 155

Izdavač/Editor: Klinika za dječje bolesti Zagreb, 10000 Zagreb, Klaićeva 16

Paediatr Croat. Godište 68 • Zagreb, srpanj–rujan 2024. • Broj 3 (str. 123–164)

Paediatr Croat. 2024;68:123-7
IZVORNI ZNANSTVENI ČLANAK / *ORIGINAL SCIENTIFIC PAPER*
www.paedcro.com
http://dx.doi.org/10.13112/PC.2024.21

Safety of pediatric cardiac catheterisation procedures performed in rural India in a catheterisation lab setup for adult work

Alisha Akhani[1], Jaishree Ganjiwale[2], Bhadra Trivedi[3], Somashekhar Nimbalkar[4]

Introduction: *The congenital heart disease (CHD) makes the largest group of congenital defects children are born with. The conservative estimate points towards 1% prevalence of CHD among the newborn. In India, each year approximately 2.4 lakh children are born with CHD, which is largest in the world. There are very centres offering paediatric cardiology services in India and they are unevenly distributed. Because of this, a lot of paediatric patients with CHD get treated at an adult cardiology facility, not always equipped with proper setup to handle complexities associated with paediatric cardiology work. The study aims to assess the safety and complications associated with paediatric cardiology catheterization-based procedures in a Cath lab is primarily used for adult cardiology work.*

Methods: *The current study is a retrospective review of pediatric cardiac cath-lab-based procedures performed between April 2018 and March 2021.*

Results: *During the study, 110 pediatric patients underwent 110 cath-lab-based procedures. A total of 20 procedures were performed as an emergency, and 90 were performed as planned procedures. Out of 110 procedures performed, 86.4% were completed without complications. Minor complications were observed in 9.1% of the procedure. Major complications were seen in 3 patients, and two patients died.*

Conclusion: *The analysis shows that the complications associated with pediatric cardiac procedures performed on rural-based cath-lab oriented toward adult cardiology work are comparable to those of other large-volume pediatric cardiac centres.*

Key words: CONGENITAL HEART DEFECTS; CARDIAC CATHETERIZATION; PEDIATRICS; PATIENT SAFETY

INTRODUCTION

Congenital heart diseases (CHD) constitute a significant component of congenital birth defects. As per an estimate in 2011, CHD accounts for nearly 25% of all congenital birth defects (1). The prevalence of CHD globally is estimated to be 1.8 per 100 live births in 2017 (2). *Saxena et al.* estimated that around 240 thousand children are born with CHD each year in India, contributing to 10% of infant mortality (3). A status report by *Ramakrishnan* showed that only around 90 centres are dedicated to pediatric cardiology work. These centres are not uniformly distributed across the country (4). Many adult cardiology centres in various parts of the country care for pediatric patients with congenital heart diseases. Such centres are not always well-equipped to manage pediatric cardiology cases and post-procedure complications. The study aims to assess the safety and complications associated with pediatric cardiology catheterization-based

[1] Pramukhswami Medical College, Bhaikaka University, Karamsad, India
[2] Central Research Services, Pramukhswami Medical College & Shree Krishna Hospital, Bhaikaka University, Karamsad, India
[3] Department of Pediatrics, Parul University, Vadodara, India
[4] Department of Neonatology, Pramukhswami Medical College & Shree Krishna Hospital, Bhaikaka University, Karamsad, India

Correspondence to:
Bhadra Trivedi, MD, consultant Pediatric Cardiologist & Professor; Department of Pediatrics; Parul University, Vadodara, India;
e-mail: bhadra81@gmail.com

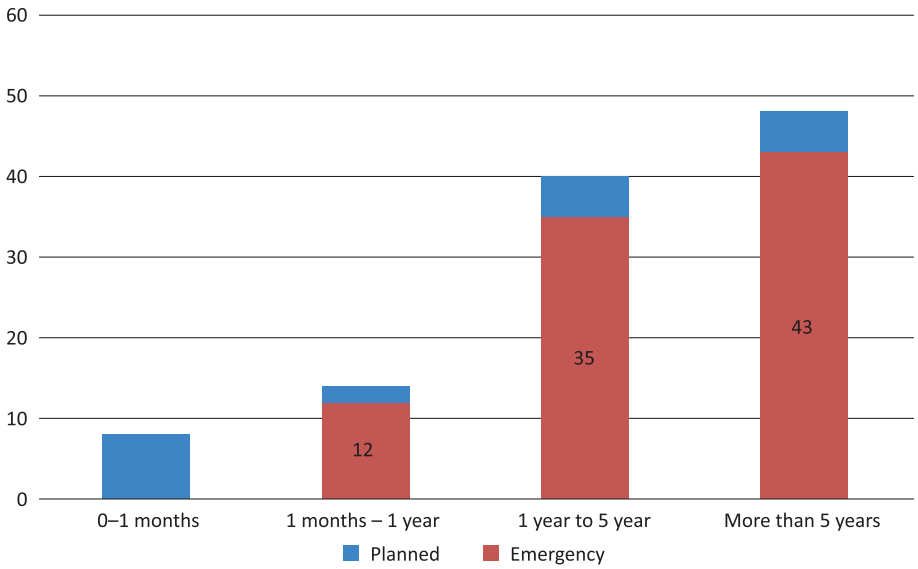


FIGURE 1. The distribution of cases in various age groups.

procedures in a centre in rural areas where the cath lab is primarily set up for adult cardiology work.

METHOD

The Ethics Committee of the institute approved the study. The study Design is a retrospective review. This is a review of complications of pediatric cardiac cath-lab-based procedures performed between April 2018 and March 2021 at B and M Patel Cardiac Centre at Bhaikaka University in Karamsad, Anand, India. The study included all the cath-lab procedures performed by a pediatric cardiologist. The patients' procedure notes, in-hospital documents, ICU documents, discharge summaries, and death summaries were reviewed. Patients with incomplete documents were excluded from the analysis. The classification of complications was adopted from a study by *Tokel et al.* (5). The statistical analysis was conducted using Stata 14 software.

RESULTS

110 pediatric patients underwent 110 cath-lab-based diagnostic or therapeutic procedures during the study period. All of them were included in the analysis. There were 63 female patients, which is 57% of all patients. The mean age of the patients included in the study is 65.56 months (IQR –

TABLE 1. Emergency and planned cases performed each calendar year

Year	Emergency	Planned	Total
2018	3	21	24
2019	5	47	52
2020	9	15	24
2021	3	7	10
Total	20	90	110

TABLE 2. Procedures performed in a specified period at the centre

Procedure	Count	Per cent
Percutaneous device closure of patent ductus arteriosus	33	30.00
Percutaneous device closure of the atrial septal defect	13	11.82
Percutaneous balloon pulmonary valvotomy (BPV)	13	11.82
Diagnostic angiogram	12	10.91
Percutaneous balloon aortic valvotomy	6	5.45
Percutaneous balloon coarctoplasty	6	5.45
Catheterisation for operability in shunt lesions	6	5.45
Pre-Fontan diagnostic angiograms	10	9.09
Percutaneous device closure of the ventricular septal defect	3	2.73
Balloon atrial septostomy for TGA / TAPVC	2	1.82
Percutaneous device closure of the ASD with BPV	2	1.82
Coil embolisation	1	0.91
Fontan fenestration closure	1	0.91
Percutaneous closure of PDA with BPV	1	0.91
Pericardial effusion drainage	1	0.91

TABLE 3. Categorization of complications during pediatric cardiac catheterization

Category	Count	Per cent
1 No Complication	95	86.4 %
2 Minor Complication	10	9.1 %
3 Major Complication (including sentinel events)	3	2.7 %
4 Death (Included in Group 3)	2	1.8 %

Classification of complications as described by Tokel et al. [5]

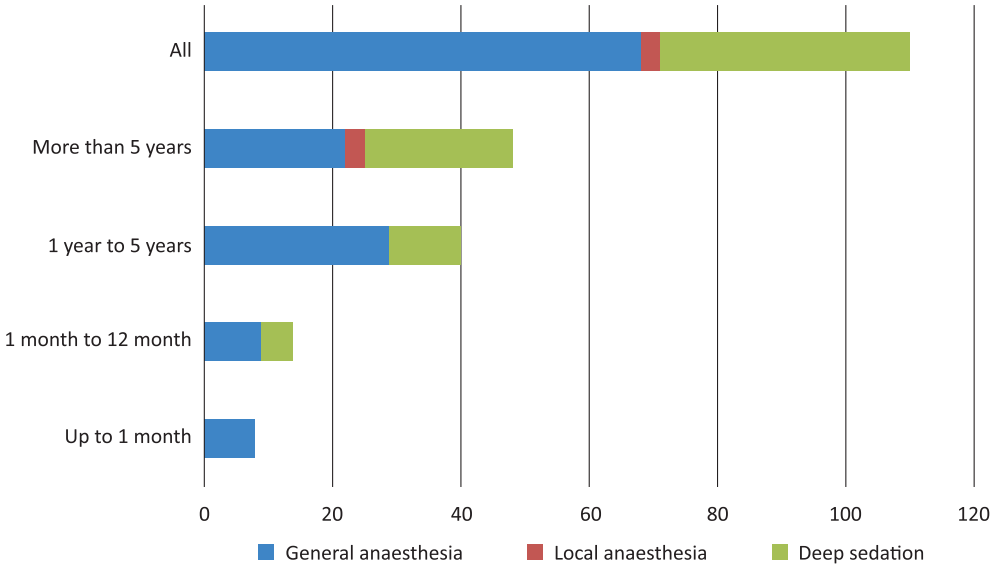


FIGURE 2. Anaesthesia plans for procedures vs age group of patients.

93.22 months). The mean weight of study participants is 13.7 kg, while the range is 2.3 kg to 44.13 kg (IQR – 9.9 kg).

Patients' mean height and weight were 95.95 cm and 13.769 kg, respectively. The mean BSA was 0.5996, and the mean hospital stay was 2.3 days. Patients were further divided into four age groups (Figure 1).

The total number of emergency procedures was 20 (18%) (Table 1). 80% (88) of all patients had acyanotic congenital heart disease.

Percutaneous PDA closure was performed in 33 patients, making up the largest group. Non-interventional diagnostic procedures were performed on 28 patients (Table 2). On the second day of the procedures, 96 children were either discharged or transferred to the surgical department (in case of diagnostic catheterisation)).

Out of 110 procedures performed, 86.4% were performed without complications, according to the classification of complications by *Tokel et al.* (5) , Minor complications were observed in 9.1% of the procedure. Major complications were seen in 3 patients, and two patients died (Table 3).

In 3 patients, there was difficulty in deploying the device. Minor arrhythmias were encountered in 3 patients, while significant arrhythmia developed in 1. There was a procedure failure in 1 patient and a change of anaesthesia plan in 2 patients. Device embolisation occurred in 1 patient, while in 2 patients, there was a vascular compromise. The death occurred in 2 patients.

General anaesthesia was administered to 68 patients, of whom 67.8% were younger than five years. About 54% of those over five years old had anaesthesia without intubation (Figure 2).

DISCUSSION

The study reviews 110 procedures performed by a pediatric cardiologist. The therapeutic procedures were 78 %, while the remaining were diagnostic. It is similar to the results published by *Vincent et al.* in 2015 from the data collected in the IMPACT registry (6).

The analysis showed that 13.6 % of the procedures had associated complications. Major complications were seen in 2.7 % of the procedures. The overall complications reported by *Lee et al.* from Seoul were 16.2%, and severe complications were reported at 1.15% (7). Although the overall complications are comparable between the two studies, the major complications are higher in our study.

(A) Minor arrhythmia - Minor arrhythmias were observed in 3 procedures. *Tokel et al.* reported minor arrhythmia in 2.3 % of the population who underwent pediatric catheterization (5). Similar results were published in 1998 in Canada, where the reported incidence of minor arrhythmia was 2.1% (8).

(B) Arrhythmia requiring abandoning the procedures - A 22-month-old male child weighing 7.5 kg with restricted peri-membranous VSD was planned for device closure, and a complete heart block was developed while the device was deployed. The occluder device was returned to the sheath; the rhythm immediately returned to normal. Data published by *Tokel et al.* showed a 3% incidence of significant arrhythmia (5), while it was 0.9 % in our review. In their study, *Taner et al.* reported a lower incidence of significant arrhythmia of 1.2 % (9).

(C) Vascular Compromise –Two cases had post-procedure femoral venous occlusion. A study published in 2014

reported a 2.7% incidence of a vascular compromise requiring heparin infusion for 12-72 hours (10). Another review from a large volume centre in Canada showed 165 arterial vascular and nine venous complications in 4952 catheterisations (8).

(D) Change of Anesthesia Plan - An intra-procedural change of anaesthesia from non-intubated anaesthesia to intubation and general anaesthesia (GA) was done in two patients. It is like the incidence reported in an extensive sample review of 13611 patients, where 1.77% of participants had to be converted to general anaesthesia (11).

(E) Device Embolization – One atrial septal defect occluder device embolisation incidence was in the study. In Ackermann's review of 238 ASD device closures, the incidence of embolisation in intra-procedure was 0.8%, and post-procedure was only 0.4% (12). *Rossi et al.* reported zero incidences of device embolisation associated with ASD device closure (13). Immediate embolisation of the ASD occluder device is related to the defect's anatomy and the primary operator's skill and experience (14).

(F) Death - Two patients died following the procedures. The first case was a 3-day-old child weighing 3.2 kg who was presented to ICU in shock and sepsis. The child had transposition of great arteries and underwent an emergency balloon atrial septostomy. Following the procedure, the shock state persisted, and the child succumbed. The second case was multiorgan dysfunction with significant pericardial effusion and tamponade effects. The child underwent emergency pericardiocentesis with a transfusion of fresh frozen plasma. However, the child did not improve and died of multiorgan failure. *Vitiello et al.* reported a 1.2% incidence of mortality in their review in 1998 (8). With progressive improvement, the mortality has reduced to a range of 0.05% to 1%, as reported by *Manda et al.* in 2021 (16).

(G) Procedure failure – Emergency balloon pulmonary valvotomy was attempted in a six-month-old 4 kg female child. But despite several attempts, the pulmonary valve could not be crossed; the procedure was abandoned. *Ghaffari et al.* reported a procedure failure rate of 19% for balloon pulmonary valvotomy (17). Another study reported a failure rate of 15% for balloon pulmonary valvotomy in infants (18).

CONCLUSION

The analysis shows that the complications associated with pediatric cardiac procedures performed on rural-based cath-lab oriented toward adult cardiology work are comparable to those of other large-volume pediatric cardiac centres. The incidence of device embolisation is significantly higher than expected from large-volume centres. The limited sample size is a limiting factor.

REFERENCES

1. Dolk H, Loane M, Garne E, a European Surveillance of Congenital Anomalies (EUROCAT) Working Group. Congenital Heart Defects in Europe: Prevalence and perinatal mortality, 2000 to 2005. Circulation 2011;123(8):841–9.
2. Zimmerman MS, Smith AGC, Sable CA, et al. Global, regional, and national burden of congenital heart disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Child Adolesc Health 2020;4(3):185–200.
3. Saxena A, Relan J, Agarwal R, et al. Indian guidelines for indications and timing of intervention for common congenital heart diseases: Revised and updated consensus statement of the Working group on management of congenital heart diseases. Ann Pediatr Cardiol. 2019;12(3):254.
4. Ramakrishnan S. Pediatric cardiology: Is India self-reliant? Ann Pediatr Cardiol. 2021;14(3):253.
5. Tokel K, Gümüş A, Ayabakan C, Varan B, Erdoğan İ. Complications of cardiac catheterization in children with congenital heart disease. Turk J Pediatr. 2018;60(6):675–83.
6. Vincent RN, Moore J, Beekman RH III, et al. Procedural characteristics and adverse events in diagnostic and interventional catheterisations in paediatric and adult CHD: initial report from the IMPACT Registry. Cardiol Young. 2016;26(1):70–8.
7. Lee KE, Seo YJ, Kim GB, et al. Complications of cardiac catheterization in structural heart disease. Korean Circ J. 2016;46(2):246.
8. Vitiello R, McCrindle BW, Nykanen D, Freedom RM, Benson LN. Complications associated with pediatric cardiac catheterization. J Am Coll Cardiol. 1998;32(5):1433–40.
9. Kasar T. Doğumsal kalp hastalığı olan pediatrik hastalarda kalp kateterizasyonu sırasında gelişen ritim bozuklukları. Turk Kardiyol Dern Ars. 2018;46(8).
10. Kumar P, Joshi VS, Madhu PV. Diagnostic pediatric cardiac catheterization: Experience of a tertiary care pediatric cardiac centre. Med J Armed Forces India. 2014;70(1):10–6.
11. Lin CH, Desai S, Nicolas R, et al. Sedation and anesthesia in pediatric and congenital cardiac catheterization: A prospective multicenter experience. Pediatr Cardiol. 2015;36(7):1363–75.
12. Ackermann S, Quandt D, Hagenbuch N, et al. Transcatheter atrial septal defect closure in children with and without fluoroscopy: A comparison. J Interv Cardiol. 2019:1–9.
13. Rossi RI, Cardoso C de O, Machado PR, Francois LG, Horowitz ESK, Sarmento-Leite R. Transcatheter closure of atrial septal defect with Amplatzer® device in children aged less than 10 years old: Immediate and late follow-up. Catheter Cardiovasc Interv. 2008;71(2):231–6.
14. Gokaslan G, Ustunsoy H, Deniz H, et al. Urgent surgical management for embolized occluder devices in childhood: single center experience. J Cardiothorac Surg. 2012;7(1).
15. Agarwal SK, Ghosh PK, Mittal PK. Failure of devices used for closure of atrial septal defects: Mechanisms and management. J Thorac Cardiovasc Surg. 1996;112(1):21–6.
16. Manda YR, Baradhi KM. Cardiac Catheterization Risks and Complications. In: StatPearls. Treasure Island (FL): StatPearls Publishing; June 5, 2023.
17. Ghaffari MR, Ghaffari, Sagafy. Pulmonary valve balloon valvuloplasty compared across three age groups of children. Int J Gen Med. 2012;5:479.
18. Saad MH, Roushdy AM, Elsayed MH. Immediate- and medium-term effects of balloon pulmonary valvuloplasty in infants with critical pulmonary stenoses during the first year of life: A prospective single center study. J Saudi Heart Assoc. 2010;22(4):195–201.

SAŽETAK

Sigurnost kateterizacije srca u pedijatrijskoj populaciji izvođenih u ruralnoj indiji u kateterizacijskom laboratoriju za odrasle

Alisha Akhani, Jaishree Ganjiwale, Bhadra Trivedi, Somashekhar Nimbalkar

Uvod: *Prirođene srčane greške čine najveću skupinu prirođenih mana s kojima se djeca rađaju, s prevalencijom od 1% u novorođenačkoj dobi. U Indiji se svake godine rađa oko 2,4 milijuna djece s prirođenim srčanim greškama, tj. najviše u svijetu. U Indiji postoji veliki broj centara koji zbrinjavaju takve pacijente no oni su neravnomjerno raspoređeni. Zbog toga se veliki broj pedijatrijskih bolesnika liječi u kardiološkim ustanovama za odrasle koje nisu uvijek opremljene odgovarajućom aparaturom za rješavanje komplikacija pedijatrijske populacije. Cilj studije je procijeniti sigurnost i komplikacije povezane s pedijatrijskim kardiološkim postupcima koji su provedeni u kateterizacijskom laboratoriju koji se primarno koristi za kardiološko zbrinjavajnje odrasle populacije.*

Metode: *Učinjena je retrospektivna analiza pedijatrijskih kardioloških kateterizacijskih postupaka koji su izvedeni između travnja 2018. i ožujka 2021.*

Rezultati: *Ukupno 110 pedijatrijskih pacijenata bilo je podvrgnuto 110 kateterizacijskih zahvata. U hitnom zbrinjavanju učinjeno je ukupno 20 zahvata, a elektivno ukupno 90 zahvata. Od 110 izvedenih zahvata, 86.4% je završeno bez komplikacija. Manje komplikacije uočene su u 9,1% zahvata. Veće komplikacije zabilježene su kod 3 bolesnika, a dvoje bolesnika je preminulo.*

Zaključak: *Zaključno, komplikacije povezane s pedijatrijskim kardiološkim zahvatima koji se izvode u ruralnom kateterizacijskom laboratoriju orijentiranom na zbrinjavanje odraslih bolesnika usporedive su s onima u drugim pedijatrijskim kardiološkim centrima velikog volumena.*

Ključne riječi: PRIROĐENE SRČANE GREŠKE; KATETERIZACIJA SRCA; PEDIJATRIJA; SIGURNOST PACIJENATA

Paediatr Croat. 2024;68:128-36
IZVORNI ZNANSTVENI ČLANAK / *ORIGINAL SCIENTIFIC PAPER*
www.paedcro.com
http://dx.doi.org/10.13112/PC.2024.22

Rehabilitation services for children with disabilities during the COVID-19 pandemic in the United Arab Emirates: Experiences of parents

Sunitha Bhagavathi Mysore[1], Dragana Djuric[1], Adam Zeghan[2], Areen Oudeh[3], Belal Al Qerem[4], Abdulla Al Humaidan[4], Amina Hussain Salem Alyafei[4], Muhammed Al Jarrah[1]

Introduction: *The Covid -19 pandemic brought changes in professional practice across the globe. Children with disabilities received rehabilitation services remotely throughout the lockdown periods to contain the virus in the United Arab Emirates. This paper explores the experiences of parents of children with disabilities who received remote rehabilitation services during the Covid-19 pandemic.*

Methods: *A survey was developed by the study team in English and Arabic. Demographic data, characteristics of children, family circumstances, access to rehabilitation, use of assistive tools, financial and psychological implications on parents and children, and future use of remote therapy. It was deployed to the parents through the rehabilitation centers and was analyzed using descriptive statistics with frequencies and percentages.*

Results: *The survey was completed by 239 parents whose children with disabilities received the rehabilitation services remotely mainly through telerehabilitation. The pressure and psychological impact on parents were high, reporting frustration (44.8%), and anxiety (59.8%), although (70.3%) recognized the importance of continued care for the child.*

Conclusion: *Telerehabilitation was the means during the pandemic to ensure continued care in the UAE. In the future, remote rehabilitation will be appropriate in specific situations when there is limited or no access to the center. Future research should explore the continued use of telerehabilitation and its effectiveness.*

Key words: COVID-19; TELEREHABILITATION; CHILDREN WITH DISABILITIES

INTRODUCTION

The COVID- 19 pandemic has seen changes in professional practice across the globe. Almost all sectors working with non-essential services were closed for the first few days to reduce the spread of infection including rehabilitation centers in the United Arab Emirates (UAE). But within a span of fortnight, it was encouraged health and rehabilitation centers to consider alternate ways of providing services for those requiring ongoing care. The importance of continued care for the disabled were crucial and one of the cost-effective ways to continue care in their own homes during the Covid-19 pandemic that included synchronized video calls through telerehabilitation, pre-recorded therapeutic videos and online programs (1-4).

[1] Fatima College of Health Sciences, Abu Dhabi, UAE
[2] Cerebral Palsy Foundation, Amman, Jordan
[3] Star Key Health, Abu Dhabi, UAE
[4] Zayed Higher Organization for People of Determination, Abu Dhabi, UAE

Correspondence to:
Dr. Sunitha Bhagavathi Mysore, Principal Lecturer in Physiotherapy; Fatima College of Health Sciences, Al Mafraq, PO box no. 3798; Abu Dhabi, United Arab Emirates; e-mail:Sunitha.Mysore@actvet.gov.ae

Due to the restriction of movements imposed to contain the virus, residents were confined to their homes for over a year in the United Arab Emirates (UAE). This included even children with disabilities, who normally would receive a range of integrated services including special education and therapeutic interventions by multidisciplinary teams. Remote rehabilitation services, mainly through telerehabilitation, were offered in the UAE to the children with disabilities (1).

Prior to the pandemic, the use of telerehabilitation was highly limited for children with disabilities (5) although it was an accepted and feasible means of providing therapy (6, 7). It was reported to be comparable to usual care (8). There have been articles on the quick utilization of telerehabilitation during the COVID-19 pandemic (9-11) that changed practice experiences for all stakeholders within the rehabilitation settings. *Camden and Silva* (2021) suggest considering family-centeredness of the services offered remotely as the implementation of telerehabilitation was a quick response to COVID-19 situation. However, there were no published studies in the UAE on the provision of rehabilitation services and parents' experience during the lockdown of the COVID-19 pandemic when this study was undertaken.

The main aim of this study was to investigate the rehabilitation services provision by exploring the experiences of parents of children with disabilities during the COVID-19 pandemic. This paper explored the access to rehabilitation services, engagement of parents and children during the therapy and challenges faced by parents during the COVID-19 pandemic in 2020 with the following specific research questions.

