

MEDICINSKI GLASNIK

Official publication of the Medical Association of Zenica-Doboj Canton, Bosnia and Herzegovina
Volume 20, Number 1, February 2023.

ISSN 1840-0132

MEDICINSKI GLASNIK

Published and copyright by: Medical Assotiation of Zenica-Doboj Canton; Address: Zenica, 72000,
Bulevar kralja Tvrtka I 4, Bosnia and Herzegovina;

tel./fax: +387 32 444 270; Email: ljkozedo@bih.net.ba, medicinskiglasnik@gmail.com,

web site: <http://www.ljkozedo.ba>

For ordering information please contact: Jasenko Žilo, ljkozedo@bih.net.ba; Access to this journal is
available free online trough: www.ljkozedo.ba

The Journal is indexed by MEDLINE, EMBASE (Exerpta Medica), Scopus, EBSCO; ISSN 1840-0132

DTP by: Graphic and web design studio "B Panel" Zenica, Zmaja od Bosne bb,
www.bpanel.ba, e-mail: info@bpanel.ba, tel. +387 32 441 291;

Printed by:

MINEX TRADE d.o.o., Marjanovića put 78, 72000 Zenica, Bosna i Hercegovina

Medicinski Glasnik

Official Publication of the Medical Association of
Zenica-Doboj Canton
Bosnia and Herzegovina

EDITOR-IN-CHIEF

Selma Uzunović, *Zenica, Bosnia and Herzegovina*

DEPUTY EDITOR

Besim Prnjavorac, *Tešanj, Bosnia and Herzegovina*

RESEARCH INTEGRITY EDITOR

Larisa Gavran, *Zenica, Bosnia and Herzegovina*

MANAGING EDITOR

Tarik Kapidžić, *Zenica, Bosnia and Herzegovina*

EDITORS

Solmaz Abdolrahimzadeh, *University of Rome "Sapienza", Rome, Italy*
Luiz Ronaldo Alberti, *Federal University of Minas Gerais, Belo Horizonte Brazil*
Mutay Aslan, *Akdeniz University, Antalya Turkey*
Adem Balić, Adem Balić, *IVF Center "Dr Balić", Tuzla, Bosnia and Herzegovina*
Dubraka Bartolek, *Clinical Hospital "Merkur", Zagreb, Croatia*
Branka Bedenić, *Clinical Hospital Centre, Zagreb, Croatia*
Iva Christova, *National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria*
Asja Čelebić, *University of Zagreb, Zagreb, Croatia*
Josip Čulig, *"Andrija Štampar" Teaching Institute of Public Health, Zagreb, Croatia*
Filip Čulo, *University of Mostar, Mostar Bosnia and Herzegovina*
Jordan Dimanovski, *Clinical Hospital "Sestre milosrdnice", Zagreb, Croatia*
Branko Dmitrović, *Clinical Hospital, Osijek, Croatia*
Davorin Đanić, *General Hospital "Dr. Josip Benčević", Slavonski Brod, Croatia*
Ines Drenjančević, *University of Osijek, Osijek, Croatia*
Harun Drljević, *Cantonal Hospital, Zenica, Bosnia and Herzegovina*
Mukaddes Esrefoglu, *Bezmialem Vakıf University, Istanbul, Turkey*
Ivan Fističić, *Institute for Women's Health, Zagreb, Croatia*
Roberta Granese, *University Hospital "G. Martino", Messina, Italy*
Simona Gurzu, *University of Medicine and Pharmacy, Tîrgu Mureș, Romania*
Diane Medved Harper, *University of Louisville, Louisville, United States of America*
Lejla Ibrahimagić-Šeper, *Health Centre, Zenica, Bosnia and Herzegovina*
Tatjana Ille, *Gulf Medical University, Ajman, United Arab Emirates*
Slobodan M. Janković, *University of Kragujevac, Kragujevac, Serbia*
Vjekoslav Jerolimov, *University of Zagreb, Zagreb, Croatia*
Ioan Jung, *University of Medicine and Pharmacy, Tîrgu Mureș, Romania*
David Kovacevic, *Yale University, New Haven, United States of America*
Sven Kurbel, *University of Osijek, Osijek, Croatia*
Robert Lovrić, *University of Osijek, Osijek, Croatia*
Snježana Pejičić, *Clinical Hospital Centre, Banja Luka, Bosnia and Herzegovina*
Belma Pojskić, *Cantonal Hospital, Zenica, Bosnia and Herzegovina*
Asja Prohić, *Clinical University Centre, Sarajevo, Sarajevo, Bosnia and Herzegovina*
Velimir Profozić, *Polyclinic "Dr. Zora Profozić", Zagreb, Croatia*
Amira Redžić, *University Sarajevo, Sarajevo, Bosnia and Herzegovina*
Halima Resić, *Clinical Center, University of Sarajevo, Sarajevo, Bosnia and Herzegovina*
Suad Sivić, *Institute for Health and Food Safety, Zenica, Bosnia and Herzegovina*
Sonja Smole-Možina, *University of Ljubljana, Ljubljana, Slovenia*
Vladimir Šimunović, *University of Mostar, Mostar, Bosnia and Herzegovina*
Ekaterine Tskitishvili, *University of Liege, Liege, Belgium*
Aylin Türel Ermertcan, *Celal Bayar University, Manisa, Turkey*
Adrijana Vince, *Infectious Diseases Clinic "Dr. Fran Mihaljević", Zagreb, Croatia*
Jasmina Vraneš, *Andrija Štampar Teaching Institute of Public Health, Zagreb, Croatia*