1. How did the parents or carers organized themselves to manage the child with disability at home while managing other commitments (other children, their work) in the UAE during COVID-19?
2. What services and support were offered to the parents or carers from the rehabilitation centers?
3. What were the challenges faced for utilizing the rehabilitation services during the COVID-19 pandemic?
4. What were the psychological implications of receiving therapy since the pandemic?

METHODS

The study was conducted in the pandemic during the lockdown period in the UAE between January to April 2021. The intended participants for this study were the parents of children with disabilities receiving services from rehabilitation centers. The survey link for the study was sent to major rehabilitation centers, requesting them to forward it to the parents of the children receiving rehabilitation services, as the researchers did not have direct access to the parents. A period of four weeks was allotted for completing the survey, and a follow-up request was sent to the centers in the second week to encourage parents to participate in the study.

The researchers for the study were from the centers providing rehabilitation services for children with disabilities in collaboration with a higher education institution based in the Emirates of Abu Dhabi. Ethical approval for the study was granted from the higher education institution (No: IN-TSTF013PHY20). The survey was developed by the research team based on the concepts of remote therapy and considering the lockdown situation in the UAE during COVID-19 in the year 2020.

The survey questions were in both English and Arabic and were validated using two-step processes. Firstly, the face and content validity were done by two experts in the field and the pilot was sent to eight parents from one rehabilitation center in Abu Dhabi. Minor modifications were made following the validation process that increased the clarity of questions.

In order to meet the aims of this research, the questionnaire was developed with five different sections with the likely responses. The responses were added with a wider variety of choices with multiple response questions or with dichotomous response of 'yes or no' rather than open-ended questions. The details of the five sections are outlined below:

1. The first domain was on family circumstances that explored the number of children, work, ability in managing between disabled and other children, responsible person for providing rehabilitation at home for the child, main obstacles, and access to rehabilitation.

2. The second domain explored in detail the rehabilitation services offered, the child's co-operation and engagement to therapy at home.

3. The third domain included questions regarding access and use of assistive devices such as what assistive tools were available for the child, accessibility to the equipment or devices for therapy and maintenance services offered or available during the pandemic.

4. The fourth domain explored the psychological implications that the child and the parents had during the lockdown. The questions were related to differences in relationships between siblings and disabled child, negative and positive impact on the child and parent.

5. The fifth and the final section was to seek the parents' suggestions on the remote rehabilitation if continues for longer during the pandemic or had to be adopted in the future post pandemic

The survey was analyzed using descriptive statistics. Frequency and percentages were used to present the data.

RESULTS

Demographic data and family circumstances

The survey was filled by a total of 239 parents of children with disabilities. The responses to this survey were received from the six emirates of the UAE. The most responses were from the Emirate of Abu Dhabi (84.4%), Dubai (9.8%), Sharjah (2.7%), Ajman (1.8%), Fujairah (0.9%) and Ras Al Khaima (0.4%).

Male respondents were slightly higher (56.1%) than females (43.9%) as the surveys were filled either the mother or father of the child. Mother being the main carer of the child at home (78.7%), followed by father (9.2%) and other family members or nanny (12.1%).

The average number of children within these families was reported to be four, and about 75.3% respondents have one disabled child in their family. Approximately 66% of the respondents reported having difficulty managing the children with disabilities at home during the COVID -19 pandemic. This was mainly due to other commitments at home with other children (28.9%) and lack of support from other family members (23%) and work commitments (28.9%).

The type of disabilities that the children had were diverse including cognitive, physical, behavioral, sensory impairments and multiple disabilities, with largest number of children on the autism spectrum as shown in Fig. 1

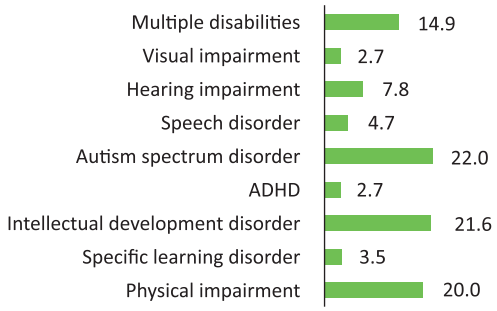


FIGURE 1. Type of disabilities.

The parents reported that the child spent most of the time at home on the phone or tablet (65.1%), playing with siblings (43.5%), some helped parents in household chores (18.8%), doing craft work (16.5%) and some children not being active (25.95).

Rehabilitation Services during COVID-19 pandemic

The services received during the lockdown were Physiotherapy (44.8%), Occupational Therapy (49.4%), Speech therapy (45.4%), Special Education (34.6%), Social Counselling (14.2%), Psychological (10.2%), Hearing Solutions (4%).

The types of rehabilitation services received during the pandemic were either home visits (30%) or tele rehabilitation (70%). The frequency of therapy was similar to pre-pandemic (47%), less than the pre-pandemic (49%) and more than pre-pandemic (4%).

In accessing telerehabilitation, the participants reported several enables and barriers. One of the largest enablers was that therapists were setting appointments well in advance for the parents to organize themselves (22.6%). Other enablers are provided in Table 2. There were a number of barriers being reported as the parents were busy managing home and other children (51.9%) and also was the financial issues (35.1). The other barriers are listed in Table 2.

6.15% of parents expressed that it was challenging to provide therapy at home and one of them was child being child's non-cooperation (13.8%) and poor co-operation (19.8%). Despite these challenges, 68.2% reported to cope well with children during the therapies at home.

The parents felt that the child did not pay enough attention during telerehabilitation (56%), or that it was rejected by the child (36%), lacked fun and engaging activities (25%), and caused tiredness due to multiple sessions (5%). 30.6% of parents reported weight gain of the child during the lockdown.

The parents reported changes in certain aspects of child's function and reported improved communication (20%), improved daily activities, especially dressing and eating (20.8%), better social interaction (13.3%), grasping and holding (11.4%) and walking (10.6%).

Access and use of assistive devices

52% of the parents reported having access to assistive devices to carry on with the therapy at home. Assistive devices used at home were communication aids (37.6%), daily living aids (33.3%), mobility aids (27.1%), & visual aids (11.4%). The access to maintenance services of assistive devices during the lockdown was reported by 24.7%.

Psychological changes and impact during the lockdown

Most parents (82%) reported changes in behavior in the child during the lockdown. Most of the parents felt that their child would have been happier receiving therapy at the center (57.6%) when compared to telerehabilitation

TABLE 1. Demographic details and family circumstances (N=239).

Characteristics	Attribute	Frequency, %
Gender of respondents	Male	56.1
	Females	43.9
Main carer of the child with disability at home	Mother	78.7
	Others	22.3
Gender of children with disabilities	Male	61.6
	Females	38.4
Ages of children, (years)	0-4	11.8
	5-9	27.8
	10-14	28.2
	15-18	14.5
	18+	17.5
Number of children with disabilities in the family	One child	75.7
	Two	8.4
	More than two	15.9
Employment status of parents	Not working since covid	10.5
	Full time employment	62.0
	Part time employment	18.3
	Never worked	9.2
*Leisure activities	Use of electronic devices	65.1
	Playing with siblings	43.5
	Helping parents	18.8
	Craft work	16.5
	No activity	25.9
Negative behavior of the disabled child during the lockdown	Aggression	25.9%
	Lack of motivation to work or study	36.4%
	Complaining of tiredness	15.1%
Reported improved relationship between disabled child with the other siblings. The siblings were	More empathetic	38.1
	Supportive	34.3
	Caring	36
	Increased sharing while playing	33.5
	Acceptance	23.4
Comparison of child status between pre-pandemic and during pandemic	No difference	42.7
	Deterioration	27.8
	Improvement	25.1

*more than 100% due to multiple options

TABLE 2. Enablers and barriers to telerehabilitation (N=239).

* Enablers	Frequency, %
Clear and timely appointments	22.6
Safe environment at home	14.6
Flexible hours	14.6
Training parents on the technical aspects of telerehabilitation	13
Provided lecture materials and resources on therapies	9.2
Provided electronic such as laptop or tablet to run telerehabilitation at home	2.9
* Barriers	
Busy with other children and tasks at home	51.9
Financial issues	35.1
Fear of applying therapy at home	23.8
Lack of informational services	23.8
Lack of tools and equipment	21.8
Internet or device problems	19.2
Other technical issues	11.3

*more than 100% due to multiple options

(11.8%), children showed aggression (25.9%), were in low mood (26.4%), lacked motivation to work or study (36.4%), consumed more time than usual (16.3%), lack of social interaction (41.8%), complained of tiredness (15.1%), lack of sleep (20.9%) and feeling anxious (25.1%).

The parents also reported improved relationships between siblings during the lockdown period (70%). Siblings became more empathetic towards the disabled sibling, (38.1%), showed much more supportive (34.3%) and caring attitude towards the sibling (36%) and improved sharing of their gadgets and toys with the sibling (33.5%) and accepting into the playgroup (23.4%) than pre-pandemic times - shown in Table 1.

Most parents (79%) reported that they themselves noticed changes in their own physical, psychological, and social well-being such as feeling worrying about their child's future (59.8%), feeling helplessness (44.8%), tiredness and exhaustion (29.7%), lack of personal time (28.5%), lack of sleep (18.8%) and reduced work efficiency (18%).

Parents perspectives suggestions on continuing remote rehabilitation during and post pandemic

Parents reported that they recognized the high (70.3%) to moderate importance (16.7%) of continued rehabilitation services for their child. Most parents preferred sessions in the center with social distancing (63%) , the blended approach between online and tele-rehabilitation (28%) and home rehabilitation or no therapy at all (9%). Due to closure of the centers and till the access services in the center,

79.1% of parents reported that tele rehabilitation was the best available option.

The parents were asked to indicate if and in what situations telerehabilitation should be applicable in the future. The responses were if the child was unable to go to the center due to illness (39.3%), not physically being in the country (26.4%) or during a vacation (24.7%) to ensure the continuity of care. In case of online sessions being continued, the parents expressed the need for ongoing training on giving therapies, using assistive devices, technological support, time management and psychological support.

DISCUSSION

The main objective of this study was to explore the experiences of parents of children with disabilities who received remote rehabilitation services, particularly during the lockdown period in the UAE. The survey response rate was higher from Abu Dhabi when compared to the other 6 Emirates. The survey was sent through the centers to the parents as the researchers of this study did not have access to the parents, hence there was no opportunity to check how many parents were contacted by the center within each Emirate.

This study involved mainly families with an average of four children, one of whom were disabled. The mother was the main carer for the children as seen in our study. More than 50% of the parents worked during the COVID-19 pandemic while caring for other children who were at home with online classes, this placed an increased pressure on the parents. During post-COVID times we assume that when the other children are at school, it might be possible for parents to focus much more on their child with disabilities if a telerehabilitation session is offered.

Most children in our study had multiple disabilities, which increased complexities and challenges for parents in managing the children (12) especially with reduced access during the pandemic (13). As most children received therapy from more than one specialty - most receiving Speech and Language therapy, Occupational therapy, and Physiotherapy alongside Special education. These two disciplines are highly hands-on requiring physical strength and variety of equipment, thus carrying out therapy at home proved challenging for carers (14). Even in the centre, most children receive therapy from multi-disciplinary teams, and it is highly challenging to plan this on telerehabilitation sessions. Telerehabilitation for those with multiple disabilities will always be challenging for parents and adherence to it is also highly difficult (15). Hence, it is more beneficial to children who do not have complex issues.

Besides, there was not enough equipment or readiness of parents to provide therapy at home despite getting guidance from the therapists. Nearly one fourth of the participants reported having technical challenges such as difficulty using specific educational programs, internet issues like the study by *Pinkerton et al.* (2022) (16). However, these issues were much higher during the pre-pandemic (17). With the pandemic lasting for over two years, the parents might have learnt to overcome technical challenges, and it will be interesting in future studies to explore the current competencies of parents for accessing and using technologies related to telerehabilitation.

Djuric et al., (2022) reported that various public platforms and social media were utilized in spreading awareness for parents regarding the importance of continued care for children during COVID-19 in the UAE (1). Additionally, most participants in our study reported to have received information and plans prior to online assessment and treatment. The rehabilitation centers engaging effectively in spreading the awareness about the importance of continued care and having provided all the necessary training including safe home environment, technical support telerehabilitation can be embedded into their regular training now in post-COVID times (8, 18).

Our study highlighted the importance of accessibility and maintenance of assistive devices for the child to continue therapy and function effectively at home. Of those requiring assistive devices, only half of the participants reported having access to the equipment or tools. Only a few basic assistive devices were used by the children such as ADL tools, communication aids, mobility, and visual aids with limited access to maintenance services. For some of the equipment such as wheelchairs, although there could have been an opportunity for teleassessment, it is best to get the physical check done at the service center for technical accuracy (19). Accessing assistive devices could be a challenge and this is particularly seen in low and middle-income countries (20). However, in the UAE due to high funding and good infrastructure, access, or affordability to most assistive devices were not a major issue. Although these assistive devices may not be suitable for home use, this opens opportunities for developing suitable home-use assistive devices (21).

The negative effects during the lockdown were not only seen in children but on the parents as well. Some of the previous studies have shown that children's activities and behaviors are directly related to the parents' psychological and social well-being; (22, 23). The anxiety levels among parents or caregivers of children with intellectual and developmental disabilities were very high even during the pre-pandemic with elevated depression symptoms (24). Although our study did not correlate children's activity and behavior to parents' psychological wellbeing, they reported tiredness and were anxious about their child's future. Fur-

ther, telerehabilitation was not a recognized form of treatment by the medical insurance during the first few months of the lockdown in the UAE, might have added to the financial stress (1). Also, many parents were either not working or doing part-time work during the lockdown, further adding to the financial stress. Setting up support groups for parents would have relieved their stress and anxiety (25, 26).

Social interaction for children is vital as it has psychological and therapeutic benefits. These benefits were noticed in the study done by *Cacioppo et al.* (2021) (27). Further, 80% of the parents reported the therapies provided by tele rehab were different from the normal services within the centers and we believe that the deteriorations observed could be the therapies being less effective, and child's lesser engagement during therapies. This could be due to the majority of children in our study being school age; this would differ if the children were of pre-school age, as telerehabilitation (28) was a good addition to home program in a study done by *Sel et al.* (2023) (29).

In the survey, the parents reported that the child was bored being at home during the pandemic - this was in contrast to pre-pandemic as they had lot of outdoor and institution-based activities such as robotics, cycling, hydrotherapy, thus not needing online treatment. This makes a good case for children to physically attend the sessions in the center based on post-COVID times. On the other hand, there are multiple benefits for using telerehabilitation especially when there is restricted or limited access to centers due to illness of the child or parents' (30). Now in post-pandemic times, telerehabilitation can be used as an adjunct but it is not meant to replace face-to-face session (31).

Our study showed that the number of therapy sessions provided was lower when compared to the ones received in the center - not only due to the lack of equipment, but also because certain services can only be provided by trained therapists with special skills. Therefore, if tele-rehabilitation services were to be offered effectively, it is best for therapists to be trained and certified (32). This then means therapists can decide how and what type of interventions are suitable through telerehabilitation (33). Observation regarding the progression during telerehabilitation was mixed from significant improvement to significant deterioration. However, our study could not correlate this to the type of therapy sessions and/or to the complexity of condition, which is one of the limitations of our study. The studies in the future must consider and conduct correlation studies.

Our study showed that the most improvements were seen in communication skills but in the areas that required special therapeutic handling, such as fine and gross motor skills, improvements were to a lesser extent.

In situations where accessing therapy in the center is difficult, effective transfer of therapies from the gym to home becomes necessary. This requires good co-operation between parents and therapists with a well-structured, goal-oriented, individually tailored program based on environment and physical space (14, 34-38).

Most research on telerehabilitation (including our study) during the pandemic employed surveys to capture the experiences but future research should focus on controlled clinical trials. *Hurtubise et al.* (2022) (39) has proposed four-year longitudinal multicentric action research involving training and implementation of family centered telerehabilitation by pediatric therapists. For the blended approach to be effective and successful, the parents or caregivers must be a core member receiving appropriate training. The experiences reported during the pandemic could be reflected on the current and future use of telerehabilitation for children with disabilities (28).

There are no reports of any major safety concerns or any harmful effects on a child's health (8). One fourth of the participants reported not having instructions on safe handling during the telerehabilitation sessions. Furthermore, our study did not consider different types of safety issues such as falls. Future studies can consider this aspect. Clear planning, communication and collaboration between parents and therapists is a key to success for telerehabilitation (39, 40).

CONCLUSION

There has been a paradigm shift in the use of remote rehabilitation, specifically tele-rehabilitation between the pre and post pandemic. Research on its' use for children with disabilities has been increasing since the pandemic when compared to pre-COVID times. Telerehabilitation gained its central position during COVID-19 and there have been efforts to use it effectively by overcoming administrative and technical barriers. Since the pandemic, there have been ongoing efforts in increasing the quality of online services. As remote rehabilitation was a popular means of providing continued care during the pandemic, the time, resources, and funding were allocated towards development and application of it. Telerehabilitation can be in the future used as a blended approach for education and supervised home program purposes and also, when physical access to the center is difficult. Future research should compare the continued use of telerehabilitation and its effectiveness. Also, one of the limitations of our study was that most response was from Abu Dhabi which could potentially have geographical bias and could impact on the generalizability of the results. So, future studies should consider exploring other emirates.

Acknowledgments

The authors would like to extend their gratitude to the Abu Dhabi Statistics Center for assisting in data collection and to Dr. Cathrine Tadyanemhandu & Ms. Ana Anjos & Ms. Dhruti Mysore for their contributions to proof reading and feedback of this manuscript.

REFERENCES

1. Djuric D, Mysore S, Zeghan A, Oudeh A, Al Qerem B, Al Humaidan A, Al Jarrah M. Pediatric rehabilitation services during COVID-19 pandemic in the United Arab Emirates, Serbian Archives of Medicine 2022; 150(11-12): 636-642: https://doi.org/10.2298/SARH220722105D.
2. Prvu Bettger J, & Resnik L J. Telerehabilitation in the Age of COVID-19: An Opportunity for Learning Health System Research. Physical therapy. 2020; 100(11);1913–1916. https://doi.org/10.1093/ptj/pzaa151
3. Provenzi L, Grumi S, Borgatti R. Alone With the Kids: Tele-Medicine for Children With Special Healthcare Needs During COVID-19 Emergency. Front Psychol. 2020 Sep 9;11:2193. doi: 10.3389/fpsyg.2020.02193. PMID: 33013567; PMCID: PMC7509132.
4. Provenzi L, Grumi S, Gardani A, Aramini V, Dargenio E, Naboni C, Vacchini V, Borgatti R; Engaging with Families through On-line Rehabilitation for Children during the Emergency (EnFORCE) Group. Italian parents welcomed a telehealth family-centred rehabilitation programme for children with disability during COVID-19 lockdown. Acta Paediatr. 2021 Jan;110(1):194-196. doi: 10.1111/apa.15636. Epub 2020 Nov 6. PMID: 33098116.Olson CA, McSwain SD, Curfman AL, Chuo J. The Current Pediatric Telehealth Landscape. Pediatrics. 2018;141(3):e20172334. doi: 10.1542/peds.2017-2334. PMID: 29487164.
5. Little LM, Pope E, Wallisch A, Dunn W. Occupation-Based Coaching by Means of Telehealth for Families of Young Children With Autism Spectrum Disorder. Am J Occup Ther. 2018;72(2):7202205020p1-7202205020p7. doi: 10.5014/ajot.2018.024786. PMID: 29426380.
6. Tomines A. Pediatric Telehealth: Approaches by Specialty and Implications for General Pediatric Care. Adv Pediatr. 2019;66:55-85. doi: 10.1016/j.yapd.2019.04.005. Epub 2019 May 27. PMID: 31230700.
7. Ogourtsova T, Boychuck Z, O'Donnell M, Ahmed S, Osman G, Majnemer A. Telerehabilitation for Children and Youth with Developmental Disabilities and Their Families: A Systematic Review. Phys Occup Ther Pediatr. 2023;43(2):129-175. doi: 10.1080/01942638.2022.2106468. Epub 2022 Aug 30. PMID: 36042567.
8. Camden C, Silva M. Pediatric Teleheath: Opportunities Created by the COVID-19 and Suggestions to Sustain Its Use to Support Families of Children with Disabilities. Phys Occup Ther Pediatr. 2021;41(1):1-17. doi: 10.1080/01942638.2020.1825032. Epub 2020 Oct 6. PMID: 33023352.
9. Tenforde AS, Borgstrom H, Polich G, Steere H, Davis IS, Cotton K, O'Donnell M, Silver JK. Outpatient Physical, Occupational, and Speech Therapy Synchronous Telemedicine: A Survey Study of Patient Satisfaction with Virtual Visits During the COVID-19 Pandemic. Am J Phys Med Rehabil. 2020 Nov;99(11):977-981. doi: 10.1097/PHM.0000000000001571. PMID: 32804713; PMCID: PMC7526401.
10. Badawy SM, Radovic A. Digital Approaches to Remote Pediatric Health Care Delivery During the COVID-19 Pandemic: Existing Evidence and a Call for Further Research. JMIR Pediatr Parent. 2020;3(1): e20049. doi: 10.2196/20049. PMID: 32540841; PMCID: PMC7318926.
11. Horn EM, Kang J. Supporting Young Children with Multiple Disabilities: What Do We Know and What Do We Still Need To Learn? Topics Early Child Spec Educ. 2012;31(4):241-248. doi: 10.1177/0271121411426487. PMID: 24574575; PMCID: PMC3932659.
12. Sutter EN, Francis LS, Francis SM, Lench DH, Nemanich ST, Krach LE, Sukal-Moulton T, Gillick BT. Disrupted Access to Therapies and Impact on Well-Being During the COVID-19 Pandemic for Children with Motor Impairment and Their Caregivers. Am J Phys Med Rehabil. 2021;100(9): 821-830. doi: 10.1097/PHM.0000000000001818. PMID: 34091465; PMCID: PMC8366513.
13. Bican R, Christensen C, Fallieras K, Sagester G, O'Rourke S, Byars M, Tanner K. Rapid Implementation of Telerehabilitation for Pediatric Patients During Covid-19. Int J Telerehabil. 2021;13(1): e6371. doi: 10.5195/ijt.2021.6371. Erratum in: Int J Telerehabil. 2021;13(1): e6386. PMID: 34345345; PMCID: PMC8287708.
14. Pagaki-Skaliora M, Morrow E, Theologis T. Telehealth and Remote Interventions for Children with Cerebral Palsy: Scoping Review. JMIR Rehabil Assist Technol. 2022;9(4):e36842. doi: 10.2196/36842. PMID: 36041012; PMCID: PMC9629344
15. Pinkerton LM, Murphy A, Bruckner E, Risser H. Therapy service delivery for children with disabilities during COVID-19: Parent perceptions and implementation recommendations. J Community Psychol. 202;51(6): 2430-2441. doi: 10.1002/jcop.22899. Epub 2022 Jun 13. PMID: 35695353; PMCID: PMC9350374.
16. Thiyagarajan A, Grant C, Griffiths F, Atherton H. Exploring patients' and clinicians' experiences of video consultations in primary care: a systematic scoping review. BJGP Open. 2020;4(1): bjgpopen20X101020. doi: 10.3399/bjgpopen20X101020. PMID: 32184212; PMCID: PMC7330183.
17. Tanner K, Bican R, Boster J, Christensen C, Coffman C, Fallieras K, Long R, Mansfield C, O'Rourke S, Pauline L, Sagester G, Marrie J. Feasibility and Acceptability of Clinical Pediatric Telerehabilitation Services. Int J Telerehabil. 2020;12(2):43-52. doi: 10.5195/ijt.2020.6336. PMID: 33520094; PMCID: PMC7757654.
18. Graham F, Boland P, Grainger R, Wallace S. Telehealth delivery of remote assessment of wheelchair and seating needs for adults and children: a scoping review. Disabil Rehabil. 2020;42(24):3538-3548. doi: 10.1080/09638288.2019.1595180. Epub 2019 Apr 23. PMID: 31014120.
19. Adugna MB, Nabbouh F, Shehata S, Ghahari S. Barriers and facilitators to healthcare access for children with disabilities in low and middle income sub-Saharan African countries: a scoping review. BMC Health Serv Res. 2020;20(1):15. doi: 10.1186/s12913-019-4822-6. PMID: 31906927; PMCID: PMC6945633.
20. Mensah-Gourmel J, Thépot M, Gorter JW, Bourgain M, Kandalaft C, Chatelin A, Letellier G, Brochard S, Pons C. Assistive Products and Technology to Facilitate Activities and Participation for Children with Disabilities. Int J Environ Res Public Health. 2023;20(3):2086. doi: 10.3390/ijerph20032086. PMID: 36767453; PMCID: PMC9915405.
21. Dhiman S, Sahu PK, Reed WR, Ganesh GS, Goyal RK, Jain S. Impact of COVID-19 outbreak on mental health and perceived strain among caregivers tending children with special needs. Res Dev Disabil. 2020; 107:103790. doi: 10.1016/j.ridd.2020.103790. Epub 2020 Oct 6. PMID: 33091712; PMCID: PMC7538124.
22. Ahmed MZ, Ahmed O, Aibao Z, Hanbin S, Siyu L, Ahmad A. Epidemic of COVID-19 in China and associated Psychological Problems. Asian J Psychiatr. 2020; 51:102092. doi: 10.1016/j.ajp.2020.102092. Epub 2020 Apr 14. PMID: 32315963; PMCID: PMC7194662
23. Scherer N, Verhey I, Kuper H. Depression and anxiety in parents of children with intellectual and developmental disabilities: A systematic review and meta-analysis. PLoS One. 2019;14(7): e0219888. doi: 10.1371/journal.pone.0219888. PMID: 31361768; PMCID: PMC6667144.
24. Gruebner O, van Haasteren A, Hug A, Elayan S, Sykora M, Albanese E, Naslund J, Wolf M, Fadda M, von Rhein M. Digital Platform Uses for Help and Support Seeking of Parents with Children Affected by Disabilities: Scoping Review. J Med Internet Res. 2022 Dec;24(12): e37972. doi: 10.2196/37972. PMID: 36472896; PMCID: PMC9768636.
25. Park GA, Lee ON. The Moderating Effect of Social Support on Parental Stress and Depression in Mothers of Children with Disabilities. Occup Ther Int. 2022; 2022:5162954. doi: 10.1155/2022/5162954. PMID: 35359427; PMCID: PMC8938151.

26. Cacioppo M, Bouvier S, Bailly R, Houx L, Lempereur M, Mensah-Gourmel J, Kandalaft C, Varengue R, Chatelin A, Vagnoni J, Vuillerot C, Gautheron V, Dinomais M, Dheilly E, Brochard S, Pons C; ECHO Group. Emerging health challenges for children with physical disabilities and their parents during the COVID-19 pandemic: The ECHO French survey. Ann Phys Rehabil Med. 2021;64(3):101429. doi: 10.1016/j.rehab.2020.08.001. Epub 2020 Aug 18. PMID: 32818674; PMCID: PMC7434423.
27. Krasovsky T, Silberg T, Barak S, Eisenstein E, Erez N, Feldman I, Guttman D, Liber P, Patael SZ, Sarna H, Sadeh Y, Steinberg P, Landa J. Transition to Multidisciplinary Pediatric Telerehabilitation during the COVID-19 Pandemic: Strategy Development and Implementation. Int J Environ Res Public Health. 2021;18(4):1484. doi: 10.3390/ijerph18041484. PMID: 33557395; PMCID: PMC7914913.
28. Sel SA, Günel MK, Erdem S, Tunçdemir M. Effects of Telerehabilitation-Based Structured Home Program on Activity, Participation and Goal Achievement in Preschool Children with Cerebral Palsy: A Triple-Blinded Randomized Controlled Trial. Children (Basel). 2023;10(3):424. doi: 10.3390/children10030424. PMID: 36979982; PMCID: PMC10047243.
29. Hall JB, Woods ML, Luechtefeld JT. Pediatric Physical Therapy Telehealth and COVID-19: Factors, Facilitators, and Barriers Influencing Effectiveness-a Survey Study. Pediatr Phys Ther. 2021;33(3):112-118. doi: 10.1097/PEP.0000000000000800. PMID: 34086621; PMCID: PMC8212883.
30. American Physical Therapy Association. (2019). Position on telehealth. American Physical Therapy Association. https://www.apta.org/apta-and-you/leadership-and-governance/policies/telehealth
31. Brennan D, Tindall L, Theodoros D, Brown J, Campbell M, Christiana D, Smith D, Cason J, Lee A. A blueprint for telerehabilitation guidelines. Int J Telerehabil. 2010;2(2):31-4. doi: 10.5195/ijt.2010.6063. PMID: 25945175; PMCID: PMC4296793.
32. Brennan D, Tindall L, Theodoros D, Brown J, Campbell M, Christiana D, Smith D, Cason J, Lee A. A blueprint for telerehabilitation guidelines. Int J Telerehabil. 2010;2(2):31-4. doi: 10.5195/ijt.2010.6063. PMID: 25945175; PMCID: PMC4296793.
33. Camden C, Pratte G, Fallon F, Couture M, Berbari J, Tousignant M. Diversity of practices in telerehabilitation for children with disabilities and effective intervention characteristics: results from a systematic review. Disabil Rehabil. 2020;42(24):3424-3436. doi: 10.1080/09638288.2019.1595750. Epub 2019 Apr 12. PMID: 30978110.
34. Rabatin AE, Lynch ME, Severson MC, Brandenburg JE, Driscoll SW. Pediatric telerehabilitation medicine: Making your virtual visits efficient, effective and fun. J Pediatr Rehabil Med. 2020;13(3):355-370. doi: 10.3233/PRM-200748. PMID: 33136081.
35. Kairy D, Tousignant M, Leclerc N, Côté AM, Levasseur M, Researchers TT. The patient's perspective of in-home telerehabilitation physiotherapy services following total knee arthroplasty. Int J Environ Res Public Health. 2013;10(9):3998-4011. doi: 10.3390/ijerph10093998. PMID: 23999548; PMCID: PMC3799503.
36. Boronat S. Neurologic Care of COVID-19 in Children. Front Neurol. 2021; 11:613832. doi: 10.3389/fneur.2020.613832. PMID: 33679571; PMCID: PMC7935545.
37. Hurtubise K, Gaboury I, Berbari J, Battista MC, Schuster T, Phoenix M, Rosenbaum P, Kraus De Camargo O, Lovo S, Pritchard-Wiart L, Zwicker JG, Beaudoin AJ, Morin M, Poder T, Gagnon MP, Roch G, Levac D, Tousignant M, Colquhoun H, Miller K, Churchill J, Robeson P, Ruegg A, Nault M, Camden C. Training Intervention and Program of Support for Fostering the Adoption of Family-Centered Telehealth in Pediatric Rehabilitation: Protocol for a Multimethod, Prospective, Hybrid Type 3 Implementation-Effectiveness Study. JMIR Res Protoc. 2022;11(10):e40218. doi: 10.2196/40218. PMID: 36306158; PMCID: PMC9652740.
38. Chivate S, Sharma M, Shaikh A, Satarkar C. Benefits and Challenges of Telerehabilitation Use By Pediatric Physiotherapists During the COVID-19 Pandemic In Western and Southern India: A Cross-Sectional Survey. Int J Telerehabil. 2022;14(1):e6466. doi: 10.5195/ijt.2022.6466. PMID: 35734383; PMCID: PMC9186904.
39. Frigerio P, Del Monte L, Sotgiu A, De Giacomo C, Vignoli A. Parents' satisfaction of tele-rehabilitation for children with neurodevelopmental disabilities during the COVID-19 pandemic. BMC Prim Care. 2022;23(1):146. doi: 10.1186/s12875-022-01747-2. PMID: 35668377; PMCID: PMC9170348.

SAŽETAK

Usluge rehabilitacije za djecu s teškoćama u razvoju tijekom COVID-19 pandemije u Ujedinjenim Arapskim Emiratima: iskustva roditelja

Sunitha Bhagavathi Mysore, Dragana Djuric, Adam Zeghan, Areen Oudeh, Belal Al Qerem, Abdulla Al Humaidan, Amina Hussain Salem Alyafei, Muhammed Al Jarrah

Uvod: *Covid-19 pandemija donijela je promjene u profesionalnoj praksi diljem svijeta. Djeca s teškoćama u razvoju u Ujedinjenim Arapskim Emiratima primala su usluge rehabilitacije na daljinu tijekom razdoblja karantene radi suzbijanja virusa. Ovaj rad istražuje iskustva roditelja djece s teškoćama u razvoju koja su primila usluge rehabilitacije na daljinu tijekom Covid-19 pandemije.*

Metode: *Istraživački tim je izradio anketu na engleskom i arapskom jeziku. Demografski podaci, karakteristike djece, obiteljske prilike, pristup rehabilitaciji, korištenje pomoćnih sredstava, financijske i psihološke implikacije na roditelje i djecu te buduća upotreba terapije na daljinu. Roditeljima je raspoređen kroz rehabilitacijske centre i analiziran je pomoću deskriptivne statistike s učestalostima i postocima.*

Rezultati: *Anketu je ispunilo 239 roditelja čija su djeca s teškoćama u razvoju primala usluge rehabilitacije na daljinu uglavnom putem telerehabilitacije. Pritisak i psihološki utjecaj na roditelje bili su visoki, iskazujući frustraciju (44,8%) i anksioznost (59,8%), iako (70,3%) prepoznaje važnost kontinuirane brige za dijete.*

Zaključak: *Telerehabilitacija je tijekom pandemije bila sredstvo za osiguranje kontinuirane skrbi u UAE. U budućnosti će rehabilitacija na daljinu biti primjerena u određenim situacijama kada je pristup centru ograničen ili nikakav. Buduća bi istraživanja trebala istražiti daljnju upotrebu telerehabilitacije i njezinu učinkovitost.*

Ključne riječi: COVID-19; TELEREHABILITACIJA; DJECA S TEŠKOĆAMA U RAZVOJU

Paediatr Croat. 2024;68:137-42
IZVORNI ZNANSTVENI ČLANAK / *ORIGINAL SCIENTIFIC PAPER*
www.paedcro.com
http://dx.doi.org/10.13112/PC.2024.23

Excessive pharmaceutical pricing and repercussions on paediatric health services

Dominik Vuletić*

Context: *Paediatric pharmaceutics have a significant share in expensive drugs. Recent years have seen significant calls for intervention against high prices for pharmaceutical products. The prohibition of prices that are excessive as a form of abuse of dominance is considered as Competition law violation in the European Union Law and national legal orders of its Member States. Majority of the Organization for Economic Cooperation and Development (OECD) member countries have similar prohibitions in their respective Competition laws with important exemption of United States (US) Antirust Law, although there is some indication of change in US exactly in the area of pharmaceutical sector. Regulation of excessive prices also exists in Competition laws of all BRICS (Brazil, Russian Federation, India, China, and South Africa) countries. The problem of excessive prices in pharmaceutics is one of the emerging themes in Competition law literature and case law development. This is the area where intellectual property rights, usually patent protection, collide with competition rules. Costs of research and development for such pharmaceutics are often very high emphasizing the need for balance between colliding legitimate interests: access to health and research development.*

Aim: *To present regulatory and case law development of application of excessive prices as form of abuse of dominance in pharmaceutical sector with emphasis on paediatric health services.*

Data source: *OECD, PubMed, Google Scholar, Scopus.*

Conclusion: *Balance between competition rules on excessive prices as form of abuse of dominance and intellectual property rights in the area of expensive paediatric pharmaceutics can be regarded as suboptimal. Thus, there is a need for further regulatory development and application of rules on excessive prices in that field.*

Keywords: LEGAL ASPECTS; COURT DECISIONS; PEDIATRICS; DRUG AND NARCOTIC CONTROL

INTRODUCTION

Recent years have seen significant calls for intervention against high prices for pharmaceutical products, and there have been a number of competition enforcement cases regarding exploitative excessive pricing in this sector (1). Excessive pharmaceutical pricing represents one of the most contentious issues in legal and political discourse and has recently gained renewed attention by courts, competition authorities and political forces on both sides of the Atlantic (2). The British Medical Journal dedicated a special issue in 2020 to achieving fair pricing (3). One study from 2020 demonstrated that global expenditure on pharmaceuticals increased 56% between 2007 and 2017 (4). Paediatric pharmaceutics have a significant share in expensive drugs including the most expensive drugs in world, as we will demonstrate further in this paper.

In the European Union Competition Law excessive pricing by dominant undertaking/undertakings or association of undertakings is considered to be a violation Article 102 of

* University of Zagreb, Faculty of Economics and Business

Correspondence to:
Ass. prof. Dominik Vuletić; Faculty of Economics;
Trg J. F. Kennedyja 6, 10000 Zagreb; Croatia;
E-mail: dvuletic@efzg.hr

The Treaty on the Functioning of the European Union (TFEU). Thus, abusive conduct of dominant undertaking that consist in directly or indirectly imposing unfair purchase or selling prices or other unfair trading conditions, as stipulated in TFEU (5), can emerge in a form of excessive prices. Similar provision is contained in Article 54 of the European Economic Area (EEA) Agreement (6). Member States of EU have harmonized their competition laws with EU Competition Law so regulation of excessive prices is the correspondent.

The European Court of Justice has in 1975 in *General Motors Continental NV v. Comm'n* (7) case introduced that this prohibition of unfair prices and trading conditions can relate to excessive prices. It held that dominant undertaking service price is unfair if it is excessive in relation to the economic value of the service provided. In far better known case that was adjudicated several years later - *United Brands* case (8) - the Court established approach for determination of excessive prices. In that case Commission held that *United Brands* (UBC), big producer and exporter of bananas, charged the price of bananas to its customers in Germany, Denmark, the Netherlands that are considerably higher, sometimes by as much as 100%, than the prices charged to customers in Ireland and therefore produce for it a substantial and excessive profit in relation to the economic value of the product supplied (6). Court held that excess in prices could be determined objectively if it were possible for it to be calculated by making a comparison between the selling price of the product in question and its cost of production, which would disclose the amount of the profit margin. The Court held that excess in price is therefore to be determined in answering the question whether the difference between the costs actually incurred and the price actually charged is excessive, and, if the answer to this question is in the affirmative, whether a price has been imposed which is either unfair in itself or when compared to competing products (8). Conclusion of the Court concluded that Commission did not succeeded to prove excess in prices. Failure on the Commission part to provide analysis of UBC cost structure analysis was paramount to such judicial decision (UBC was found to be in abuse of dominance in other aspects but execs in prices was not sufficiently proven).

In *Bodson v. Pompes Funèbres* case (9) from 1988 the Court of Justice held that the excess in price can be determined by comparing what the dominant undertaking had charged in other markets in which it is subject to more intense competition (6). Method of comparison with other markets was further elaborated a year later in *Tournier* case (10), in which the Court required objective justification for price difference from the similar/comparable markets. In some cases, the Court held that prices exceeding the competitive benchmark in other markets between 25% to 40% were excessive, while other decisions concerned larger differences. In more recent case law, the Court in *AKKA/LAA* case from 2017 (11) held that there is no minimal threshold in price difference, it only required difference is significant and persistent. After the judgment in *United Brands* case two-limb test is frequently used in the assessment of the excess in price.

Particular problem are markets that are naturally monopolistic. Good example for this is Commission decision in *Port of Helsingborg* case from 2004 (12). In that case Commission held that that there is no sufficient evidence to conclude that the port charges have no reasonable relation to the economic value of the services provided by the port to the ferry-operators. The problem of the assessment by using comparative markets method in this kind of situation is locational monopoly. Port of Helsingborg is located in the southwest of Sweden, at the narrowest point of Øresund between Sweden and Denmark. Thus, there is literally no sufficiently comparable market or ferry route in whole of the EU method (6). Similarly, naturally monopolistic markets frequently occur in markets of pharmaceutical products.

Specific expanding area of case-law in EU Competition law is exactly in the field of pharmaceuticals. Leading case here is the Commission decision in *Aspen* case from 2020 (13). Case relates to excessive pricing of six cancer medicines in the European Economic Area (excepting Italy which adjudicated the matter in national proceedings also revoking excessive prices as abuse of dominance) by Aspen, an international pharmaceutical company headquartered in South Africa. The patent protection for the aforementioned medicines expired more than 50 years ago. Aspen imposed price increases by threatening to de-list or to withdraw the medicines. After having imposed the increased prices, often by several hundred percent, Aspen maintained the high prices (with profit margins over 80% and higher). Aspen also did not carry out any research and development or add any improvements or enhancements to commercialisation or distribution. Medicines in question did not have generic substitutes in Europe so the dependency of patients and health systems on Aspen's products made demand highly inelastic and customers vulnerable to exploitation. Case ended with Aspen commitment to reduce net prices for each of the medicines in all of the EEA Member States where price levels might raise concerns. The price reduction would be on average around 73% for the medicines across the EEA. The reduced net prices would apply for a period of 10 years.

Regulation of excessive pricing exists in all of the Organization for Economic Co-operation and Development Member countries except US, Canada, Mexico, Australia and New Zealand (14). US Antitrust Law under the influence of the Chicago School of Economics is still lead by the idea of self-

correcting markets that is estranged to excessive pricing as a concept. However, such practices can sometimes be categorised under general provisions of Sherman Act that addresses monopolization and attempts to monopolize not relating to excessive pricing. Furthermore, such views on excessive prices have been questioned from doctrinal point of view (15). Signs of possible acceptance in US Antitrust Law can be detected exactly in the area of pharmaceutical pricing practices (6). Example form US case law is *In re Nexium (esomeprazole)* case from 2014 that involves pay-for-delay agreements of AstraZeneca and their impact on competition and consumer prices (16). Regulation of excessive prices exists in competition laws of all BRICS countries (6).

PATENT PROTECTION EXPIRED VS PATENT PROTECTED PHARMACEUTICALS

Majority of developing case law in various jurisdictions relating to excessive prices of pharmaceuticals concerns situation where patent protection, as most common intellectual property right, expired. This was the situation in EU *Aspen* case, as we have seen form the introduction (as well in the Italian national proceedings in the same case). Described regulatory emphasis on pharmaceutics where patent protection expired has been clearly demonstrated in one study from 2023 (17). Usual preferred remedy for excess in prices of such pharmaceuticals (where patent protection expired) would be in lowering the barriers for entry on the relevant market for substitutes product/products. Especially preferred by the medical drug regulators are generic medicines. However, this is not always possible, as we have seen in the *Aspen* case - simply there were no substitute generics available at that time in Europe. Among crucial contributing factors for the existence of entry barriers, along with the costs of research and development, is time. Reason for time as limiting factor is that pharmaceutics standardly, weather original or generic, both in the EU and globally, may only be placed on particular relevant market after they have obtained a marketing authorisation. A marketing authorisation can be obtained through national authorisation or through a centralised procedure in EU, before the European Medicines Agency. Irrespective of the procedure, obtaining a marketing authorisation even for generic medicines is a resource-intensive and long process that, in principle, can take between 12 and 18 months for generic medicines and even longer for originator medicines. Competition Law regulators (either national regulators or DG Competition of the European Commission) can step-in in such situations when surge in prices occurs and are there are no available market substitutes with application of excessive prices as abuse of dominance.

Regulatory application of excessive prices as a form of abuse of dominance in patent protected pharmaceuticals is much less frequent, practically non-existent. Standard doctrinal explanation for this state is the intrinsic collision between intellectual property rights, that are exclusive in nature (patent protection in particular), and Competition law that promotes competition and non-exclusivity. However, there has been a very substantial application of Competition law on patent protection rights in other area outside excessive prices, including for example rules on agreements between undertakings and merger control. Real reason for rarity of application of excessive process as form of abuse of dominance in patent protected pharmaceuticals is reluctance on the part of regulators to initiate such proceedings. Excessive prices are viewed as controversial (not accepted in some jurisdictions like US) part of Competition law. Furthermore, excessive prices are considered as exploitative abuse and not as exclusionary abuse and thus not an enforcement priority. This reasons influenced on the small number of cases in which excessive pricing was determined within the EU Competition Law in general (18).

CASE STUDY IN PEADIATRICS: EXCESSIVE PRICES AND SPINRAZA®

Despite the rarity there is no legal reasoning that would exclude application of the legal institute of excessive prices (in jurisdiction where they are stipulated) on the patent protected pharmaceuticals. Recorded lack of Competition law enforcement in patent protected pharmaceuticals is therefore suboptimal. Good example for that is exactly in the area of paediatric pharmaceutics in the case of Spinraza®.

Spinraza® (nusinersen) is a medication used in treating spinal muscular atrophy (SMA) associated with a mutation in the SMN1 gene. Since the condition it treats is so rare Spinraza® entered in the realm of pharmaceuticals unofficially named 'orphan drugs'. Biogen, multinational biotechnology company, since 2015 holds patent rights on Spinraza®. Spinraza's® pricing is largely a 'black box' because of confidentiality clauses in pricing agreements with health authorities or insurers (19). Following their own investigations, the civil society groups estimate that the drug has a price of €210,000–280,000 per year per patient in Italy and of €529,800 per patient in the first year and €264,900 per year per patient thereafter in Belgium (17). The worldwide annual revenue for the product was around US$2 billion through 2018–2021. If 11,000 patients receive the medicine in one year, this puts the average worldwide price per patient per year at US$181,818 (17). Biogen says it bases its pricing on 'clinical benefit' and the 'prices of other orphan drugs' (19). However, consumer protection associations and civil society groups object in Italy and Belgium that Biogen invested US$648 million in the development of the medi-

TABLE 1. The list of the most expensive pharmaceuticals in the United States for paediatric use (source: www.drugs.com, April 1, 2024)

Generic name	Brand name	Diagnosis
Atidarsagene autotemcel	Lenmedly® (Libmedly®)	Metachromatic leukodystrophy
Delandistrogene moxeparvovec-rokl	Elevidys®	Duchenne Muscular Dystrophy
Elivaldogene autotemcel or eli-cel	Skysona®	Cerebral Adrenoleukodystrophy
Betibeglogene autotemcel or beti-cel	Zyteglo®	Beta-thalassemia
Onasemnogene abeparvovec-xioi	Zolgensma®	Spinal Muscular Atrophy
Metreleptin	Myalept®	Lipodystrophy/Leptin deficincy
Naxitamab-gqgk	Danyelza®	Neuroblastoma
Lonafarnib	Zokinvy®	Progeria and Progeroid Laminopathies

cine (20). If this is correct, then (based on the aforementioned average worldwide price per patient per year) Biogen would have recouped its direct R&D costs after treating 3,564 patients in one year (17).

It should be noted that generics to Spinraza® have been developed so application of excessive prices is not only applicable remedy to deal with high prices of this pharmaceutics. Biogen has faced scrutiny and investigation regarding the pricing of Spinraza®. Main reason is of course its high cost, which in some patients was up to $750,000 for the first year and around $375,000 for subsequent years. However, formal publicly available proceedings against Biogen for excessive prices of Spinraza® have not yet been publicized in any of the major jurisdictions (consumer protection associations have reported Biogen to Competition authorities in Italy and Belgium). If any national competition authority or DG Competition initiate proceedings usual steps in application of Competition law will be applied: determination of relevant market and assessment whether Biogen is in the position of dominance on that market prior to the determination of possible price excess in Spinraza®.

REPERCUSSIONS IN PAEDIATRIC HEALTH CARE SERVICES

Eight out of ten pharmaceuticals listed as the most expensive in the US in April 2024 have indication for use in paediatric population – Table 1 represents a list of most expensive pharmaceuticals for paediatric use. Similar situation is in the EU (with addition of exagamglogene autotemcel). Interestingly, only four pharmaceutics from the list can be found in the pharmaceuticals base in Croatia in 2024. Moreover, only two (Zolgensma®, Myalept®), are included in the medication list by the Croatian Health Insurance Fund (HZZO).

The most expensive medicine in the world currently is also a 'orphan drug' - atidarsagene autotemcel produced by Orchard Pharmaceutics, approved in US in March 2024 under the name Lenmeldy® (branded as Libmeldy® in Europe) with price per treatment exceeding four million US dollars. Its' efficacy in preventing disease symptoms or stabilizing progression was proven also in the clinical setting (21), however, the cost, as with many orphan drugs, raises concerns.

High prices of pharmaceuticals contribute to unequal healthcare accessibility worldwide. Variety of prices within and between the companies and generic drugs that are not necessarily cheaper are some of the reasons many countries, especially low-income, still face great challenges providing care for children with cancer (22). Even greater discrepancies in access to medicines and more unmet needs face paediatric patients with rare diseases as orphan drug developments are concentrated in only few therapeutic areas, as also shown in the Table 1 (23). The excessive cost has profound implications not only for oncology patients and children with metabolic diseases, but across the paediatric healthcare services, especially for children with neurological disorders, but also, for, example, for patients treated by the paediatric nephrology teams (24, 25). High price of previously described Spiranza influenced late broadening of indications of the drug in Croatia on the medication list of the Croatian Health Insurance Fund in 2019 after public outcry and treatments of patients abroad.

Stringer and more activist (by the Competition regulators) application of rules on excessive prices as form of abuse of dominance, especially in patent protected pharmaceuticals (in jurisdictions where they are applicable), could therefore be one of the effective tools in combating such inequality and access to health as fundamental right.

CONCLUSION

The main conclusion of this paper is that balance between competition rules on excessive prices as form of abuse of dominance and intellectual property rights in the area of expensive patent protected paediatric pharmaceutics can be regarded as suboptimal and there is a need for further regulatory development and activism on the side competition regulators. Even in those jurisdictions that do not have excessive prices, like US, possible regulatory change if it is to

come it will be most likely in the area pharmaceutical sector. Specially influenced is paediatric health care since majority of most expensive pharmaceuticals have indication for use in paediatric population. Stringer and more activist application of excessive prices as form of abuse of dominance can be an effective tool in combating inequality of healthcare accessibility and access to health as fundamental human right.