EDITORIAL ASSISTANT

Hakija Bečulić, *Zenica, Bosnia and Herzegovina*

Secretary: Jasenko Žilo

Proofreader: Glorija Alić (English)

MEDICINSKI GLASNIK

Official Publication of the Medical Association of Zenica-Doboj Canton, Bosnia and Herzegovina

Volume 20, Number 1, February 2023

Free full-text online at: www.ljkzedo.com.ba, and www.doaj.org (DOAJ, Directory of Open Access Journals)

Original article	Comparative analysis of the effects of dalteparin and reviparin on perioperative blood loss in patients with extracapsular hip fractures treated with intramedullary nailing	1
	Mirza Sivo, Faruk Lazović, Đemil Omerović, Tarik Kapidžić, Adnan Papović, Mirza Omerčević, Harun Selimović	
	Comparison of dexmedetomidine alone or with other sedatives for paediatric sedation during magnetic resonance imaging: a systematic review	7
	Rudy Vitraludyono, Arie Utariani, Elizeus Hanindito	
	Clitorea ternatea flower extract induces platelet-derived growth factor (PDGF) and GPx gene overexpression in ultraviolet (UV) B irradiation-induced collagen loss	15
	Rizka Sofyanti Putri, Agung Putra, Chodidjah, Dewi Masyitah Darlan, Setyo Trisnadi, Siti Thomas, Nur Dina Amalina, Rizky Candra Irawan	
	Relation between thyroid hormonal status, neutrophil-lymphocyte ratio and left ventricular systolic function in patients with acute coronary syndrome	22
	Mirela Halilčević, Edin Begić, Amela Džubur, Alen Džubur, Buena Aziri, Azra Durak-Nalbantić, Alden Begić, Ammar Brkić, Ena Gogić, Orhan Lepara	
	Trends in stroke thrombolysis rate in Bosnia and Herzegovina: a hospital-based observation study	28
	Marija Bender, Stjepan Čović, Matea Baranik, Sandra Lakičević, Inge Klupka-Sarić	
	Can laboratory and clinical parameters predict the occurrence of acute arterial occlusion in COVID-19 patients?	32
	Kristian Karlović, Gojko Bogdan, Pejana Rastović, Martin Kajić	
	Minimally invasive mini-thoracotomy access as a surgical method in state-of-the-art treatment of single-vessel coronary heart disease	38
	Edin Kabil, Nermir Granov, Ilirijana Haxibeqiri-Karabdić, Sanja Grabovica, Ermina Mujičić, Slavenka Štraus, Bedrudin Banjanović, Muhamed Djedović	
	Parameters in predicting the risk of a prolonged hospital stay in patients with acute exacerbation of chronic obstructive pulmonary disease: a single-centre experience	45
	Aida Mujaković, Belma Paralića, Besim Prnjavorac, Orhan Lepara, Almir Fajkić, Edin Begić, Avdo Kurtović, Midhat Čizmić, Mirad Odošević	
	Correlation between clinical outcomes and patients' satisfaction using tarsoconjunctival - Hughes flap for the reconstruction of eyelid defects	52