Abbreviations:

OECD – Organization for Economic Cooperation and Development
US – United States of America
BRICS – Brazil, Russian Federation, India, China, and South Africa
TFEU – Treaty on the Functioning of the European Union
EEA – European Economic Area
UBC – United Brands
EU – European Union
SMA – Spinal muscular atrophy

REFERENCES

1. Organization for Economic Cooperation and Development OECD. Excessive Prices in Pharmaceutical Markets [Internet]. 2018 [cited 2024 May 28]. Available from: http://www.oecd.org/daf/competition/excessive-pricing-in-pharmaceuticals.htm
2. Kianzad B, Minssen T. How Much Is Too Much? Defining the Metes and Bounds of Excessive Pricing in the Pharmaceutical Sector. European Pharmaceutical Law Review. 2018;2(3): 133 – 148
3. Achieving Fair Pricing of Medicines - Special Collection of the BMJ: British Medical Journal. 2020:368.
4. Morgan, S. Pricing of pharmaceuticals is becoming a major challenge for health systems. BMJ: British Medical Journal. 2020:368, 1–4.
5. Treaty on the Functioning of the European Union (Consolidated version 2016) OJ C 202, 7.6.2016.
6. Vuletić, D. Excessive Pricing in the European Union Competition Law and Comparative Context: Towards Stronger Regulation or Abandonment? Book of Proceedings 113th International Scientific Conference on Economic and Social Development. 2024:755-772.
7. Case 26-75 General Motors Continental NV v Commission of the European Communities, ECLI:EU:C:1975:150
8. Case 27/76 United Brands Company and United Brands Continentaal BV v Commission of the European Communities, ECLI:EU:C:1978:22
9. Case 30/87 Corinne Bodson v SA Pompes funèbres des régions libérées. ECLI:EU:C:1988:2210
10. Case 395/87 Ministère public v Jean-Louis Tournier, ECLI:EU:C:1989:319
11. Case C-177/16 Autortiesību un komunicēšanās konsultāciju aģentūra / Latvijas Autoru apvienība v Konkurences padome, ECLI:EU:C:2017:689
12. Commission Decision Case COMP/A.36.568/D3 – Scandlines Sverige AB v Port of Helsingborg
13. Commission Decision Case AT. 40394 ASPEN dt
14. Organization for Economic Cooperation and Development OECD. Excessive Prices Internet]. 2011 [cited 2024 May 28]. Available from: online: https://www.oecd.org/competition/abuse/49604207.pdf
15. Ezrachi A, Gilo, D. Are Excessive Prices Really Self-Correcting? Journal of Competition Law and Economics. 2008
16. In re Nexium (Esomeprazole) Antitrust Litigation, 968 F. Supp. 2d 367 (D. Mass. 2013).
17. Veraldi JD. Excessive Pricing in Pharmaceuticals under Article 102 TFEU. European Journal of Risk Regulation. 2023:1-21.
18. Butorac Malnar V, Pecotić Kaufman J, Petrović S, Akšamović, D, Liszt, M. Competition and State Aid Law [Pravo tržišnog natjecanja i državnih potpora]. University of Zagreb, Law Faculty. 2021.
19. Simoens S, Huys I. Market access of Spinraza (Nusinersen) for spinal muscular atrophy: intellectual property rights, pricing, value and coverage considerations. Gene Ther. 2017 Sep;24(9):539-541.
20. Altroconsumo. Spinraza unfairly priced. Italian and Belgian antitrust authotrities urged to investigate on drug. [Internet] 2019 [cited 2024 May 28]. https://www.altroconsumo.it/organizzazione/international/press-releases/2019/spinraza-unfairly-priced-italian-and-belgian-antitrust-authorities-urged-to-investigate
21. Messina M, Gissen P. Atidarsagene autotemcel for metachromatic leukodystrophy. Drugs Today (Barc). 2023;59(2):63-70. doi:10.1358/dot.2023.59.2.346191
22. Martei YM, Iwamoto K, Barr RD, Wiernkowski JT, Robertson J. Shortages and price variability of essential cytotoxic medicines for treating children with cancers. BMJ Glob Health. 2020;5(11):e003282. doi:10.1136/bmjgh-2020-003282
23. Rodriguez-Monguio R, Spargo T, Seoane-Vazquez E. Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients' health needs?. Orphanet J Rare Dis. 2017;12(1):1.
24. Chen G, Sharif B, Gerber B, et al. Epidemiology, healthcare resource utilization and healthcare costs for spinal muscular atrophy in Alberta, Canada. J Med Econ. 2021;24(sup1):51-59.
25. Karpman D, Höglund P. Orphan drug policies and use in pediatric nephrology. Pediatr Nephrol. 2017;32(1):1-6. doi:10.1007/s00467-016-3520-4

SAŽETAK

Prekomjerno visoke cijene lijekova i njihov utjecaj na pružanje zdravstvenih usluga u pedijatriji

Dominik Vuletić

Kontekst: *Pedijatrijski lijekovi imaju značajan udio u skupim lijekovima. Posljednjih godina zabilježeni su značajni zahtjevi za intervencijom prema visokim cijenama farmakoloških proizvoda. Zabrana prekomjerno visokih cijena kao oblika zlouporabe vladajućeg položaja smatra se kršenjem prava tržišnog natjecanja u pravu Europske unije i nacionalnim pravnim porecima njezinih država članica. Većina zemalja članica Organizacije za ekonomsku suradnju i razvoj (OECD) ima slične zabrane u svojim propisima o tržišnom natjecanju uz važan izuzetak Sjedinjenih Američkih Država (SAD), iako i tamo postoje neke naznake promjena upravo u području farmaceutskog sektora. Regulacija prekomjerno visokih cijena kao povrede prava tržišnog natjecanja također postoji u propisima svih država članica BRICS-a (Brazil, Ruska Federacija, Kina, Indija, Južna Afrika). Problem prekomjerno visokih cijena u farmaceutskom sektoru jedna je od razvijajućih tema u literaturi prava tržišnog natjecanja i razvoju sudske prakse. Ovo je područje u kojem se pravo intelektualnog vlasništva, tipično patentna zaštita, sukobljava s pravilima tržišnog natjecanja. Troškovi istraživanja i razvoja takvih lijekova često su vrlo visoki, naglašavajući potrebu za ravnotežom između sukobljenih legitimnih interesa: pristupa zdravlju i razvoja istraživanja.*

Cilj: *Predstaviti razvoj zakonodavstva i sudske prakse u primjeni pravnog instituta prekomjerno visokih cijena kao oblika zlouporabe vladajućeg položaja u farmaceutskom sektoru s naglaskom na pedijatrijske zdravstvene usluge.*

Izvor podataka: *OECD, PubMed, Google Scholar, Scopus*

Zaključak: *Ravnoteža između pravila tržišnog natjecanja o prekomjerno visokim cijenama kao obliku zlouporabe vladajućeg položaja i prava intelektualnog vlasništva u području skupih pedijatrijskih lijekova može se smatrati sub-optimalnom. Stoga postoji potreba za daljnjim regulatornim razvojem i primjenom instituta prekomjerno visokih cijena u tom području.*

Ključne riječi: PRAVNI ASPEKTI; SUDSKE ODLUKE; PEDIJATRIJA; KONTROLA LIJEKOVA I NARKOTIKA

Paediatr Croat. 2024;68:143-7
IZVORNI ZNANSTVENI ČLANAK / *ORIGINAL SCIENTIFIC PAPER*
www.paedcro.com
http://dx.doi.org/10.13112/PC.2024.24

Effect of treatment on quality of life of rural asthmatic children

Prasad Muley, Dave Hemal, Dave Hardik, Sargam Bhatt, Vaibhavi Mithaiwala*

Introduction: *Medications relieve symptoms of asthma but affected children are significantly bothered by physical, educational and emotional impairments. Urban studies from India evaluated on how this disease affects quality of life. Aim of our study was to evaluate quality of life of rural asthmatic children both before as well as after the treatment.*

Methods: *Asthmatic children 7 to 17 years visiting to rural tertiary care teaching hospital were included. Tool used for the study was Pediatric Asthma Quality of Life Questionnaire - Standard (PAQLQS) which were measured at the time of inclusion and four weeks after treatment. It assessed the QOL (Quality of Life) under symptoms, activity limitation and emotional function domains. Mean difference in pre and post treatment PAQLQ score was assessed.*

Results: *Total 46 children were included from rural setup. Majority were male 60% and had a normal BMI (54%) which was followed by undernutrition (28%). Majority children in both age group 7-11 year and 12-17 year, presented with moderate asthma (80%) and (62%) (according to GINA 2022) respectively followed by mild. The rural cohort post treatment showed significant improvement in individual ($p<0.005$) as well as in overall PAQLQ post treatment ($p<0.002$).*

Conclusion: *The study has highlighted that good asthma control even after short duration of treatment helped in improvement quality of life of affected children. To maintain quality of life it is expected that the patient remains adhered to proper treatment.*

Key words: ASTHMA; QUALITY OF LIFE; RURAL POPULATION

INTRODUCTION

Asthma is a chronic inflammatory disease of the lower airways of the lungs, which may need recurrent hospitalization. The overall burden of asthma is increasing worldwide, particularly among children (1). The recent Global Asthma Study (GAN) phase reported that the global prevalence of asthma was 11% in children aged 6–7 years and 9.1% among children aged 13–14 years (2).

Children with persistent asthma may be able to breathe normally with the help of medications but may experience asthma exacerbation of varying severity resulting in significant number of hospitalizations, interference in routine daily activities and school absenteeism leading to poor school performance, low self-image, and disruption of family life (3 ,4, 5). Thus, children with asthma are troubled not only by symptoms such as shortness of breath, cough and wheeze but are also bothered by the physical, social, educational and emotional impairments.

Hence, when a child is diagnosed with bronchial asthma, all the attention is focused on helping the child. After knowing about the illness of their child, parents show a series of reactions that may be a mix of guilt, sorrow, denial and anger. They go through intense emotional and psychological stress and may have fewer resources of emotional gratification. They struggle to cope with the financial costs and are confronted with new and unexpected experiences. Thus, the burden of the disease affects patients and their families alike (6, 7).

There has been tremendous interest in the measurement of "Quality of Life" (QOL) in chronic disorders in both adults and children over the last two decades. With increasing inci-

* Parul University, Post Limda (Waghodia), Vadodara. Gujarat. India 391760

Correspondence to:
Hardik Dave, DNB, Assistant Professor Department of Pediatrics;
PIMSR, Parul University; Post. Limda (Waghodia) Vadodara. 391760;
e-mail: ihardikdave@gmail.com

dence and burden of pediatric asthma, the assessment of QOL among these patients has become need of the day. Such assessment yields several benefits such as aiding in the monitoring of treatment, better understanding of the patient's feelings and enhancing communication between clinicians and patients (8).

The Pediatric Asthma Quality of Life Questionnaire (PAQLQ) is an example of such attempts. The questionnaire developed and validated by Juniper et al. (9) reveals areas of functions that are important to patients with asthma including physical and emotional functions. The PAQLQ was also designed to be an evaluative instrument that is sensitive to small changes over time, within the patients and therefore is appropriate for capturing the effect of an intervention in a clinical trial. PAQLQ has been validated and applied to the assessment of the QoL of asthmatic children in USA, Europe and some Asian countries (9, 10, 11).

Majority of studies on quality of life among asthmatic children and its impact on parents have been carried out in western countries. Indian setup where word "Asthma" itself is considered dreadful, there is hardly any significant data on how this disease affects quality of life of asthmatic children We could hardly find studies conducted in India and none of them has been carried out exclusively in rural setup where approach towards chronic diseases is altogether different.

METHODS

The prospective study was carried out from June 2022 to April 2023. in Parul Sevashram hospital catering to rural population of Gujarat and Madhya Pradesh.

All the asthmatic patients aged between 7 and 17 years, diagnosed, classified and treated with the help of GINA 2022 guidelines were eligible to participate (12). Patients, who provided consent/ascent to participate, were able to communicate directly with the interviewer in Hindi or Gujarati and capable of performing a maneuver of PEFR and spirometry, included in the study. The children with illnesses other than asthma that might have an impact on health-related Quality Of Life (QOL) e.g. intellectual impairment, history of recurrent chest infections, on oral steroids anytime in the 2 weeks prior to data collection, already diagnosed as asthma previously and on preventer therapy were excluded.

Sample size - An estimated prevalence rate of childhood asthma in India ranges from 2% to as high as 23%. Assuming lowest prevalence of 2%, at 95% confidence limits and 3% absolute precision, calculated sample size is 42. Accounting 10% for refusals, the sample size is further increased to 46. The participants for the study were selected by purposive sampling.

Data were collected through a structured interview to obtain information regarding demographics, family, socioeconomic history and history of allergies.

Detailed clinical history and examination was carried out. Clinical assessment of nutritional status was done by measuring weight and height using standardized scales. Body mass index (BMI) was calculated and classified as per the WHO charts. All efforts were made to confirm diagnosis in already clinically diagnosed cases of asthma by objective criteria such as Pulmonary Function Test (PFT).

PAQLQ questionnaire which were used in this study is already validated and used multiple times in past in various languages. The PAQLQ is a disease-specific questionnaire for children with asthma. It was intended to assess QOL in children between 7 and 17 years old children. In this study, the standardized version of the interviewed-administered versions was used. It has been shown that children as young as 7 years old could easily complete the questionnaire and could accurately understand questions. It includes 23 items in three domains, i.e., activity limitation, symptoms and emotional functions. Response to each item ranges from 1 (indicating maximum impairment) to 7 (no impairment at all). Results were expressed as the mean score per item for each of the domains as well as for overall quality of life. Therefore, both the domains and overall scores range from 1-7. Patients were asked to recall impairments they have experienced during the previous week. All the asthmatic children were analyzed by ACS score after 1 week and 4 weeks of enrollment and graded accordingly.

Data were analyzed using IBM SPSS (Version.17) software. The demographic particulars were expressed as percentage. QOL were presented as mean scores and comparison of QOL of pre and post treatment by using Paired sample t test. A P-value of < 0.05 were considered statistically significant.

RESULTS

A total of 46 children with newly diagnosed asthma were enrolled, with the proportion of males being 60.86%. When the cohort was divided into two groups, 54.5% (N=25) belonged to the younger age group (7-11 years), as shown in Table 1. 54.4% of the children with asthma in our study had a normal BMI. 41% of participants had a family history of allergic disease, the most common being allergic rhinitis (19.5%). In our study, 65% cooked with biomass and 45% of asthmatic children had a history of contact with pets (Table 1). Most children belonged to a low socioeconomic class according to the Kuppusamy classification (56.5%, N=26).

According to the 2022 GINA guidelines, the severity of asthma was classified, with most participants having moderate

TABLE 1. Base Line Demographics characteristics

S.no	Characterstics	Frequency	%
1	Age		
	7-11 years	25	54.34%
	12-17 years	21	45.64%
2	Sex		
	Male	28	60.86%
	Females	18	39.14%
3	Nutrition status		
	Undernourished	13	28.2%
	Normal	25	54.3%
	Overweight	6	13%
	Obese	2	4.3%
4	Family history of Allergic Disorder	19	41%
	Asthma	8	17.3%
	Allergic rhinitis	9	19.5%
	Urticaria	4	8.6%
	Food allergy	1	2.1%
5	Exposure to pets	21	45.6%
6	Exposure to Tobacco smoke (passive)	23	50%
7	Exposure to Biomass fuel	30	65%

persistent asthma (71.7%), while 2.2 of patients had severe persistent asthma (Figure 1). Patients with mild persistent asthma received preventive therapy with inhaled corticosteroids. Moderate and severe persistent asthmatics were treated with corticosteroids and long-acting beta-agonists as MART therapy according to the GINA guidelines 2022 (12).

Based on the clinical severity of asthma (ACS), children were categorized separately as well-controlled, partially controlled, and poorly controlled at each visit. According to the ACS score determined before and after treatment, there was a decrease in asthma severity after treatment (Table 2).

When the PAQLQ was evaluated, statistically significant improvements were found in the individual areas of activity

TABLE 2. Asthma Control as per Asthma Clinical Severity Score (ACS)

Status	Pre-treatment No (%)	Post-treatment No (%)
Well controlled	7 (15.21%)	13 (28.3%)
Partially controlled	37 (80.4%)	33 (71.7%)
Poorly controlled	2 (4.5%)	0

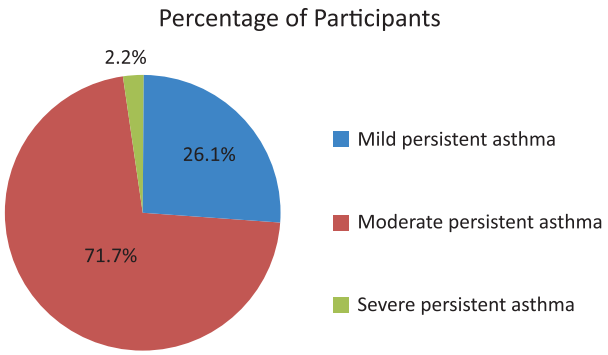


FIGURE 1. Grading of asthma at the time of diagnosis

limitation, symptoms and emotions. There was also a significant change in the mean PAQLQ total score (P<0.002), demonstrating an overall improvement in the child's condition as a result of the medical intervention (Table 3).

DISCUSSION

Quality of life in asthmatic children with asthma is measured on perception of symptoms, activity limitation and emotional factors along with clinical symptoms. Study has observed that a higher prevalence of asthma in the younger age groups was consistent with the widely believed concept of "children outgrow their allergies" (13) which was like our study. In our study, most children belonged to low and middle socioeconomic class. Similar results are seen in study from *Gomes P et al.,* which highlights that asthma is no longer limited to high socioeconomic class and it can affect the quality of life of affected children irrespective of socioeconomic class (14). Australian study by *Knibbs LD et al.* identified gas stove's role in significant proportion of the childhood asthma burden, as our study reports where use of Biomass fuel was associated in 65% of participants (15). Majority of newly diagnosed asthmatics with varying severity of our study were male (60.86%) which was similar to study by *Nogueira KT et al.* (16).

Most of the children in both age groups suffered with moderate persistent asthma similar to findings of other studies (7, 16). Positive family history of allergy and exposure to pets 41% and 45% were found in present study (17). *Ratageri et al.* found that family history of allergic rhinitis and asthma and exposure with tobacco smoke had strong association

TABLE 3. Mean PAQLQS Score -Pre and Post treatment

QOL domain	Pre –treatment Mean (SD)	Post treatment Mean (SD)	Mean Difference	T- Palue	P value
Activity (5)	4.421 (0.574)	5.886 (0.258)	-1.468	2.35	0.0015
Symptoms (10)	4.09 (0.43)	5.63 (0.24)	-1.54	1.83	<0.0003
Emotion (8)	4.255 (0.27)	5.13 (0.171)	-0.875	1.89	<0.0002
Grand Total	4.25 (0.164)	5.54 (0.386)	-1.29	2.91	0.002

with development of asthma in children, which is similar to findings of our study (18). Although obesity figured as an associated risk factor for asthma, in our study 54.34% of children had normal BMI. The findings are consistent with study done by *Battula et al.* (19).

Study signifies the importance of asthma control and its impact on the quality of life of the affected patient. It highlights post treatment significant improvement in all three domains as well as overall PAQLQ score. Similar findings as the present study were observed in study done by *Nair et al.* (20) and *Juniper et al.* (9) In our study participants showed improvement in all 3 domains individually as well as there was overall improvement in PAQLQ score. *Nair et al.* found overall improvement in PAQLQ score but didn't have significant improvement in emotional domain. This difference may be because principally our patients were from rural part of India, contrast to *Nair et al.* study who had recruitment from urban background. Apart from that *Nair et al.* used mini PAQLQ which has 13 items (emotional -4) in three domains while in present study Original PAQLQ was used which has 23 (emotional -8) items.

Limitation and Strengths

As this was a hospital-based study with a small sample size and short follow-up period, the results may not be accurately generalizable to the community. Therefore, a similar study with a large sample size should be conducted. Previous studies looking specifically at quality of life have been conducted in adults, but there are very few in the pediatric population. Our study differs slightly from other studies because the patients we recruited were from the rural part of the country where the concept of quality of life is somewhat different

CONCLUSION

Control of asthma symptoms should not be the only goal of management of asthma, but it should focus more on overall quality of life of the patients. Our study has highlighted that good asthma control even after short duration of treatment helped in improvement in quality of life of affected children in all domains i.e. symptoms, activity and emotions. To maintain such improvement, it is strongly advisable that patients should adhere with treatment to get best possible long-term outcome. Here we propose to conduct similar multicentric trials with larger sample sizes involving both urban and rural population to get better insight.

Acknowledgement

PAQLQS (original both Hindi and Gujarati version) adapted with prior permission of Elizabeth Juniper.

Abbreviations:

PAQLQ – Pediatric Asthma Quality of Life Questionnaire
QOL – Quality of Life
GINA – Global Initiative for Asthma
BMI – Body Mass Index
WHO – World Health Organization
PFT – Pulmonary Function Test
MART – Maintenance And Reliever Therapy
ACS – Asthma Clinical Severity

REFERENCES

1. Asher I, Pearce N. Global burden of asthma among children. Int J Tuberc Lung Dis. 2014;18(11):1269–78. doi:10.5588/ijtld.14.0170
2. García-Marcos L, Asher MI, Pearce N, et al. The burden of asthma, hay fever and eczema in children in 25 countries: GAN Phase I study. Eur Respir J. 2022;60:2102866. doi: 10.1183/13993003.02866-2021.
3. Okelo SO, Wu AW, Krishnan JA, Rand CS, Skinner EA, Diette GB. Emotional quality-of-life and outcomes in adolescents with asthma. *J Pediatr*. 2004;145(4):523-529. doi:10.1016/j.jpeds.2004.06.0434. Goeman DP, Thien FCK, Abramson MJ, et al. Patients' views of the burden of asthma: a qualitative study. Med J Aust. 2002;177(6):295–9. doi:10.5694/j.1326-5377.2002.tb04786.x
5. Gustafsson D, Olofsson N, Andersson F, Lindberg B, Schollin J. Effect of asthma in childhood on psycho-social problems in the family. J Psychosom Res. 2002;53(6):1071–5. doi:10.1016/s0022-3999(02)00340-9
6. Sennhauser FH, Braun-Fahrländer C, Wildhaber JH. The burden of asthma in children: a European perspective. *Paediatr Respir Rev*. 2005;6(1):2-7. doi:10.1016/j.prrv.2004.11.001
7. Singh M. The burden of asthma in children: an Asian perspective. *Paediatr Respir Rev*. 2005;6(1):14-19. doi:10.1016/j.prrv.2004.11.0038. Annett RD. Assessment of health status and quality of life outcomes for children with asthma. *J Allergy Clin Immunol*. 2001;107(5 Suppl):S473-S481. doi:10.1067/mai.2001.114949
9. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. *Qual Life Res*. 1996;5(1):35-46. doi:10.1007/BF00435967
10. Sanjuás C, Alonso J, Ferrer M, Curull V, Broquetas JM, Antó JM. Adaptation of the Asthma Quality of Life Questionnaire to a second language preserves its critical properties.> *J Clin Epidemiol*. 2001;54(2):182-189. doi:10.1016/s0895-4356(00)00297-311. Elizabeth C, Suzanna S, Tim CF, Shek LP, Mital R, Bee Wah L. Pediatric asthma quality of life questionnaire: validation in children from Singapore. *Asian Pac J Allergy Immunol*. 1999;17(3):155-161.
12. Reddel HK, Bacharier LB, Bateman ED, et al. Global Initiative for Asthma Strategy 2021: Executive Summary and Rationale for Key Changes. Am J Respir Crit Care Med. 2022;205(1):17-35. doi:10.1164/rccm.202109-2205PP
13. Pal R, Dahal S, Pal S. Prevalence of bronchial asthma in Indian children. Indian J Community Med. 2009 Oct;34(4):310-6. doi: 10.4103/0970-0218.58389.
14. Gomes P, Clemax Couto Sant'Anna, Maria. Quality of Life in Children with Asthma in Rio de Janeiro, Brazil. *Indian J Pediatr*. 2013;80(7):544-548. doi:10.1007/s12098-012-0930-615. Knibbs LD, Woldeyohannes S, Marks GB, Cowie CT. Damp housing, gas stoves, and the burden of childhood asthma in Australia. *Med J Aust*. 2018;208(7):299-302. doi:10.5694/mja17.00469
16. Nogueira KT, Silva JRL, Lopes CS. Quality of life of asthmatic adolescents: assessment of asthma severity, comorbidity, and lifestyle. *J Pediatr (Rio J)*. 2009;85(6):523-530. doi:10.2223/JPED.1957
17. Lau S, Wahn U. Pets—good or bad for individuals with atopic predisposition? *J Allergy Clin Immunol*. 2003;112(2):263-264. doi:10.1067/

mai.2003.166818. Ratageri VH, Kabra SK, Dwivedi SN, Seth V. Factors associated with severe asthma. *Indian Pediatr*. 2000;37(10):1072-1082.
19. Battula M, Arunashekar P, Nagarajan VP. A Prospective Study to Assess the Quality of Life in Children with Newly Diagnosed Asthma and Their Caregivers using the Pediatric Asthma Quality of Life Questionnaire. *J Prim Care Community Health*. 2020;11:2150132720961272. doi:10.1177/2150132720961272
20. Nair S, Nair S, Sundaram KR. A prospective study to assess the quality of life in children with asthma using the pediatric asthma quality of life questionnaire. Ind JACI. 2014;28(1):13. *doi:* 10.4103/0972-6691.134210

SAŽETAK

Utjecaj liječenja na kvalitetu života djece astmatičara u ruralnim sredinama

Prasad Muley, Dave Hemal, Dave Hardik, Sargam Bhatt, Vaibhavi Mithaiwala

Uvod: *Medikamentozna terapija značajno ublažava simptome astme, ali bolest u djece utječe i na psihološke, socioekonomske i obrazovne aspekte života. Studije urbanih područja Indije procijenile su kako ova bolest jasno utječe na kvalitetu života. Cilj našeg istraživanja bio je procijeniti kvalitetu života djece s astmom u ruralnim sredinama prije i nakon liječenja.*

Metode: Prospektivna studija provedena je nakon dobivanja etičkog odobrenja, a uključena su djeca s astmom u dobi od 7 do 17 godina iz ruralnih sredina Indije. Alat korišten za studiju bio je standardizirani upitnik kvalitete života pedijatrijske astme - Standard (PAQLQS) koji je mjeren u vrijeme uključivanja u studiju i četiri tjedna nakon liječenja. Procijenio je QOL (Quality of Life) u domenama simptoma, ograničenja aktivnosti i emocionalnih funkcija. Procijenjena je srednja razlika u PAQLQ rezultatu prije i nakon liječenja.

Rezultati: *Ukupno je uključeno 46 djece iz ruralnih sredina. Većina ispitanika su bili su muškog spola (60%), urednog indeksa tjelesne mase (ITM, 54%) nakon čega je značajn broj ispitanika bio pothranjen (28%). Većina djece u obje dobne skupine 7-11 godina i 12-17 godina imala je umjerenu astmu (80%) odnosno (62%) (prema GINA 2022.) nakon koje je slijedila blaga astma. Ruralna kohorta nakon liječenja pokazala je značajno poboljšanje kod ispitanika ($p < 0,005$), kao i u ukupnom PAQLQ nakon liječenja ($p<0,002$).*

Zaključak: *Ovom studijom smo pokazali da je dobra kontrola astme nakon kratkog trajanja liječenja značajno utjecala na kvalitetu života oboljele djece. U cilju poboljšanja kvalitete života, bolesnicima se preporuča pridržavanje preporučenog liječenja.*

Key words: ASTMA; KVALITETA ŽIVOTA; RURALNA POPULACIJA

Paediatr Croat. 2024;68:148-54
PREGLED / *REVIEW*
www.paedcro.com
http://dx.doi.org/10.13112/PC.2024.25

Primjena ibuprofena u pedijatrijskoj populaciji

Blaženka Kljaić Bukvić[1,2,3], Radenka Kuzmanić Šamija[4,5], Silvije Šegulja[4,5]

Vrućica je čest klinički simptom, uzrok zabrinutosti roditelja i najčešći razlog posjeta pedijatru i hitnoj pedijatrijskoj službi. Upravo zabrinutost zbog vrućice često je uzrokom neopravdane primjene medikamentozne terapije. Bol prati djecu u različitim patološkim stanjima tijekom odrastanja. Iako se naglašava važnost percepcije boli i primjene analgetika, i dalje je bol u pedijatrijskoj populaciji nedovoljno prepoznata.

Ibuprofen je jedan od najčešće primjenjivanih lijekova u pedijatrijskoj populaciji, u indikacijama kao što je snižavanje vrućice te ublažavanje boli i upale u različitim bolestima.

Farmakološka svojstva ibuprofena upućuju na dobar sigurnosni profil uz dobru učinkovitost što pridonosi njegovoj raširenoj primjeni. Najčešće očekivane neželjene reakcije, s obzirom na mehanizam djelovanja, poput gastrointestinalnog krvarenja, u dječjoj dobi su rijetke. U zdravog djeteta nema neželjenog djelovanja na bubreg, međutim, u stanjima dehidracije ili bubrežne bolesti, potrebno je prvo nadoknaditi volumen tekućine, a potom primijeniti ibuprofen. S obzirom na široku primjenu tijekom vrućice uzrokovane infekcijom, u nekim stanjima navodi se povezanost s težim kliničkim infekcijama kože i dišnog sustava. Također, povezuje se s pogoršanjima astme te većim rizikom za astmu ukoliko je primijenjen tijekom trudnoće i prvih godina života. Međutim, ovakve povezanosti treba potkrijepiti metodološki primjereno oblikovanim istraživanjima.

Stoga, u ovom radu kroz pregled literature prikazujemo učinkovitost i sigurnost primjene ibuprofena u pedijatrijskoj populaciji u različitim patološkim stanjima.

Ključne riječi: IBUPROFEN; ANALGEZIJA; ANTIPIREZA; ANTIINFLAMATORNI UČINAK

UVOD

Ibuprofen je jedan od najčešće primjenjivanih lijekova u pedijatrijskoj populaciji zbog širokog djelokruga djelovanja poput antipireze, analgezije i antiinflamacije. Mehanizam djelovanja koji ostvaruje inhibicijom ciklooksigenaze odgovoran je za dobar učinak, ali je povezan i s neželjenim reakcijama, poput gastrointestinalnog krvarenja ili renovaskularnih promjena. U ovom radu bit će prikazana farmakološka svojstva kroz učinkovitost i sigurnost te indikacije za primjenu u kliničkoj praksi.

FARMAKODINAMIKA IBUPROFENA

Ibuprofen je prvi derivat propinske kiseline (izo-butil-propan-fenolska kiselina), u skupini nesteroidnih protuupalnih lijekova (eng. *non-steroidal anti-inflammatory drugs, NSAIDs*). Sintetiziran je 1969. godine kao sigurnija alternativa do tada primjenjivanom aspirinu (1). U sljedećim godinama, unatoč sintezi novih molekula, postaje najprimjenjivaniji analgetik/antipiretik u pedijatrijskoj i adultnoj populaciji (2). Ibuprofen je mješavina stereoizomera, S(+), koji je snažni inhibitor prostaglandina i R(-) enantiomera, koji postaje aktivan u crijevu

[1] Odjel za pedijatriju, Opća bolnica „Dr Josip Benčević“, Ulica Andrije Štampara 42, Slavonski Brod
[2] Fakultet za dentalnu medicinu i zdravstvo, Sveučilište Josipa Jurja Strossmayera u Osijeku, Crkvena 21, Osijek
[3] Medicinski fakultet u Osijeku, Sveučilište Josipa Jurja Strossmayera u Osijeku, Crkvena 21, Osijek
[4] Fakultet zdravstvenih studija u Rijeci, Sveučilište u Rijeci, Ulica Viktora Cara Emina 5, Rijeka
[5] Pediatrics Plus Poliklinika za djecu i mlade, Meštrovićeva 2, Rijeka

Adresa za dopisivanje:
Odjel za pedijatriju OB Dr. Josip Benčević; Andrije Štampara 42; 35000 Slavonski Brod; e-mail: blazenka.bukvic@gmail.com

i jetri te pridonosi sigurnosti lijeka (3). Učinkovitost ibuprofena ostvaruje se putem inhibicije enzima ciklooksigenaze-1 i ciklooksigenaze-2 (eng. *cyclo-oxygenase-1, COX-1 i cyclo-oxygenase-2, COX-2*) koji kataliziraju konverziju arahidonske kiseline u prostaglandin H. Brojni enzimi ga dalje modificiraju za proizvodnju bioaktivnih prostanoida, kao što su prostaciklin, tromboksan A2 te prostaglandini D2 (PGD2), E2 (PGE2) i F2 (PGF2). Ovi prostanoidi utječu na imunološki, kardiovaskularni, gastrointestinalni, renovaskularni i središnji živčani sustav. Najvažniji učinak je inhibicija daljnje sinteze prostaglandina koji su odgovorni za bol, vrućicu i upalu. Inhibicija COX-1 i COX-2 je kompetitivna i reverzibilna.

Farmakokinetska obilježja ibuprofena značajno se ne mijenjaju odrastanjem djeteta. Primijenjen oralno na prazan želudac, više od 80% primjenjene doze se apsorbira iz gornjeg dijela probavnog sustava te unutar sat vremena doseže vršne serumske koncentracije. Uzimanje ibuprofena s hranom smanjuje vršnu serumsku koncentraciju za 30% dok je ukupna apsorpcija ibuprofena nepromijenjena. Hrana ublažava nuspojave poput iritacije želudca i erozija (4). Primjena rektalnim putem, zbog lošije apsorpcije, ima manju biorasположivost nego primjena oralnim putem. Terapijske koncentracije se postižu tek 45 minuta nakon primjene i ostaju u tim granicama 4 sata (5). Stoga se prednost daje oralnoj primjeni. Ibuprofen je snažno vezan uz proteine plazme (>99%). Ima kratko vrijeme poluživota ($t_{1/2}$ je oko 2 sata), čime se objašnjava najmanja učestalost probavnih nuspojava u odnosu na druge NSAIDs. Metabolizam ibuprofena odvija se putem enzimatskog P450 citokrom enzimatskog sustava. Oko 45-79% peroralne doze lijeka izlučuje se u obliku metabolita unutar 24 sata. Ibuprofen ima mogućnost prolaska u središnji živčani sustav i u cerebrospinalni likvor te dobru distribuciju u tkiva i sinoviju.

Ibuprofen je jedini NSAID koji se može primijeniti od rane dojenačke dobi (u djece starije od 3 mjeseca i/ili u djece s tjelesnom masom većom od 5 kilograma).

Preporučena dnevna doza ibuprofena u djece od 3 mjeseca do 12 godina ibuprofena iznosi 20-30 mg/kg podijeljeno u 3-4 pojedinačne doze. Može se ponoviti svakih 6-8 sati. Maksimalna preporučena dnevna doza u djece iznosi 40 mg/kg tjelesne mase.

U djece iznad 12 godina preporučena dnevna doza ibuprofena iznosi 1200 - 1800 mg, podijeljeno u 3-4 pojedinačne doze. Može se ponoviti svakih 6-8 sati. Maksimalna preporučena dnevna doza za odrasle iznosi 2400 mg.

SIGURNOST IBUPROFENA

Učinak na probavni sustav i loša gastrointestinalna podnošljivost očekuje se s obzirom na COX-1 inhibiciju i blokadu sinteze citoprotektivnih prostaglandina E. Međutim, istraživanja pokazuju da je ibuprofen od svih NSAIDs povezan s najmanje neželjenih učinaka na probavni sustav. Tome pridonosi kratko vrijeme poluživota s kompetitivno-reverzibilnom COX inhibicijom. Istraživanja pokazuju kako ibuprofen ima jednaku učestalost hospitalizacija od 1% zbog neželjenih događaja kao i paracetamol. Krvarenje iz probavnog sustava uočeno je u četvero djece liječeno ibuprofenom, što čini rizik od 7,2 na 100 000 djece, međutim, nije bilo razlike u odnosu na grupu liječenu paracetamolom. Studija nije zabilježila rizik od hospitalizacija zbog zatajenja bubrega ili anafilaksije (6). Izvješće o predoziranju ibuprofenom nisu zabilježila hepatotoksičnost (7).

Ibuprofen ima mali učinak na funkciju bubrega i krvni tlak u zdrave djece. Međutim, inhibicija sinteze prostaglandina E2 (PGE2) i prostaglandina I (PGI) u uvjetima kao što je dehidracija, hipovolemija i kronična bubrežna bolest može biti važna u održavanju protektivnog učinka na bubrežnu funkciju. U populacijskim istraživanjima velikog broja djece liječene ibuprofenom nije zabilježeno akutno zatajenje bubrega (6). Pojedinačna rijetka izvješća opisuju djecu s reverzibilnom renalnom insuficijencijom, zabilježenom za vrijeme akutne febrilne bolesti praćene dehidracijom tijekom koje je primijenjen ibuprofen (8). Stoga se preporuča oprez kod primjene ibuprofena u liječenju akutne febrilne bolesti praćene dehidracijom (znojenje, proljev, povraćanje). Ibuprofen i drugi NSAIDs mogu uzrokovati egzacerbaciju astme u djece s aspirin potaknutom respiratornom bolesti (eng. aspirin exacerbated respiratory disease, AERD). Aspirin, ibuprofen i drugi NSAID pokazuju križnu reaktivnost. Ukoliko se provodi oralna provokacija ibuprofenom, prevalencija AERD u djece i adolescenata s blagom i umjerenom astmom iznosi 2% (9). Pretpostavljeni mehanizam za pogoršanje astme je inhibicija COX-1 i COX-2, kojom se pojačava aktivnost lipooksigenaze i proizvodnja leukotriena koji potiču bronhokonstrikciju (10). S obzirom na ovaj fenotip astme, postavljena je premisa kako primjena ibuprofena u djeteta s astmom u akutnom febrilnom stanju može potaknuti pogoršanje astme. Više je istraživanja koja odbacuju ovu hipotezu, te dokazuju sigurnost primjene ibuprofena u djece s astmom, koja nemaju senzitizaciju na ibuprofen (11, 12). Međutim, potrebno je u anamnezi provjeravati jesu li pogoršanjima astme prethodila uzimanja NSAIDs te sumnjiva opažanja objektivizirati provokacijom (11). Epidemiološka istraživanja povezuju prenatalnu i ranu postneonatalnu izloženost ibuprofenu i paracetamolu s rizikom za kasniju pojavu astme. Neka od istraživanja nalaze pozitivnu povezanost pa treba naglasiti da se zbog pristranosti rizik umanjuje ukoliko se uzme u obzir da je svaki antipiretik uzet zbog infekcije (13).

INTERAKCIJE IBUPROFENA S DRUGIM LIJEKOVIMA

U cilju smanjenja mogućnosti nuspojava ne preporuča se uzeti ibuprofen s drugim lijekovima iz skupine NSAID (npr.

acetilsalicilatnom kiselinom). Također, ibuprofen može utjecati na druge lijekove ili na njega mogu utjecati drugi lijekovi. Primjerice, lijekovi koji su antikoagulansi (aspirin/acetilsalicilatna kiselina, varfarin, tiklopidin) kao i lijekovi koji snižavaju visoki krvni tlak (inhibitori angiotenzin konvertirajućeg enzima poput kaptoprila, beta-blokatori poput atenolola, antagonisti receptora angiotenzina-II kao što je losartan). Primjena s varfarinom povećava rizik od krvarenja, dok primjena s acetilsalicilnom kiselinom (niskim dozama) može dovesti do smanjenog učinka razrjeđivanja krvi. Primjena s antihipertenzivima može smanjiti njihov učinak. Istodobna primjena ibuprofena i lijeka poput digoksina može pojačati njegov učinak. Primjena ibuprofena i glukokortikoida, odnosno selektivnih inhibitora ponovne pohrane serotonina, može povećati rizik od krvarenja u probavnom sustavu. Primjena ibuprofena s metotreksatom pojačava njegov učinak, a istodobna primjena s takrolimusom i/ili ciklosporinom može dovesti do oštećenja bubrega. U interakciji s kinolonskim antibioticima dovodi do povećanog rizika od konvulzija, a interakcija s zidovudinom pojačava rizikom od krvarenja u zglobove kod osoba s hemofilijom i HIV infekcijom (14).

SIGURNOST IBUPROFENA U NEONATALNOJ DOBI

Novorođenčad se razlikuje od starije djece u apsorpciji, distribuciji i metabolizmu lijekova. Oralna primjena u novorođenčadi rezultira nepredvidivom ili smanjenom apsorpcijom kao posljedica nepravilnog pražnjenja želuca, alkalnog želučanog pH i smanjene funkcije crijeva i žuči. Želučani pH ne počinje padati do osmog ili desetog dana života. Rektalna apsorpcija relativno je brza u novorođenčadi. Smanjenje mišićnog krvotoka i mala mišićna masa čini intramuskularnu primjenu nepredvidivom, a povećana propusnost kože ubrzava apsorpciju lijeka transdermalnim putem. Smanjeni serumski albumin i ukupni protein, prisutnost fetalnog hemoglobina, povećani bilirubin i smanjeno masno tkivo u novorođenčadi u odnosu na odrasle rezultiraju povećanom slobodnom frakcijom lijeka, smanjenim volumenom distribucije hidrofobnih lijekova i povećanim volumenom distribucije hidrofilnih lijekova. Svi trenutno klinički dostupni NSAID su više hidrofilni iako u plazmi teže ka albuminu (15). Stoga se ibuprofen ne preporučuje za antipirezu ili bolove u novorođenčadi i djece do 3 mjeseca starosti, odnosno tjelesnom masom manjom od 5 kilograma. Nadalje, ibuprofen je kontraindiciran u nedonoščadi zbog moguće prirođene srčane bolesti kod koje je prohodnost duktusa arteriozusa neophodna za zadovoljavajući plućni ili sustavni protok krvi te zbog mogućeg aktivnog krvarenja, osobito intrakranijalnog krvarenja (16).

Ibuprofen ima dobar sigurnosti profil tijekom dojenja, jer se izlučuje u vrlo malim količinama u majčinom mlijeku, koje predstavljaju manje od 1% ukupne dnevne doze za dojeno dijete (17).

PRIMJENA IBUPROFENA KAO ANALGETIKA

Akutne bolesti u dječjoj dobi često su praćene osjećajem boli različitog intenziteta. Ublažavanje boli u djece najčešće nije optimalno zbog samog neprepoznavanja i straha od primjene analgetika što rezultira njihovim subdoziranjem ili neprimjenjivanjem. Neliječena bol može utjecati na usporeno cijeljenje rane, dovesti do anksioznosti, preosjetljivosti i straha od medicinskih intervencija.

Analgetski učinak ibuprofena temelji se na protuupalnom učinku te na djelovanju na nociceptore. PGE2 i PGI2 oslobođeni tijekom upalnih zbivanja smanjuju prag osjetljivosti nociceptora i potiču perifernu senzitizaciju. Ibuprofen inhibicijom sinteze upalnih medijatora smanjuje osjetljivost nociceptora (18). U umjerenoj do teškoj boli primjenjuju se opioidi, dok se blaga do umjerena bol može liječiti ibuprofenom i paracetamolom. Izbor analgetika ovisi o trajanju boli, vrsti boli i podležećim bolestima. Prednost se daje oralnoj primjeni analgetika zbog jednostavnosti i bezbolnosti. Pri provođenju analgezije treba predvidjeti očekivanu pojavu boli te primijeniti analgetike u vremenski određenim intervalima. Najčešći oblici akutne boli u pedijatriji su grlobolja, uhobolja, glavobolja, zubobolja, postraumatska mišićno-koštana bol i postoperacijska bol. Reumatske bolesti mogu biti podloga akutnoj i kroničnoj boli. Ibuprofen je najčešće istražen NSAID u ublažavanju akutne boli u djece (19).

Akutne traumatske ozljede mišićno-koštanog sustava, uključujući prijelome, modrice i uganuća, su među najčešćim uzrocima posjete hitnoj službi. Ibuprofen se pokazao jednako učinkovit u ublažavanju boli, kao i opiodi oksikodon te kombinacija paracetamola i kodeina. Pokazao je i bolji učinak u analgeziji nekompliciranih prijeloma, pretpostavlja se zbog proutupalnog učinka (20).

Vodeći simptom upale srednjeg uha je uhobolja. U djece starije od 2 godine u prvih 24 do 48 sati blagi klinički oblici upale srednjeg uha mogu se pratiti bez uvođenja antibiotika, međutim, primjena analgetika je neodgodiva (21). U težim oblicima, kada je primjena antibiotika neophodna, inicijalno uvođenje analgetika ublažava bol do početka djelovanja antibiotika. Ibuprofen je učinkovitiji u ublažavanju boli u odnosu na placebo. Istraživanja pokazuju i veću učinkovitost ibuprofena u odnosu na paracetamol, iako s niskom razinom dokaza (22, 23).

Primjerena analgezija i antipireza preporuča se za ublažavanje boli ili vrućice u djece s tonzilofaringitisom. Iako ibuprofen i paracetamol imaju jedan učinak, prednost se daje ibuprofenu kod eksudativnog tonzilofaringitisa i limfadenitisa zbog protuupalnog učinka (22).

Potrebno je razmotriti analgeziju kod zubobolje uzrokovane karijesom ili bol tijekom dentalnih intervencija (24). Kombinacija preintervencijske i postintervencijske doze ibuprofena je učinkovitija od paracetamola u kontroli boli kod ortodontskih

postupaka. Nicanje zuba u dojenačkoj i ranoj dječjoj dobi često je povezano s pojačanim slinjenjem, nezadovoljstvom, iritabilnošću, blagim porastom tjelesne temperature. Osim suportivnih mjera, kod izraženijeg ometanja svakodnevnih aktivnosti preporuča se primjena analgetika (25).

Poslijeoperacijska bol u pedijatrijskoj populaciji je najčešće podcijenjena, a primjena analgetika subdozirana, što može dovesti do prolongirane hospitalizacije, komplikacija i neželjenih psiholoških učinaka. Više je razloga za subdoziranje ili neprimjenu analgetika poput kvantifikacije bola u novorođenačkoj ili dojenačkoj dobi, nepoznavanje patofiziologije boli i manji broj registriranih analgetika u dječjoj dobi. Najveća kritika pedijatrijskih pacijenta na jednodnevnu kirurgiju je upravo poslijeoperacijska bol (26). Ibuprofen pokazuje učinkovitost uz dobar sigurnosni profil u manjim operacijskim zahvatima poput korekcije hernije, hipospadije, hidrokele te kod cirkumcizije i orhidopeksije. Naime još je i učinkovitiji u prevenciji boli. Stoga se kod očekivane poslijeoperacijske boli primjenjuje proaktivni pristup: rano uvođenje analgezije uz kontinuiranu primjenu dok se očekuje trajanje boli. Dobar je učinak na kontrolu boli nakon adenoidektomije, bez utjecaja na povećanje rizika od poslijeoperacijskog krvarenja.

PRIMJENA IBUPROFENA KAO ANTIREUMATIKA

Nesteroidini protuupalni lijekovi, u prvom redu ibuprofen i naproksen, su temelj inicijalnog liječenja i dio gotovo svake terapijske kombinacije u dječjoj reumatologiji. Ibuprofen je temelj inicijalnog liječenja oligo/poliartikularnog oblika juvenilnog idiopatskog artritisa niskog stupnja aktivnosti, a s progresijom težine bolesti dodatak je lijekovima koji modificiraju bolest i/ili kortikosteroidima (27). Primjenjuje se u dozi od 30-40 mg/kg/dan u 3-4 doze. Kod blažih oblika bolesti zadovoljavajući rezultati se mogu postići primjenom dnevne doze od 20 mg/kg podijeljeno u 3-4 pojedinačne doze. Ibuprofen je pokazao dobru učinkovitost i u tranzitornom sinovitisu kuka, koji se javlja u djece predškolske dobi (28). Najčešće osteohondroze, Legg-Calvé-Perthesova te Osgood-Schlatterova bolest javljaju se u djece školske dobi, a osnova terapije je osteoartikularno rasterećenje i mirovanje. Međutim, ibuprofen s analgetskim i protupalnim djelovanjem, ubrzava ublažavanje boli (29).

PRIMJENA IBUPROFENA KAO ANTIPIRETIKA

Hipotalamus regulira održanje tjelesne temperature tijela. Razina regulacije je povišena u vrućici (infekcija, oštećenje tkiva, maligna bolest), a ova stanja povećavaju produkciju citokina (interleukina-1, interleukina-6, tumorskog čimbenika nekroze, interferona). Inicijalna faza termo regulacije odgovor je na endogene pirogene zbog otpuštanja ceramida u preoptičkoj regiji hipotalamusa. Druga faza nastaje zbog indukcije COX-2 i formacije PGE2. PGE2 prolazi krvno moždanu barijeru i djeluje na receptore prostaglandin E1 (EP1) i prostagladin E3 (EP3) na termosenzitivnim neuronima. Potom hipotalamus diže temperaturu i produkciju topline (tresavica) te sprječava gubitak topline. Ibuprofen sprječava sintezu PGE2, Dolazi do periferne vazodilatacije, povećava se protok krvi kroz kožu te znojenje što sve dovodi do snižavanja temperature, a ostvaruje brzi antipiretički učinak već nakon 15 minuta s djelovanjem do 8 sati (30).

SMJERNICE STRUČNIH DRUŠTAVA O ANTIPIRETSKIM MJERAMA

Vrućica je jedan od najčešćih simptoma u zdravstvenom zbrinjavanju pedijatrijske populacije. Unatoč dobro poznatoj činjenici kako je vrućica simptom, a ne bolest, i kako je ona fiziološki mehanizam organizma u obrani od infekcije, ona je i česti uzrok roditeljske zabrinutosti. Nema dokaza da vrućica pogoršava tijek bolesti i da uzrokuje trajne neurološke posljedice. Primarni cilj zbrinjavanja djeteta s vrućicom je poboljšati opće stanje i ublažiti nelagodu djeteta, a ne snižavanje tjelesne temperature na normalne vrijednosti.

Farmakoterapijske mjere zbrinjavanja vrućice uključuju primjenu antipretika. U zdravog djeteta s vrućicom europske i američke smjernice preporučaju primjenu jednog lijeka, monoterapiju, kada se mogu primijeniti paracetamol u dozi od 10-15 mg/kg svakih 4-6 sati (dnevna doza 90 mg/kg/dan) ili ibuprofen 10 mg/kg/dan svakih 6-8 sati (maks. dnevna doza 40 mg/kg) (31, 32). Recentni izvori preporučaju inicijalnu primjenu paracetamola s obzirom na dobar sigurnosni profil očitovan kroz njegovu višegodišnju primjenu (33, 34). Naglašava se i kako odabir antipretika najčešće ovisi o preferencijama roditelja koji započinju medikamentoznu antipirezu i bez savjetovanja s liječnikom. U djece s kroničnim bolestima, odabir antipiretika ovisi o patološkom mehanizmu. Stoga se u djece sa stanjima poput Kawasakijeve bolesti, poremećaja koagulacije i dehidracije, prednost daje paracetamolu, dok se isti lijek izbjegava u kroničnoj bolesti jetre. U kliničkoj praksi moguća je kombinacija oba antipretika te njihova alternirajuća (izmjenična) primjena. Ukoliko se uspoređuje učinkovitost, monoterapije ili kombinacije lijekova (paracetamola i ibuprofena), rezultati nisu jednoznačni, međutim, neka istraživanja upućuju kako ibuprofen ima brže djelovanje i dulje djeluje u prva 4 sata, dok je kombinacija lijekova superiornija u odnosu na monoterapiju u snižavanju temperature tijekom 24 sata (35). Dokazana je učinkovita antipireza, ali bez poboljšanja nelagode. Nema sigurnih dokaza da je veća učinkovitost kombinacijske ili izmjenične primjene antipiretika. Potrebna su daljnja istraživanja sigurnosti, učinkovitosti kombinacijske/izmjenične terapije, kao i učinka medikamentozne antipireze za poboljšanje općeg stanja i ublažavanje nelagode djeteta. Stoga stručna društva daju prednost oda-

biru jednog antipretika ukoliko vrućica dovodi do nelagode djeteta, a ne podržavaju redovnu primjene kombinacije i/ili izmjenične primjene antipiretika. Ukoliko vrućica uzrokuje nelagodu koja traje uz monoterapiju, može se pokušati s izmjeničnom primjenom antipiretika. Fizikalne mjere snižavanja vrućice imaju minimalni učinak (oblozi, kupke), a mogu povećati osjećaj nelagode koji redovito prati vrućicu, stoga se ne preporučuju u rutinskoj primjeni, bez prethodnog davanja antipiretika (31, 32, 36, 37).

IBUPROFEN U OSTALIM STANJIMA

Upotreba ibuprofena u većoj kumulativnoj dozi tijekom snižavanja vrućice u kućnim uvjetima može biti povezana s težim kliničkim tijekom i komplikacijama pneumonije uključivo i empijem (38). Iako istraživanja ne potvrđuju uzročnu povezanost, upućuju kliničara da u respiracijskim infekcijama težeg kliničkog tijeka primijeni dodatnu dijagnostičku obradu.

Upotreba ibuprofena u cističnoj fibrozi i pratećim infekcijama omogućava kontrolu upalne reakcije imunološkog sustava i brže rješavanje infekcija što je potvrđeno nizom studija (39).

Ibuprofen treba izbjegavati tijekom primjene acetilsalicilne kiseline (ASA) u liječenju Kawasaki sindroma s obzirom na to da ibuprofen antagonizira antitrombotski učinak ASA (40).

U virusnih infekcija praćenih tvrdokornijom vrućicom česta je upotreba ibuprofena. Najčešće komplikacije vodenih kozica su bronhitis, pneumonija te sekundarne infekcije kože. Istraživanja povezuju primjenu ibuprofena kao antipiretika u djece s varičelama s razvojem komplikacija poput nekrotizirajućeg fasciitisa ili empijema kod pneumonije (41, 42). Iako postoje metodološka ograničenja ovih istraživanja, uputno je pratiti kliničko stanje djeteta uz oprez kod primjene ibuprofena kod pacijenata s vodenim kozicama i pnemonijom.

Prikazi bolesnika sa Steven Johnson sindrom i deficitom glukoza-6-fosfat dehidrogenaze opisuju i dokazuju i ulogu ibuprofena u pokretanju bolesti (42, 43).

Uobičajena je praksa primijeniti paracetamol ili ibuprofen preventivno prije cijepljenja ili neposredno nakon da bi se izbjegli ili smanjili simptomi povišene tjelesne temperature, bolova na mjestu aplikacije, nemira djeteta i glavobolje. Ovakva praksa može dovesti do manje učinkovitosti cjepiva. Istraživanja ukazuju da se ovaj efekt može umanjiti ili anulirati ako se lijek ne uzima prije cijepljenja i unutar 8 sati od cijepljenja. Paracetamol i ibuprofen različito djeluju na različita cjepiva. Paracetamol smanjuje učinkovitost pneumokoknog cjepiva, dok ibuprofen nema takvo djelovanje, ali nešto smanjuje učinkovitost kod cjepiva za hripavac odnosno tetanus (44). Istraživanja potvrđuju smanjenu imunogenost u preventivnoj primjeni kod konjugiranog cjepiva za Hemofilus influence (45). Klinička istraživanja u cilju jasnih kliničkih implikacija ovih opažanja na pacijente još nisu provedena. Prije cijepljenja nije uputno uzimati antipiretike i analgetike, kao ni nakon cijepljenja ako su simptomi izdržljivi, no ukoliko nisu, ibuprofen bi bilo dobro uzeti 8 sati nakon cijepljenja.

Iako ibuprofen ima dobru bubrežnu podnošljivost, studije upućuju na mogućnost akutne bubrežne ozljede posebice u djece koja imaju dehidraciju uslijed akutnog gastroenteritisa ili drugom stanju koje kompromitira glomerularnu filtraciju (46). Potreban je oprez kod primjene ibuprofena kod klinički potvrđene dehidracije. Uputno je prethodno nadoknaditi tekućinu i uspostaviti dobru diurezu.

Nedonoščad s perzistirajućim ductus arteriosusom (PDA) ima veći mortalitet, povećani rizik od plućnog edema, krvarenja i bronhopulmonalne displazije, kao i smanjenje perfuzije i dostave kisika do krajnjih organa (47). Kao rezultat toga, nedonoščad s klinički značajnim PDA trebalo bi tretirati u cilju zatvaranja duktusa. Liječenje PDA u nedonoščadi uključuje konzervativno liječenje samo suportivnom terapijom, farmakološko zatvaranje pomoću COX inhibitora (npr. indometacin, ibuprofen) te kirurško podvezivanje (48). U sustavnim pregledima randomiziranih kliničkih ispitivanja ibuprofen je bio jednako učinkovit kao indometacin u zatvaranju PDA, ali i povezan s nižim rizikom od NEC-a i prolaznom insuficijencijom bubrega te kraćim trajanjem mehaničke ventilacije (49). Doze ibuprofena za zatvaranje PDA je u početku 10 mg/kg, nakon koje slijede dvije dodatne doze od 5 mg/kg, koje se daju u intervalima od 24 sata. Ibuprofen se može primijeniti i oralno, kao jeftinija i jednostavnija varijanta u odnosu na intravenski pripravak (49). Ne preporučuje se profilaktička upotreba COX inhibitora za smanjenje učestalosti PDA.

Febrilne konvulzije (FK) su najčešći neurološki poremećaj dojenčadi i male djece, a javljaju se u 2 do 4 % djece mlađe od pet godina. FK su dobno ovisne s jakom genetskom predispozicijom. Iako su često zastrašujući za roditelje, FK uglavnom su benigna pojava i povezani su s niskim rizikom od buduće epilepsije. Otprilike jedna trećina djece će imati rekurentne FK tijekom ranog djetinjstva, a rizik je povećan u vezi s određenim kliničkim značajkama, uključujući mladu dob, nisku temperaturu pri pojavi prvog napadaja, obiteljsku povijest FK i abnormalni razvoj u vrijeme prvog napadaja. Iako je specifična patogeneza FK-a nejasna, obično se prihvaća da su uzrokovane okolišem (infekcija i vrućica) i genetskim predispozicijama (50). Liječenje antipireticima ne utječe na stopu ponavljanja febrilnih napadaja u sljedećim epizodama vrućice (51). Postoji nekoliko mogućih fizioloških razloga zašto antipiretici ne mogu spriječiti febrilne napadaje. Antipiretici olakšavaju gubitak topline, ali ne usporavaju povišenje temperature niti snižavaju temperaturni prag za konvulzije tijekom početne faze vrućice koja izaziva napadaj (51).

Glavobolja je jedan od najčešćih simptoma u neuropedijatriji. Od svih glavobolja oko 40% su tenzijske, oko 28% migrenske, a od sekundarnih osobito su opasne one koje su

posljedica tumora, krvarenja ili arterio-venskih malformacija. U akutnom napadaju migrene kod djece koriste se najčešće analgetici paracetamol 15 mg/kg (max 1g), ibuprofen 10 mg/kg (maksimalno 400-600 mg 3-4x dnevno), uz dobru hidraciju i odmor te u djece starije od 12 godina i nazalni sprej sumatriptan (52).

ZAKLJUČAK

Ibuprofen je u širokoj upotrebi u pedijatrijskoj populaciji. Koristi se najčešće kao antipiretik u vrućici s izvrsnim terapijskim odgovorom te kao analgetik i antireumatik. Osim učinkovitosti, ima i dobar sigurnosni profil. Primjena u antipirezi različitih infektivnih bolesti težeg kliničkog tijeka dovela je do saznanja o mogućoj uzročnoj vezi između lijeka i komplikacija. Iako metodološki neusklađene, primjena ibuprofena povezuje se s razvojem nekrotizirajuće upale mekog tkiva kože u tijeku varičela, kao i s razvojem empijema pluća (38, 41, 42). Za djecu od 3 mjeseca života do 8 godina najprikladnije su tekuće formulacije (oralne suspenzije). Iako se naglašava važnost provođenja većih randomiziranih istraživanja kako bi se utvrdila uzročna povezanost ibuprofena s razvojem komplikacija tijekom infektivnih bolesti, ibuprofen je, pravilno upotrijebljen, trenutno jedan od najsigurnijih lijekova za primjenu u pedijatrijskoj dobi.

LITERATURA

1. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety. Inflammopharmacology. 2009;17(6):275–342.
2. Barbagallo M, Sacerdote P. Ibuprofen in the treatment of children's inflammatory pain: a clinical and pharmacological overview. Minerva Pediatr. 2019;71(1):82–99.
3. Lee EJ, Williams K, Day R, Graham G, Champion D. Stereoselective disposition of ibuprofen enantiomers in man. Br J Clin Pharmacol. 1985;19(5):669–74.
4. Rainsford KD, Bjarnason I. NSAIDs: take with food or after fasting? J Pharm Pharmacol. 2012;64(4):465–9.
5. Vilenchik R, Berkovitch M, Jossifoff A, Ben-Zvi Z, Kozer E. Oral versus rectal ibuprofen in healthy volunteers. J Popul Ther Clin Pharmacol J Ther Popul Pharmacol Clin. 2012;19(2):e179-186.
6. Lesko SM, Mitchell AA. Renal function after short-term ibuprofen use in infants and children. Pediatrics. 1997;100(6):954–7.
7. Argentieri J, Morrone K, Pollack Y. Acetaminophen and Ibuprofen overdosage. Pediatr Rev. 2012;33(4):188–9.
8. Krause I, Cleper R, Eisenstein B, Davidovits M. Acute renal failure, associated with non-steroidal anti-inflammatory drugs in healthy children. Pediatr Nephrol Berl Ger. 2005;20(9):1295–8.
9. Debley JS, Carter ER, Gibson RL, Rosenfeld M, Redding GJ. The prevalence of ibuprofen-sensitive asthma in children: a randomized controlled bronchoprovocation challenge study. J Pediatr. 2005;147(2):233–8.
10. Ledford DK, Wenzel SE, Lockey RF. Aspirin or other nonsteroidal inflammatory agent exacerbated asthma. J Allergy Clin Immunol Pract. 2014;2(6):653–7.
11. Kanabar D, Dale S, Rawat M. A review of ibuprofen and acetaminophen use in febrile children and the occurrence of asthma-related symptoms. Clin Ther. 2007;29(12):2716–23.
12. Sherbash M, Furuya-Kanamori L, Nader JD, Thalib L. Risk of wheezing and asthma exacerbation in children treated with paracetamol versus ibuprofen: a systematic review and meta-analysis of randomised controlled trials. BMC Pulm Med. 2020;20(1):72.
13. Sordillo JE, Scirica CV, Rifas-Shiman SL, et al. Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children. J Allergy Clin Immunol. 2015;135(2):441–8.
14. HALMED. Nurofen, sažetak opisa svojstava lijeka. Dostupno na: https://www.halmed.hr/Lijekovi/Baza-lijekova/Nurofen-Forte-za-djecu-200-mg-5-ml-oralna-suspenzija-s-okusom-jagode/12933/. Pristupljeno 16.06.2024.
15. Hall RW, Anand KJS. Pain management in newborns. Clin Perinatol. 2014;41(4):895–924.
16. Persad E, Pizarro AB, Bruschettini M. Non-opioid analgesics for procedural pain in neonates. Cochrane Database Syst Rev. 2023;4(4):CD015179.
17. Drugs and Lactation Database, (LactMed®). Dostupno na: https://www.ncbi.nlm.nih.gov/books/NBK500986/. Pristupljeno 16.06.2024.
18. Yaksh TL, Dirig DM, Malmberg AB. Mechanism of action of nonsteroidal anti-inflammatory drugs. Cancer Invest. 1998;16(7):509–27.
19. Poddighe D, Brambilla I, Licari A, Marseglia GL. Ibuprofen for Pain Control in Children: New Value for an Old Molecule. Pediatr Emerg Care. 2019;35(6):448–53.
20. Clark E, Plint AC, Correll R, Gaboury I, Passi B. A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. Pediatrics. 2007;119(3):460–7.
21. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964-999.
22. Bertin L, Pons G, d'Athis P, et al. A randomized, double-blind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children. Fundam Clin Pharmacol. 1996;10(4):387–92.
23. de Sévaux JLH, Damoiseaux RA, van de Pol AC, et al. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. Cochrane Database Syst Rev. 2023;8(8):CD011534.
24. Ashley PF, Parekh S, Moles DR, Anand P, MacDonald LCI. Preoperative analgesics for additional pain relief in children and adolescents having dental treatment. Cochrane Database Syst Rev. 2016(8):CD008392.
25. McIntyre GT, McIntyre GM. Teething troubles? Br Dent J. 2002;192(5):251–5.
26. Segerdahl M, Warrén-Stomberg M, Rawal N, Brattwall M, Jakobsson J. Children in day surgery: clinical practice and routines. The results from a nation-wide survey. Acta Anaesthesiol Scand. 2008;52(6):821–8.
27. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. Arthritis Rheumatol Hoboken NJ. 2022;74(4):553–69.
28. Kermond S, Fink M, Graham K, Carlin JB, Barnett P. A randomized clinical trial: should the child with transient synovitis of the hip be treated with nonsteroidal anti-inflammatory drugs? Ann Emerg Med. 2002;40(3):294–9.
29. Weiser P. Approach to the patient with noninflammatory musculoskeletal pain. Pediatr Clin North Am. 2012;59(2):471–92.
30. Morrison SF, Nakamura K. Central neural pathways for thermoregulation. Front Biosci Landmark Ed. 2011;16(1):74–104.
31. Sullivan JE, Farrar HC. Fever and antipyretic use in children. Pediatrics. 2011;127(3):580–7.
32. Fever in under 5s: assessment and initial management. London: National Institute for Health and Care Excellence (NICE); 2021 Nov 26. PMID: 31891472.
33. Doria M, Careddu D, Iorio R, et al. Paracetamol and Ibuprofen in the Treatment of Fever and Acute Mild-Moderate Pain in Children: Italian Experts' Consensus Statements. Child Basel Switz. 2021;8(10).
34. Ward MA. Up to Date. Fever in infants and children : pathophysiology and magement. Available from: https://www.uptodate.com/contents/

fever-in-infants-and-children-pathophysiology-and-management?source=autocomplete&index=0~1&search=fever#
35. Hay AD, Costelloe C, Redmond NM, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial. BMJ. 2008;337:a1302.
36. Doria M, Careddu D, Iorio R, et al. Paracetamol and Ibuprofen in the Treatment of Fever and Acute Mild-Moderate Pain in Children: Italian Experts' Consensus Statements. Child Basel Switz. 2021;8(10).
37. McCullough HN. Acetaminophen and ibuprofen in the management of fever and mild to moderate pain in children. Paediatr Child Health. 1998;3(4):246–50.
38. Le Bourgeois M, Ferroni A, Leruez-Ville M, et al. Nonsteroidal Anti-Inflammatory Drug without Antibiotics for Acute Viral Infection Increases the Empyema Risk in Children: A Matched Case-Control Study. J Pediatr. 2016;175:47-53.e3.
39. Lands LC, Stanojevic S. Oral non-steroidal anti-inflammatory drug therapy for cystic fibrosis. Cochrane Database Syst Rev. 2007;(4):CD001505.
40. Gengo FM, Rubin L, Robson M, et al. Effects of ibuprofen on the magnitude and duration of aspirin's inhibition of platelet aggregation: clinical consequences in stroke prophylaxis. J Clin Pharmacol. 2008;48(1):117–22.
41. de Martino M, Chiarugi A, Boner A, Montini G, De' Angelis GL. Working Towards an Appropriate Use of Ibuprofen in Children: An Evidence-Based Appraisal. Drugs. 2017;77(12):1295–311.
42. Ziesenitz VC, Welzel T, van Dyk M, Saur P, Gorenflo M, van den Anker JN. Efficacy and Safety of NSAIDs in Infants: A Comprehensive Review of the Literature of the Past 20 Years. Paediatr Drugs. 2022;24(6):603–55.
43. Pankey AN, Chandar A, Isaacson G. Safety of Ibuprofen in Children With G6PD Deficiency: A Systematic Review. The Laryngoscope. 2022;132(6):1300–5.
44. Deceuninck G, De Serres G, Boulianne N, Lefebvre B, De Wals P. Effectiveness of three pneumococcal conjugate vaccines to prevent invasive pneumococcal disease in Quebec, Canada. Vaccine. 2015;33(23):2684–9.
45. Falup-Pecurariu O, Man SC, Neamtu ML, et al. Effects of prophylactic ibuprofen and paracetamol administration on the immunogenicity and reactogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugated vaccine (PHiD-CV) co-administered with DTPa-combined vaccines in children: An open-label, randomized, controlled, non-inferiority trial. Hum Vaccines Immunother. 2017;13(3):649–60.
46. Shao QH, Yin XD, Liu HX, Zhao B, Huang JQ, Li ZL. Kidney Injury Following Ibuprofen and Acetaminophen: A Real-World Analysis of Post-Marketing Surveillance Data. Front Pharmacol. 2021;12:750108.
47. Rudolph AM. The changes in the circulation after birth. Their importance in congenital heart disease. Circulation. 1970;41(2):343–59.
48. Ngo S, Profit J, Gould JB, Lee HC. Trends in Patent Ductus Arteriosus Diagnosis and Management for Very Low Birth Weight Infants. Pediatrics. 2017;139(4).
49. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. Cochrane Database Syst Rev. 2020;2(2):CD003481.
50. Tiwari A, Meshram RJ, Kumar Singh R. Febrile Seizures in Children: A Review. Cureus. 2022;14(11):e31509.
51. Hashimoto R, Suto M, Tsuji M, et al. Use of antipyretics for preventing febrile seizure recurrence in children: a systematic review and meta-analysis. Eur J Pediatr. 2021;180(4):987–97.
52. Chiang CC, Fang X, Horvath Z, et al. Simultaneous Comparisons of 25 Acute Migraine Medications Based on 10 Million Users' Self-Reported Records From a Smartphone Application. Neurology. 2023;101(24):e2560–70.

SUMMARY

Use of ibuprofen in pediatric population

Blaženka Kljaić Bukvić, Radenka Kuzmanić Šamija, Silvije Šegulja

Fever is a common clinical issue, causing concern for parents and being the most frequent reason for visits to pediatricians and pediatric emergency services. Pain accompanies children in various pathological conditions during their growth. Although the importance of pain perception and the use of analgesics is emphasized, pain in the pediatric population is still insufficiently recognized, unlike fever. Ibuprofen is one of the most commonly used medications in the pediatric population, indicated for reducing fever, as well as relieving pain and inflammation in various diseases. The pharmacological properties of ibuprofen indicate a good safety profile with effective results, contributing to its widespread use. The most commonly expected adverse reactions, considering the mechanism of action, such as gastrointestinal bleeding, are rare in children. In a healthy child, there are no adverse effects on the kidneys; however, in conditions of dehydration or kidney disease, fluid volume should be replenished before administering ibuprofen. Given its broad application during fever caused by infection, some conditions are associated with more severe clinical skin and respiratory infections. It is also linked to exacerbations of asthma and a higher risk of asthma if used during pregnancy and the early years of life.This potential association requires additional research to be methodologically confirmed.

Therefore, in this paper, through a literature review, we present the effectiveness and safety of ibuprofen use in the pediatric population in various pathological condition.

Key words: IBUPROFEN; ANALGESIA; ANTIPYRESIS; ANTI-INFLAMMATORY EFFECT

Paediatr Croat. 2024;68:155-63
PREGLED / *REVIEW*
www.paedcro.com
http://dx.doi.org/10.13112/PC.2024.26

Limfatičke malformacije

Rok Kralj[1], Danijel Cvetko[2], Ana Tripalo Batoš[3], Tomislav Baudoin[4], Elvira Kereković[1], Nada Rajačić[5], Jasminka Stepan Giljević[5], Stjepan Višnjić[1]

Limfatičke malformacije su abnormalne cistične dilatacije limfatičkih žila. Prisutne su pri rođenju no često se mogu otkriti tek u kasnijoj životnoj dobi. Jednostavne limfatičke malformacije su ograničene na pojedine anatomske regije dok kompleksnim malformacijama smatramo difuzne abnormalnosti koje mogu zahvatiti cijeli organizam. Jednostavne limfatičke malformacije se dijele na makrocistične (ciste ≥1cm) i mikrocistične (ciste <1cm). Po ISSVA klasifikaciji iz 2015. se napušta termin limfangiom i uvodi se termin limfatičke malformacije čime se želi jasno naznačiti da se ne radi o tumorskoj tvorbi. Klinički tijek je karakteriziran dugačkim asimptomatskim razdobljima s kratkotrajnim upalnim ili infektivnim epizodama te epizodama intracističnog krvarenja. Dijagnoza se kod voluminoznih promjena može postaviti na prijelazu iz drugog u treći trimestar trudnoće ultrazvučnim pregledom ili fetalnom magnetnom rezonancom. Ultrazvuk i magnetna rezonanca su dijagnostičke metoda izbora i u postpartalnom razdoblju. Svrha liječenja nije kompletno uklanjanje tvorbe, već ograničavanje simptoma u mjeri kojom bi se očuvala funkcionalnost i omogućio primjeren izgled. Metode liječenja su ekspektativna metoda kod asimptomatskih promjena, sklerozacija, kirurška resekcija, medikamentozno liječenje, lasersko liječenje te mjere fizikalne terapije.Kad nema životno ugrožavajuće opstrukcije dišnih puteva, sklerozacija je metoda izbora. Bleomicin kao sklerozacijsko sredstvo omogućava dobre rezultate uz blage nuspojave. Terapija sirolimusom (rapamicinom) u velikom postotku omogućava redukciju tvorbe, ali je važno pratiti moguće nuspojave.

Ključne riječi: LIMFATIČKE MALFORMACIJE; LIMFANGIOM; DJECA; SKLEROZACIJA; RAPAMICIN; SIROLIMUS

ETIOLOGIJA

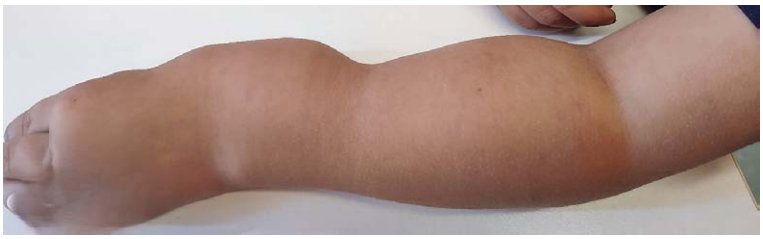
Limfatički sustav je mreža žila mezodermalnog porijekla cirkulacijski paralelan venskom sustavu (1). Limfatičke malformacije (LM) su abnormalne cistične dilatacije limfatičkih žila, a klasificiraju se kao vaskularne anomalije sporog toka *(„slow-flow")* (2-4). Prisutne su pri rođenju, ali se vrlo često otkrivaju i u kasnijoj životnoj dobi uslijed infektivnih ili upalnih epizoda druge etiologije (2). Incidencija se procjenjuje na 1,2-2,8 slučajeva na 1000 živorođene djece (5). U 50-60% slučajeva, malformacije su manifestne pri rođenju a u 80-90% slučajeva će postati evidentne do kraja druge godine života (6).

KLASIFIKACIJA

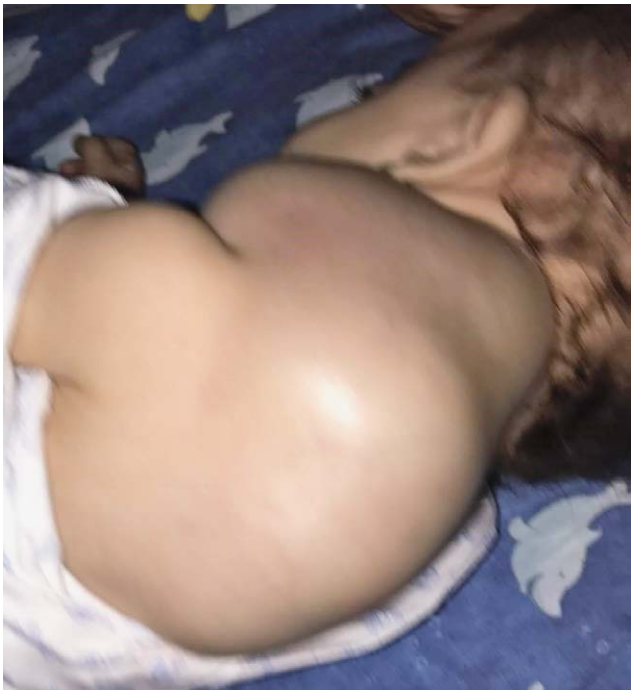
Prema ISSVA klasifikaciji vaskularnih anomalija, LM se klasificiraju kao malformacije, jednako kao i kapilarne, venske i arteriovenske malformacije. Često se javljaju kombinirane malformacije kao što su npr. kapilarno - limfatičke ili vensko - limfatičke (7). LM mogu biti ograničene na pojedine anatomske regije (jednostavne) ili se može raditi o difuznim abnormalnostima koje zahvaćaju cijeli organizam (kompleksne). Jednostavne se po veličini cista dijele na makrocistične (promjer ≥1cm), mikrocistične (promjer <1cm) i miješane. Kompleksne LM čine difuzne abnormalnosti koje uključuju središnje konduktivne limfatičke kanale a dijele se na generaliziranu limfatičku anomaliju (GLA), kaposiformnu limfangiomatozu (KL), Gorham-Stout-ovu bolest i centralnu

[1] Klinika za dječju kirurgiju, Klinika za dječje bolesti Zagreb, Klaićeva 16, Zagreb
[2] Klinički zavod za dijagnostičku i intervencijsku radiologiju, Klinička bolnica Dubrava, Avenija Gojka Šuška 6, Zagreb
[3] Zavod za dječju radiologiju, Klinika za dječje bolesti Zagreb, Klaićeva 16, Zagreb
[4] Klinika za otorinolaringologiju i kirurgiju glave i vrata, Klinički bolnički centar „Sestre milosrdnice", Vinogradska 29, Zagreb
[5] Zavod za pedijatrijsku onkologiju i hematologiju „dr. Mladen Čepulić", Klinika za dječje bolesti Zagreb, Klaićeva 16, Zagreb

Adresa za dopisivanje:
Dr. sc. Rok Kralj, dr. med.; Klinika za dječje bolesti Zagreb; Klaićeva 16, Zagreb; e-mail: rok.kralj@kdb.hr



SLIKA 1. **Limfatička malformacija desne podlaktice kod 6-godišnjeg dječaka.**



SLIKA 2. **Dvogodišnja djevojčica sa limfatičkom malformacijom vrata i gornjeg dijela leđa kod koje je došlo do naglog uvećanja tvorbe uslijed upale.**

konduktivnu limfatičku anomaliju (CKLA) (8). Smatra se i kako je kongenitalni limfedem podtip limfatičkih malformacija. Radi se nakupljanju limfe u površinskom međustaničnom prostoru što dovodi do povećanja opsega ekstremiteta. S vremenom dolazi do nakupljanja masnog i vezivnog tkiva što dovodi do daljnjeg povećanja opsega ekstremiteta. Nonne-Milroyeva bolest je dominantno nasljedni oblik primarnog kongenitalnog limfedema (9).

GENETIKA

Smatra se da bi uzrok nastanaku ovih malformacija mogla biti somatska mutacija PIK3CA gena koja dovodi do razvojne anomalije limfatičkih kanala zbog neadekvatne funkcije endotelnih stanica (10). Kod kompleksnih LM, uzrok su mutacije RAS/MAPK puta pa je tako kod Gorham Stout-ove bolesti prisutna KRAS mutacija, EPHB4 i ARAF mutacija kod centralne konduktivne limfatičke anomalije a NRAS kod generalizirane limfatičke anomalije (8).

KLINIČKA SLIKA

Limfatičke malformacije rastu proporcionalno s djetetom, a ne autonomno kao tumor te se upravo iz tog razloga preporuča napuštanje termina „limfangiom" zato što sufiks „-om" podrazumijeva da se radi o tumoru. Ipak, neki autori navode kako u periodu adolescencije postoji povišeni rizik za progresiju bolesti (12) u smislu pojave bolova ili upalnih epizoda. Makrocistične LM manifestiraju se kao okruglaste, bezbolne mase sa normalnom bojom nadležeće kože te se mogu lagano utisnuti (Slika 1.) (13). Promjer takvih cista je u pravilu veći od 1cm. Mikrocistične LM su obično tvrđe konzistencije a mogu biti duboke ili površne (unutar epidermisa ili u sluznici) te tada imaju formu prozirnih ili hemoragijskih mjehurića. Ti mjehurići mogu biti raspršeni ili u formi plakova koji se nazivaju limfangiektazije (7).

Klinički tijek je karakteriziran dugačkim asimptomatskim razdobljima s kratkotrajnim upalnim ili infektivnim epizodama te epizodama intracističnog krvarenja. Takve epizode se manifestiraju akutnim povećanjem volumena tvorbe a mogu uzrokovati bolove ili funkcijske tegobe (Slika 2).

Kod mikrocističnih LM, tijek bolesti je u pravilu usmjeren prema pogoršanju s povećanjem broja mjehurića, njihovim zadebljanjem ili krvarenjem (13). Epizode upalnih promjena uslijed infekcije ili krvarenja mogu trajati od 48 h do 1 mjesec, prosječnog trajanja oko 10 dana. U takvim situacijama se terapija sastoji od primjene analgetika (monoterapija paracetamolom ili u kombinaciji s tramadolom) antibiotika širokog spektra (amoksicilin+klavulonska kiselina kroz 6-10 dana) te kortikosteroidne terapije (prednizon ili prednizolon 0,5-2mg/kg/dan kroz 3-6 dana) (13). Posljedično takvoj epizodi, u makrocističnim LM, može doći fibromatozne promjene ciste i do spontane regresije. Smatra se kako do spontane regresije dolazi u 10% pacijenata u razdoblju od 2 do 24 mjeseca nakon upalne epizode (14, 15).

LM mogu biti lokalizirane na koži, mukoznim membranama ili podležećem tkivu (površinske) a mogu zahvaćati i unutarnje organe (duboke) (13). Mogu se naći u svim dijelovima tijela ali ponajviše u dijelovima bogatima limfom kao što su cervikalna i aksilarna regija. Mogu se naći i u području prepona, retroperitoneuma, ekstremiteta, abdomena i toraksa (11). S obzirom na to da je u području glave i vrata najgušća mreža limfatičkog sustava, u ovoj se regiji nalazi 75% LM (4).

Specifičnosti kliničke slike jednostavnih oblika limfatičkih malformacija

LM cervikofacijalne lokalizacije su često vrlo velike tvorbe koje se mogu detektirati intrauterino. Imaju spaciokompresivni učinak te mogu uzrokovati distociju ili kompromitirati dišni put u novorođenčadi (13). U situacijama kada se sumnja u moguću opstrukciju dišnih puteva kod novorođenčadi, indiciran je tzv. EXIT (*ex utero intrapartum treatment*) postupak kod kojeg se dišni put osigurava dok fetus još nije odvojen od posteljice (16). Ovaj se postupak provodi samo u specijaliziranim centrima sa adekvatnim iskustvom. Prema *Li i sur.,* indikacija za EXIT su cervikalne LM >5cm sa znacima opstrukcije jednjaka ili dišnih puteva (17). Ipak, većina cervikalnih LM su kompresibilne lezije što omogućava orotrahealnu intubaciju što otklanja potrebu za formiranjem traheostome po rođenju (18).

Kod orbitalnih LM su najčešći simptomi proptoza, orbitalna distopija, ograničenost pokreta očiju, kompresija na optički živac i slabovidnost (19,20). Zbog značajnog rizika povezanog s LM u periorbitalnom području, terapija je uvijek potrebna (20).

LM donjeg dijela lica mogu uključivati i makroglosiju i makroheliju s koštanim prerastanjem što može dovesti do poteškoća s disanjem i hranjenjem (11).

Medijastinalne LM se mogu manifestirati recidivirajućim hiloznim pleuralnim i perikardijalnim izljevima ili hiloznim ascitesom (21).

LM gastrointestinalnog trakta se mogu manifestirati enteropatijom s gubitkom proteina dok abdominopelvične LM mogu dovesti do opstrukcije crijeva, konstipacije ili pak uzrokovati pritisak na mokraćni mjehur i posljedičnu hematuriju (11). Atipične lokalizacije kao što su perikard i srce mogu rezultirati sa simptomima kao što dispneja ili repiratorni distres (22).

U području ekstremiteta, limfatičke malformacije dovode do povećenja opsega mekih tkiva i kosti što dovodi do povećanja opsega ekstremiteta (eng. overgrowth) (Slika 1.) (23).

Kompleksne forme LM

Generaliziranu limfatičku anomaliju (GLA) karakterizira prisutnost proširenih limfatičkih kanala tanke stijenke koje zahvaćaju ili jedan ili više organa, najčešće kosti i pluća (24). Simptomi su prvenstveno uzrokovani kompresijom vitalnih struktura. Smatra se da je prognoza ove bolesti u mlađoj životnoj dobi loša sa smrtnošću od 39% kod pacijenata mlađih od 16 godina (24).

Gorham Stout-ova bolest je oblik limfatičke anomalije kod koje dolazi i do invazije koštanog korteksa i osteolize (25, 26).

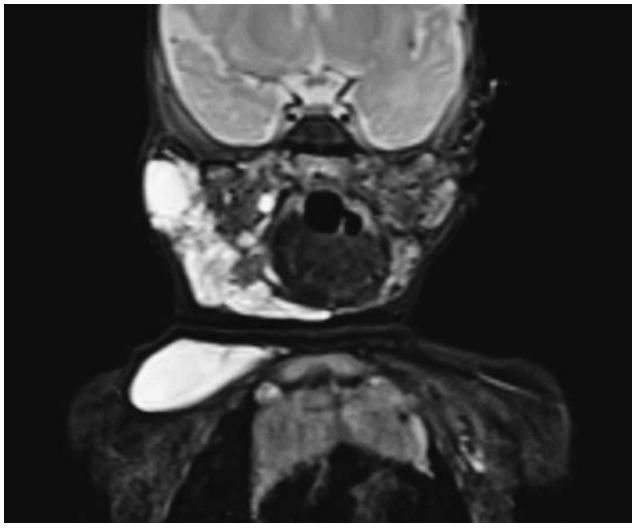
Poseban oblike difuznog oblika limfatičke anomalije je kaposiformna limfangiomatoza. Manifestira se slično kao GLA s time što se češće javlja potrošna koagulopatija (8).

Limfatičke malformacije u sklopu sindroma

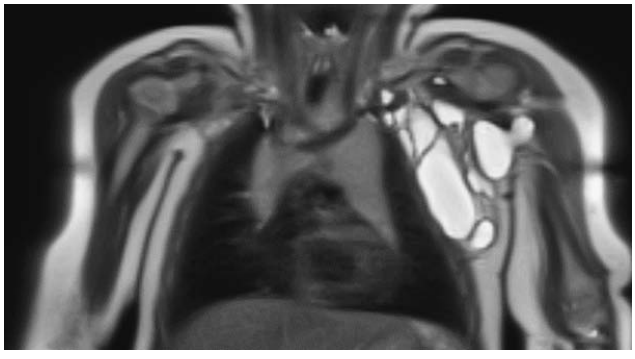
LM mogu biti dio kliničke slike genetskih sindroma kao što su kromosomopatije Down ili Turner te RAS-opatija Noonan (27). LM se mogu javiti i u sklopu sindroma pojačanog rasta (eng. *tzv. „overgrowth syndrome"*) kao što su primjerice Proteus, CLOVES, ili Klippel – Trenaunay (13).

DIJAGNOSTIKA

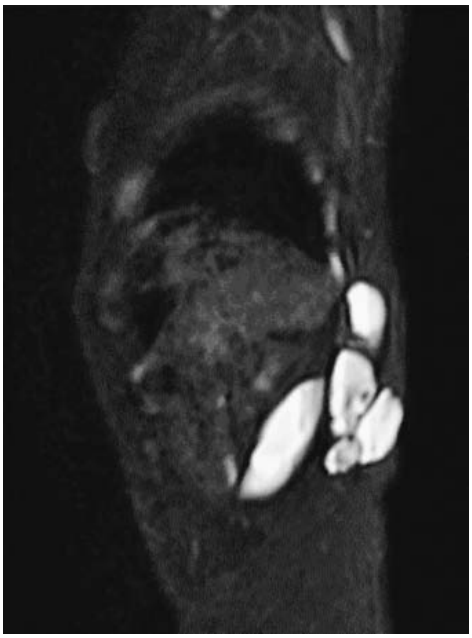
Dijagnoza opsežnih LM cervikofacijalne lokalizacije se može postaviti na prijelazu iz drugog u treći trimestar trudnoće pomoću ultrazvuka (9). U daljnjem rasvijetljavanju dijagnoze može pomoći i fetalna magnetna rezonanca (MR) (28). Ultrazvučno, makrocistične malformacije izgledaju kao kompresibilne, anehogene ciste sa tankim septama. Mikrocistične lezije se sastoje od tankih hiperehogenih šupljina



SLIKA 3. **Slika magnetne rezonance koja prikazuje policističnu, dominantno makrocističnu, limfatičku malformaciju koja se širi od parotide do apeksa pluća.**



SLIKA 4. **Slika magnetne rezonance koja prikazuje limfatičku malformaciju lijeve torakalne stijenke i aksile.**



SLIKA 5. **Slika magnetne rezonance koja prikazuje makrocističnu limfatičku malformaciju torakalne i abdominalne stijenke s utiskivanjem u neuralne foramene.**

(29). Na MR-u LM prelaze kroz pojedine slojeve mekih tkiva te daju signal tekućine u svim sekvencama ukoliko se radi o nekompliciranim lezijama (Slike 3.-5.)(29). Može biti prisutna intersticijska mast kao i pojačanje signala u T1 mjernoj slici u području septa. Ukoliko su lezije dominantno mikrocistične, mogu imati formu solidnog tkiva te izgledati kao tumor – teratom, lipoblastom ili rabdomiosarkom (29). Kod sumnje da se radi o kompleksnim LM, potrebno je učiniti MR cijelog tijela budući da postoji veća sklonost nastanku multifokalnih ili anatomski ekstenzivnih lezija (8). Biopsija je rijetko indicirana kod limfatičkih malformacija. Histološki se radi o vaskularnim kanalima obloženima endotelom, ispunjenima tekućinom bogatom proteinima s limfocitima i makrofagima te sa pozitivnim limfatičkim markerima PROX-1 i podoplanin D2-40 (30, 31).

Limfatičke žile eksprimiraju još CD34, LYVE-1 i VEGF-3 (31). Može se provesti i molekularna analiza kako bi se isključila ili potvrdila mutacija PIK3CA gena. Kod Gorham Stoutove bolesti se konvencionalnom radiografijom mogu prikazati destrukcija korteksa i gubitak kosti, prvenstveno kod starije djece ili odraslih pacijenata (8).

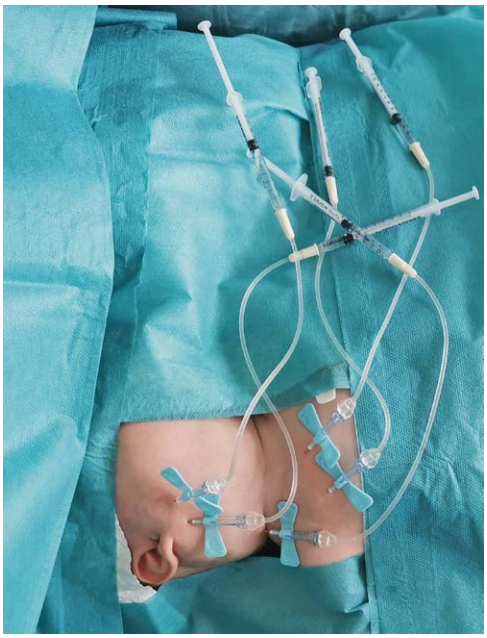
TERAPIJA

Kod limfatičkih malformacija je svrha liječenja očuvati funkcionalnost, izgled, kvalitetu života te spriječiti pogoršanje lokalnog stanja u smislu bolova i ponavljanih epizoda upale (13). S obzirom na to da upalne epizode mogu dovesti do spontane regresije, mali i asimptomatski oblici makrocističnih LM se mogu ekspektativno liječiti (13). Modaliteti liječenja uključuju sklerozaciju, kiruršku resekciju, lasersko i medikamentozno liječenje. Pacijente treba informirati o kroničnoj prirodi bolesti te činjenici da je potrebno produljeno praćenje. U liječenju bi trebao sudjelovati multidisciplinarni tim kada god je to moguće.

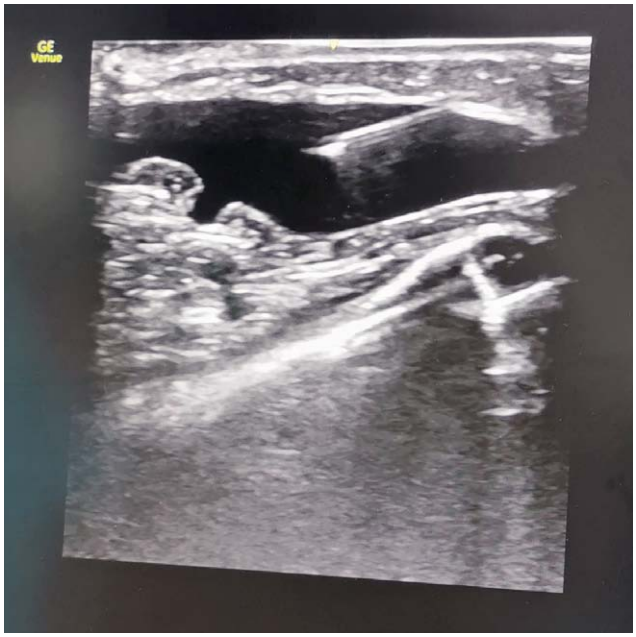
Sklerozacija

Sklerozacija je prva linija liječenja za većinu LM (32). Sklerozacijska sredstva se koriste u monoterapiji a djeluju tako što uzrokuju oštećenje endotela i upalu što dovodi do fibroze i obliteracije cista (33, 34). Provodi se tako što se najprije ciste aspiriraju, a potom se ispune sklerozacijskim sredstvom (30-50% aspiriranog volumena) (Slika 6.) (13). Sklerozacije se u dječjoj dobi uvijek provode u općoj anesteziji a pacijenti sa LM cervikofacijalne lokalizacije moraju biti intubirani. Kod opsežnih LM te kod LM retrobulbarne lokalizacije preporuča se primjena antiedematozne terapije (deksametazon) kako bi se smanjio nastanak otekline i boli poslije terapijskog postupka (29). Injiciranje se provodi pod kontrolom UZV-a (Slika 7). Ciste najčešće ne komuniciraju te je stoga potrebno više mjesta primjene za potpuni učinak. Treba voditi računa o tome da postoje vensko-limfatičke malformacije te da može doći do ulaska sklerozacijskog sredstva u venski optok (29). Isto tako treba paziti i na boju nadležeće kože a u slučaju pojave kožne diskoloracije je potrebno prekinuti tretman te primijeniti hladnu fiziološku otopinu kako bi se poticanjem površinske vazokonstrikcije smanjio rizik od nekroze nadležeće kože (29). Učinak se procijenjuje nakon 4-6 tjedana a ponekad su potrebne višekratne sklerozacije (34). Samo fokalne lezije pokazuju potpunu involuciju nakon jedne primjene te je u prosjeku potrebno 2-3 primjene kako bi se dobio adekvatan klinički rezultat (29). Razmak između pojedinih sklerozacija bi trebao biti između 3-6 mjeseci (13).

U meta analizi iz 2020., *De Maria i sur.* navode kako je kompletno izlječenje kod svih oblika LM bilo moguće kod 340 od 692 (50,5%) pacijenata tretiranih sklerozacijom. Makroskopske malformacije su kompletno izliječene u 53,1% slučajeva, mikrocistične u 35,1% a miješane u 31,1%. Doksiciklin se pokazao kao sklerozacijsko sredstvo s najvećom učinkovitošću (u 63,4% slučajeva potpuno izliječenje). Trajne nuspojave, bez obzira na vrstu sklerozacijskog sredstva su zabilježene u 1,2% slučajeva – 2 pacijenta su razvili parezu facijalnog živca a 4 pacijenta Hornerov sindrom. Ipak, uslijed terapije doksiciklinom su se trajne nuspojave javile u 5,9% slučajeva dok kod drugih sklerozacijskih sredstava nisu utvrđene trajne nuspojave (35). Učestalost prolaznih lokalnih komplikacija bila je 16% a najčešće zabilježene komplikacije su bile (prema padajućoj učestalosti) oteklina, upala, tranzitorna površinska nekroza, hematom, tranzitorne neu-



SLIKA 6. **Aplikacija sklerozacijskog sredstva u područje makrocistične limfatičke malformacije u području vrata kod 3-mjesečnog djeteta.**



SLIKA 7. **Ultrazvučna slika koja prikazuje aspiracijsku iglu u makrocističnoj limfatičkoj malformaciji.**

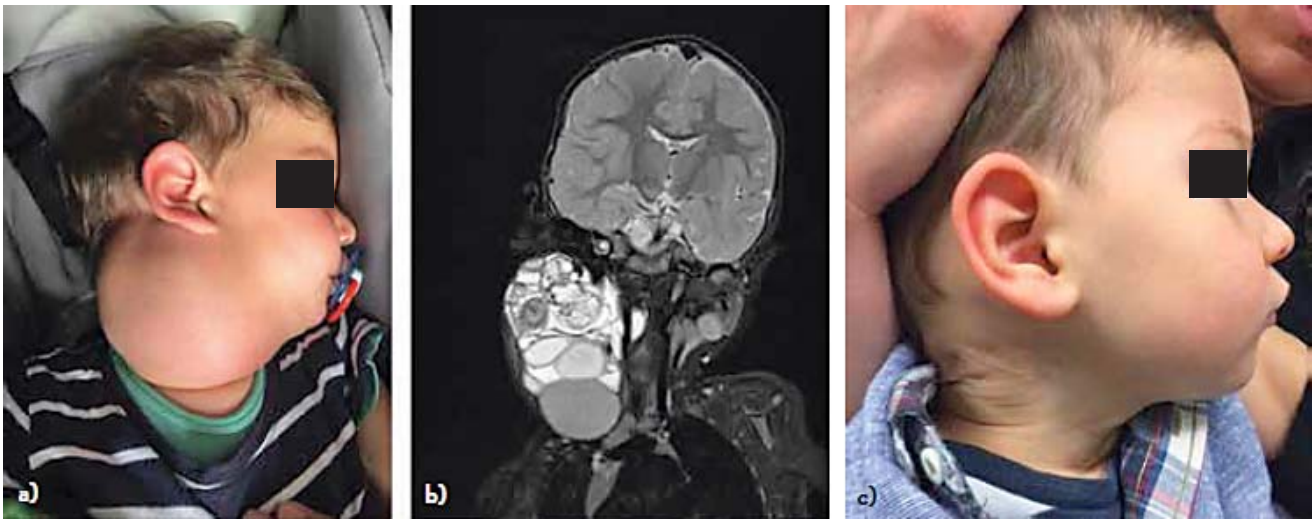
rološke komplikacije i bol. Prolazne komplikacije najčešće su zabilježene nakon korištenja bleomicina (43,9%). Kao sistemske nuspojave su najčešće zabilježeni febrilitet, metabolička acidoza, hemolitička anemija i hipotenzija i to najčešće kod OK-432 agensa (35). Istraživači zaključuju kako doksiciklin ima najveću stopu potpunog i djelomičnog terapijskog uspjeha ali i najvišu stopu trajnih nuspojava te drugu po učestalosti stopu sistemskih nuspojava u usporedbi sa ostalim agensima (35). Kao moguće nuspojave doksiciklina se spominju hipoglikemija i metabolička acidoza kod novorođenčadi (29). Natrijev tetradecil sulfat (eng. STS) je sklerozans koji se koristi kod makrocističnih malformacija a prednost mu je što uzrokuje manju oteklinu te nije neurolitičan (29). Bleomicin je antineoplastični lijek koji nakon sklerozacije uzrokuje manje izraženu upalnu rekaciju i edem mekih tkiva te je kao takav pogodan za anatomski osjetljive regije kao što su orbita, dišni putevi ili usna šupljina. Kao moguća komplikacija spominje se plućna fibroza no tek kod više od 400 internacionalnih jedinica doze za života što je značajno manje nego što se koristi u procesu sklerozacije (29). Ukoliko nema opstrukcije dišnih puteva, kod neonatalnih cervikofacijalnih oblika LM sklerozacija se smatra prvom linijom terapije. Li i sur. opisuju kako je sklerozacija bleomicinom u sklopu EXIT postupka dala vrlo dobre rezultate i u 3 slučaja intrauterino verificiranih cervikalnih LM kod kojih su bili prisutni znaci prijeteće opstrukcije dišnih puteva (17).

Kirurško liječenje

Postulati u kirurškom liječenju koje je 2000. definirao *Mulliken* vrijede i danas – fokus na jednoj anatomskoj regiji, kod rizika od velikog gubitka krvi planirati uklanjanje u više koraka, precizna preparacija uz očuvanje vaskularnih i neuralnih struktura te postavljanje drena (Slika 8.) (36). Ipak kod mikrocističnih i mješovitih oblika je kompletno kirurško liječenje najčešće nemoguće zbog brojnih infiltratitvnih lezija (37) te je u pravilu kirurško liječenje druga linija terapije. Vaskularizirani transfer limfnih čvorova se spominje kao jedan od modaliteta terapije kod sekundarnog limfedema a smatra se da do pozitivnog učinka dolazi ili zbog toga što limfni čvorovi potiču limfangiogenezu ili zato što djeluju kao limfna crpka (38-40).

Medikamentozno liječenje

Sirolimus (rapamicin) je lijek koji je široko poznat kao imunosupresivni agens koji se koristi u prevenciji odbacivanja transplantiranih solidnih organa. Unazad više od 10 godina koristi se i u liječenju LM(41-48), a djeluje na način da inhibira limfangiogenezu time što onemogućava PI3K/AKT/ mTOR signalni put. Veliki je broj studija pokazao njegovu učinkovitost u smislu da smanjuje volumen LM te olakšava simptome (bol, krvarenje, limforeja). Prvi slučaj uspješno liječenog pacijenta objavljen je 2011. godine (49). Pri terapiji sirolimusom nikada ne dolazi do potpune regresije tvorbe a učinak je u pravilu odgođen od 2 tjedna do 6 mjeseci od početka terapije (44). Nije precizno definirano koliko je dugo potrebno provoditi terapiju. Lijek se primjenjuje oralnim putem, a najčešća početna doza je 0,8 mg/m^2 po dozi, dva puta dnevno,



SLIKA 8. **a) Limfatička malformacija desne strane vrata preoperativno; b) Slika magnetne rezonance; c) Ishod nakon kirurškog uklanjanja malformacije**

u razmaku od 12 sati. Ciljna koncentracija lijeka u krvi varira između pojedinih studija, pri čemu se najčešće koriste koncentracije od 10-15 ng/ml i 5-15 ng/ml (50).

U sistematskom pregledu *Saibene i sur.* je pokazano kako je kod makrocističnih LM u 96% slučajeva zabilježen odgovor na terapiju, u 82% kod mikrocističnih i 84% kod mješovitih. Kao najčešće nuspojave se spominju ulceracije usne šupljine i respiratorne infekcije (6). Druge studije govore o hiperlipidemiji, neutropeniji i celulitisu kao najčešćim nuspojavama (50). U nekoliko studija je primjenjivan sulfametoksazol-trimetoprim kao prevencija *Pneumocystis jirovecii* pneumonije. Sirolimus se pokazao učinkovitim kod orbitalnih LM (51) a ima svoje mjesto i u liječenju sistemskih bolesti kao što je GLA (43). *Kwon i sur.* opisuju dobar učinak sirolimusa i kod intestinalnih limfangiektazija te predlažu da se koristi kao prva linija terapije (52).

Propranolol se nije pokazao učinkovitim kod LM (53, 54). Učinkovitost sildenafila je pokazalo nekoliko manjih serija, no bez čvrstih dokaza (34, 55). Alpelisib je inhibitor kinaze koji cilja PIK3 signalni put, no njegova se učinkovitost tek testira u kliničkim studijama (Venot). Bevacizumab je rekombinantno humanizirano monoklonsko antitijelo koje blokira angiogenezu inhibicijom VEGF-A, a za koje još uvijek ne postoje dovoljno čvrsti dokazi za primjenu u liječenju LM (34).

Pojedini autori opisuju kako u slučaju divovskih oblika LM, kombinacija medikamentozne terapije (sirolimus) s jednom ili više sklerozacija može omogućiti dobar ishod (56).

Mikrocistični i mješoviti oblik LM su najteži oblici za liječenje zato što pokazuju infiltrativni rast. Medikamentozna terapija sirolimusom je najučinkovitija u smislu ograničavanja simptoma a liječenje je potrebno započeti u ranom djetinjstvu kako bi se spriječio prekomjerni rast LM (13).

Sindromske LM mogu biti vrlo izazovne za liječenje jer zahtijevaju kombinirano liječenje - sklerozacije, kirurške resekcije, antikoagulantnu terapiju kod venskih abnormalnosti s trombozom, metode fizikalne terapije te, u sve većoj mjeri, sirolimus (57, 58).

Lasersko liječenje

CO2 laser ima primjenu u liječenju površinskih limfangiektazija.

Radiofrekventna ablacija se koristi kod mikrocističnih malformacija u koje je teško prodrijeti sklerozacijskim sredstvom ili kod submukoznih lezija (59).

Fizikalna terapija

Kompresivna odjeća i limfna drenaža se mogu smatrati metodama fizikalne terapije u liječenju limfatičkih malformacija. Kompresivna odjeća nije učinkovita u smanjenju simptoma kod LM (60). Manuelna limfatička drenaža isto tako nije učinkovita u redukciji LM ali može poboljšati kvalitetu života kod oboljelih pojedinaca (13).

ZAKLJUČCI

- Po ISSVA klasifikaciji iz 2015. se napušta termin limfangiom i uvodi se termin limfatičke malformacije
- Svrha liječenja nije kompletno uklanjanje tvorbe, već ograničavanje simptoma u mjeri kojom bi se očuvala funkcionalnost i omogućio primjeren izgled
- Kod ultrazvučno postavljene sumnje da je intrauterino prisutna limfatička malformacija, fetalni MR je metoda izbora u svrhu razjašnjavanja dijagnoze

– Kada nema životno ugrožavajuće opstrukcije dišnih puteva, sklerozacija je metoda izbora
– Bleomicin kao sklerozacijsko sredstvo omogućava dobre rezultate uz blage nuspojave
– Terapija sirolimusom u velikom postotku omogućava redukciju tvorbe, ali je važno pratiti moguće nuspojave

Kratice:

LM – limfatička malformacija
GLA – generalizirana limfatička anomalija
KL – kaposiformna limfangiomatoza
CKLA – centralna konduktivna limfatička anomalija
UZV – ultrazvuk
EXIT – ex utero intrapartum treatment
MR – magnetna rezonanca

LITERATURA

1. Stone OA, Stainier DYR. Paraxial mesoderm is the major source of lymphatic endothelium. Dev Cell. 2019;50:247-55. https://doi.org/10.1016/j.bjps.2015.10.045
2. Sjogren PP, Arnold RW, Skirko JR, Grimmer JF. Anatomic distribution of cervicofacial lymphatic malformations based on lymph node groups. Int J Pediatr Otorhinolaryngol. 2017;97:72–5. https://doi.org/10.1016/j.ijporl.2017.02.030
3. Wiegand S, Eivazi B, Barth PJ et al. Pathogenesis of lymphangiomas. Virchows Arch. 2008;453:1–8.
4. Hogeling M, Adams S, Law J, Wargon O. Lymphatic malformations: clinical course and management in 64 cases. Australas J Dermatol. 2011;52:186–90. https://doi.org/10.1111/j.1440-0960.2011.00777.x
5. MacArthur CJ- Head and neck hemangiomas of infancy. Curr Opin Otolaryngol Head Neck Surg2006; 14:397–405. https://doi. org/10.1097/moo.0b013e328010ba6b
6. Saibene AM, Rosso C, Felisati G et al. Sirolimus treatment for paediatric head and neck lymphatic malformations: a systematic review. Eur Arch Oto Rhin Laryng 2023; 280:3529-40.
7. Wassef M, Blei F, Adams D et al. Vascular anomalies classification: recommendations from the international society for the study of vascular anomalies. Pediatrics. 2015;136:e203–14. https://doi.org/10.1542/peds.2014-3673
8. Snyder EJ, Sarma A, Borst AJ, Tekes A. Lymphatic anomalies in children: update on imaging diagnosis, genetics, and treatment. Am J Roentgen. 2022;218(6):1089-101. https://doi.org/10.2214/AJR.21.2720
9. Bagrodia N, Defnet AM, Kandel JJ. Management of lymphatic malformations in children. Curr Opin Pediatr 2015;27:356-363. 10.1097/MOP.0000000000000209
10. Petkova M, Kraft M, Stritt S et al. Immune-interacting lymphatic endothelial subtype at capillary terminals drives lym phatic malformation. J Exp Med 2023;220(4):e20220741. https://doi.org/ 10.1084/jem.20220741
11. Kulungowski AM, Patel M. Lymphatic malformations. Inseminars in pediatric surgery 2020; 29(5):150971. https://doi.org/10.1016/j.sempedsurg.2020.150971
12. Hassanein AH, Mulliken JB, Fishman SJ, Quatrano NA, Zurakowski D, Greene AK. Lymphatic malformation: risk of progression during childhood and adolescence. J Craniofac Surg. 2012;23(1):149-52. 10.1097/SCS.0b013e3182413ea8
13. Leboulanger N, Bisdorff A, Boccara O et al. French national diagnosis and care protocol (PNDS, protocole national de diagnostic et de soins): cystic lymphatic malformations. Orphanet Journal of Rare Diseases 2023;18:10. https://doi.org/10.1186/s13023-022-02608-y
14. Phang MJ, Courtemanche DJ, Bucevska M, Malic C, Arneja JS. Spontaneously resolved macrocystic lymphatic malformations: predictive variables and outcomes. Plast Surg. 2017;25:27–31. https://doi.org/10.1177/2292550317693815
15. Perkins JA, Maniglia C, Magit A, Sidhu M, Manning SC, Chen EY. Clinical and radiographic findings in children with spontaneous lymphatic mal formation regression. Otolaryngol Head Neck Surg. 2008;138:772–7. https://doi.org/10.1016/j.otohns.2008.02.016
16. Laje P, Peranteau WH, Hedrick HL et al. Ex utero intrapartum treatment (EXIT) in the management of cervi cal lymphatic malformation. J Pediatr Surg. 2015;50:311–4. https://doi.org/10.1016/j.jpedsurg.2014.11.024
17. Li JL, Wu HY, Zhong W, Liu JR, Chen KS, Fang Q. Treatment and prognosis of fetal lymphangioma. Eur J Obstr Gyn Reprod Biol 2018;231:268-73. https://doi.org/10.1016/j.ejogrb.2018.10.018
18. Rahbar R, Vogel A, Myers LB, et al. Fetal surgery in otolaryngology: a new era in the diagnosis and management of fetal airway obstruction because of advances in prenatal imaging. Arch Otolaryngol Head Neck Surg. 2005;131(5):393-8. 10.1001/archotol.131.5.393
19. Colletti G, Biglioli F, Poli T, et al. Vascular malformations of the orbit (lymphatic, venous, arteriovenous): Diagnosis, management and results. J Craniomaxillofac Surg. 2019;47(5):726-40. https://doi.org/10.1016/j.jcms.2018.09.009
20. Shoji MK, Shishido S, Freitag SK. The use of sirolimus for treatment of orbital lymphatic malformations: a systematic review. Ophthal Plast Reconstr Surg. 2020;36:215–21. 10.1097/IOP.0000000000001518
21. Taghinia AH, Upton J, Trenor CC, et al. Lymphaticovenous bypass of the thoracic duct for the treatment of chylous leak in central conducting lymphatic anomalies. J Pediatr Surg. 2019;54(3):562-8. https://doi.org/10.1016/j.jpedsurg.2018.08.056
22. Pichler Sekulic S, Sekulic M. Primary cardiac and pericardial lymphangiomas: clinical, radiologic, and pathologic characterization derived from an institutional series and review of the literature. Virchows Archiv. 2022;480(6):1211-21.
23. Fevurly RD, Fishman SJ. Vascular anomalies in pediatrics. Surg Clin North Am 2012; 92:769–800. https://doi.org/10.1016/j.suc.2012.03.016
24. Alvarez OA, Kjellin I, Zuppan CW. Thoracic lymphangiomatosis in a child. J Pediatr Hematol Oncol. 2004;26(2):136–41.
25. Kwag E, Shim SS, Kim Y, Chang JH, Kim KC. CT features of generalized lymphangiomatosis in adult patients. Clin Imaging. 2013;37(4):723–7. https://doi.org/10.1016/j.clinimag.2012.12.003
26. Adams DM, Trenor CC, Hammill AM, et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. Pediatrics. 2016;137(2):e20153257. https://doi.org/10.1542/peds.2015-3257
27. Brouillard P, Boon L, Vikkula M. Genetics of lymphatic anomalies. J Clin Invest. 2014;124:898–904. 10.1172/JCI71614
28. Koelblinger C, Herold C, NemecS,etal. Fetal magnetic resonance imaging of lymphangiomas. J Perinat Med 2013; 41:437–43. https://doi.org/10.1515/jpm-2012-0226
29. Acord M, Srinivasan AS, Cahill AM. Percutaneous treatment of lymphatic malformations. Techniques in Vascular and Interventional Radiology. 2016 Dec 1;19(4):305-11. http://dx.doi.org/10.1053/j.tvir.2016.10.001
30. Bruder E, Perez-Atayde AR, Jundt G, et al. Vascular lesions of bone in children, adolescents, and young adults. A clinicopathologic reappraisal and application of the ISSVA classification. Virchows Arch. 2009;454(2):161-79.
31. Merrow AC, Gupta A, Patel MN, Adams DM. 2014 Revised Classification of Vascular Lesions from the International Society for the Study of Vascular Anomalies: Radiologic Pathologic Update. Radiographics. 2016;36(5):1494-516. https://doi.org/10.1148/rg.2016150197
32. Horbach SER, Lokhorst MM, Saeed P, De Goüyon Matignon De Pontouraude CMF, Rothová A, Van Der Horst CMAM. Sclerotherapy for low-flow vascular malformations of the head and neck: A systematic review of sclerosing agents. J Plast Reconstr Aesthetic Surg. 2016;69:295–304. https://doi.org/10.1016/j.bjps.2015.10.045

33. Heit JJ, Do HM, Prestigiacomo CJ et al. Guidelines and parameters: percutaneous sclerotherapy for the treatment of head and neck venous and lymphatic malformations. J Neurointerv Surg. 2017;9:611–7. https://doi.org/10.1136/neurintsurg-2015-012255
34. Lam SC, Yuen HKL. Medical and sclerosing agents in the treatment of orbital lymphatic malformations: what's new? Curr Opin Ophthalmol. 2019;30:380–5. 10.1097/ICU.0000000000000585
35. De Maria L, De Sanctis P, Balakrishnan K, Tollefson M, Brinjikji W. Sclerotherapy for lymphatic malformations of head and neck: Systematic review and meta-analysis. J Vasc Surg 2020;8(1):154-64. https://doi.org/10.1016/j.jvsv.2019.09.007
36. Mulliken JB, Fishman SJ, Burrows PE Vascular anomalies. Curr Prob Surg 2000; 37:517–84.
37. Schreiber A, Soupre V, Kadlub N et al. Does surgery of lymphatic malformations lead to an increase in superficial lymphangiectasia? A retrospective study of 43 patients. Br J Dermatol. 2019;181:1324–5. https://doi.org/10.1111/bjd.18236
38. Raju A, Chang DW. Vascularized lymph node transfer for treatment of lymphedema: a comprehensive literature review. Ann Surg 2015 May 1;261(5):1013-23. 10.1097/SLA.0000000000000763
39. Becker C, Vasile JV, Levine JL et al. Microlymphatic surgery for the treatment of iatrogenic lymphedema. Clin Plast Surg 2012; 39:385 98. https://doi.org/10.1016/j.cps.2012.08.002
40. Lin CH, Ali R, Chen SC, et al. Vascularized groin lymph node transfer using the wrist as a recipient site for management of postmastectomy upper extremity lymphedema. Plast Reconstr Surg 2009; 123:1265-75. 10.1097/PRS.0b013e31819e6529
41. Parker VER, Keppler-Noreuil KM, Faivre L et al. Safety and efficacy of low-dose sirolimus in the PIK3CA-related overgrowth spectrum. Genet Med. 2019;21(5):1189–98. https://doi.org/10.1038/s41436-018-0297-9
42. Strychowsky JE, Rahbar R, O'Hare MJ, Irace AL, Padua H, Trenor CC. Siroli mus as treatment for 19 patients with refractory cervicofacial lymphatic malformation. Laryngoscope. 2018;128:269–76. https://doi.org/10.1002/lary.26780
43. Adams DM, Trenor CC, Hammill AM et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. Pediatrics. 2016;137(2): e20153257. https://doi.org/10.1542/peds.2015-3257
44. Nadal M, Giraudeau B, Tavernier E, Jonville-Bera AP, Lorette G, Maruani A. Efficacy and safety of mammalian target of rapamycin inhibitors in vascu lar anomalies: a systematic review. Acta Derm Venereol. 2016;96:448–52. 10.2340/00015555-2300
45. Mizuno T, Fukuda T, Emoto C et al. Developmental pharmacokinetics of sirolimus: Implications for precision dosing in neonates and infants with complicated vascular anomalies. Pediatr Blood Cancer. 2017 ;64(8):e26470. https://doi.org/10.1002/pbc.26470
46. Freixo C, Ferreira V, Martins J et al. Efficacy and safety of sirolimus in the treatment of vascular anomalies: a systematic review. J Vasc Surg. 2020;71:318–27. https://doi.org/10.1016/j.jvs.2019.06.217
47. Triana P, Miguel M, Díaz M, Cabrera M, López Gutiérrez JC. Oral sirolimus: An option in the management of neonates with life-threatening upper airway lymphatic malformations. Lymphat Res Biol. 2019;17:504–11. https://doi.org/10.1089/lrb.2018.0068
48. Maruani A, Tavernier E, Boccara O et al. Sirolimus (rapamycin) for slow-flow malformations in children: the observational-phase randomized clinical performus trial. JAMA Dermatol. 2021;157:1289–98. 10.1001/jamadermatol.2021.3459
49. Reinglas J, Ramphal R, Bromwich M. The successful man agement of diffuse lymphangiomatosis using sirolimus: a case report. Laryngoscope 2011;121:1851–1854. https:// doi. org/ 10. 1002/ lary.21927
50. Wiegand S, Dietz A, Wichmann G. Efficacy of sirolimus in children with lymphatic malformations of the head and neck. Eur Arch Oto Rhin Laryng 2022;279:3801-10.
51. Shoji MK, Shishido S, Freitag SK. The use of sirolimus for treatment of orbital lymphatic malformations: a systematic review. Ophthalmic Plast Reconstr Surg 2020;36:215–21. 10.1097/IOP.0000000000001518
52. Kwon Y, Kim ES, Choe YH, Kim MJ. Individual approach for treatment of primary intestinal lymphangiectasia in children: single-center experience and review of the literature. BMC pediatrics. 2021;21:1-9.
53. Leboulanger N, Garel C, Borde ITIT, Garabedian L, Denoyelle F. Propranolol therapy for hemorrhagic lymphangioma of the tongue. Arch Otolaryngol Head Neck Surg. 2011;137:813–5. 10.1001/archoto.2011.70
54. Maruani A, Brown S, Lorette G, Pondaven-Letourmy S, Herbreteau D, Eisenbaum A. Lack of effect of propranolol in the treatment of lym phangioma in two children. Pediatr Dermatol. 2013;30:383–5. https://doi.org/10.1111/j.1525-1470.2012.01864.x
55. Wang S, Zhang J, Ge W, et al. Efficacy and safety of oral sildenafil in treatment of pediatric head and neck lymphatic malfor mations. Acta Otolaryngol. 2017;137:674–8. https://doi.org/10.1080/00016489.2016.1272135
56. Meurisse V, Denamur S, Herbreteau D et al. Efficacy of sirolimus combined with sclerotherapy for giant cervical lymphatic macrocystic malformations: two newborn cases. Eur J Dermatol. 2019;29:90–1. 10.1684/ejd.2018.3441
57. Rodriguez-Laguna L, Ibañez K, Gordo G, Garcia-Minaur S, Santos-Simarro F, Agra N, et al. CLAPO syndrome: identification of somatic activating PIK3CA mutations and delineation of the natural history and phenotype. Genet Med. 2018;20:882–9. https://doi.org/10.1038/gim.2017.200
58. Vahidnezhad H, Youssefian L, Uitto J. Molecular genetics of the PI3K AKT-mTOR pathway in genodermatoses: diagnostic implications and treatment opportunities. J Invest Dermatol. 2016;136:15–23. https://doi.org/10.1038/JID.2015.331
59. Grimmer JF, Mulliken JB, Burrows PE et al. Radiofrequency ablation of microcystic lymphatic malformation in the oral cavity. Arch Otolaryngol Head Neck Surg. 2006;132(11):1251-56. 10.1001/archotol.132.11.1251
60. Langbroek GB, Horbach SER, van der Vleuten CJM, Ubbink DT, van der Horst CMAM. Compression therapy for congenital low-flow vascular malformations of the extremities: a systematic review. Phlebology. 2018;33:5–13. https://doi.org/10.1177/0268355516684694

SUMMARY

Lymphatic malformations

Rok Kralj, Danijel Cvetko, Ana Tripalo Batoš, Tomislav Baudoin, Elvira Kereković, Nada Rajačić, Jasminka Stepan Giljević, Stjepan Višnjić

Lymphatic malformations are abnormal cystic dilatations of lymphatic vessels. They are present at birth, but often can only be detected later in life. Simple lymphatic malformations are limited to certain anatomical regions, while complex diffuse abnormalities can affect the entire organism. Simple lymphatic malformations are divided into macrocystic (cysts >1cm) and microcystic (cysts <1cm). According to the ISSVA classification from 2015, the term lymphangioma is abandoned and the term lymphatic malformation is introduced, which is intended to clearly indicate that it is not a tumor formation. The clinical course is characterized by long asymptomatic periods with short-term inflammatory or infectious episodes and episodes of intracystic bleeding. In the case of voluminous changes, the diagnosis can be made at the transition from the second to the third trimester of pregnancy by ultrasound examination or fetal magnetic resonance. Ultrasound and magnetic resonance imaging are diagnostic methods of choice in the postpartum period as well. The purpose of the treatment is not to completely remove the formation, but to limit the symptoms to the extent that would preserve functionality and provide an appropriate appearance. Treatment methods are the expectant method for asymptomatic disease, sclerotherapy, surgical resection, drug treatment, laser treatment and physical therapy measures. When there is no life-threatening airway obstruction, sclerosing is the method of choice. Bleomycin as a sclerosant provides good results with mild side effects. Therapy with rapamycin (sirolimus) allows for a large percentage of reduction in formation, but it is important to monitor possible side effects.

Key words: LYMPHATIC MALFORMATIONS; LYMPHANGIOMA; CHILDREN; SCLEROTHERAPY; RAPAMICIN; SIROLIMUS