	Nina Jovanović, Patricia Reisz-Majić, Sunita Mehic-Fazlić, Selma Terzić, Jasmina Alajbegović-Halimić, Admir Dizdarević	
	Association of HLA-B27 antigen with clinical and laboratory parameters in patients with juvenile idiopathic arthritis	58
	Adisa Čengić, Velma Selmanović, Snježana Hasanbegović, Nedim Begić, Emina Karčić, Elma Fejzić	
	Outcomes of acute kidney injury in critically ill children who need renal replacement therapy	63
	Danka Pokrajac, Admir Hadžimuratović, Ismeta Kalkan, Emina Hadžimuratović, Verica Mišanović, Duško Anić, Aida Mustajbegović-Pripoljac	
	The relationship between C-reactive protein, anthropometric parameters and lipids in menopausal transition	71
	Dženana Softić, Lejla Mešalić	
	CT advantages of potential use of polymer plastic clips in neurocranium	77
	Samir Delibegović, Mirela Delibegović, Muhamed Katka, Muamer Obhodžaš, Muhamed Ođuz	
	Risk of anterior cruciate ligament injury in population with elevated body mass index	83
	Hasan N. Alsayed, Mohammed Abdulrahman Alkhateeb, Asma Abdulaziz Aldossary, Khalid Mohsen Houbani, Yousef Mohammed Aljamaan, Yousef A. Alrashidi	

Computer-assisted navigation for intramedullary nailing of intertrochanteric femur fractures: a preliminary result	88
Michele Coviello, Francesco Ippolito, Antonella Abate, Giacomo Zavattini, Domenico Zaccari, Andrea Leone, Giovanni Noia, Vincenzo Caiaffa, Giuseppe Maccagnano	
Post-traumatic instability of the first metatarsophalangeal joint: a novel surgical technique of capsular reconstruction in a young kickboxer	95
Gianni Caizzi, Michele Coviello, Andrea Franchini, Flavia Riefoli, Florianna Palmiotto, Biagio Moretti	
Spinal cord stimulation in chronic pain treatment – first experiences in Bosnia and Herzegovina	101
Tatjana Bućma, Ostoja Savić, Tatjana Boškić, Lena Arambašić Topić, Igor Sladojević, Snježana Novaković Bursać	

Medicinski Glasnik is indexed by MEDLINE, EMBASE (Excerpta Medica), EBSCO and Scopus

Comparative analysis of the effects of dalteparin and reviparin on perioperative blood loss in patients with extracapsular hip fractures treated with intramedullary nailing

Mirza Sivo¹, Faruk Lazović², Đemil Omerović², Tarik Kapidžić¹, Adnan Papović², Mirza Omerčević¹, Harun Selimović³

¹Department of Orthopaedics and Traumatology; Canton Hospital Zenica, Zenica, ²Orthopaedics and Traumatology Clinic, Clinical Centre, University of Sarajevo, Sarajevo, ³Department of Cardiology; Canton Hospital Zenica; Bosnia and Herzegovina

ABSTRACT

Aim To determine differences between reviparin and dalteparin treatment in patients with extracapsular hip fractures treated with intramedullary nailing and their effects on perioperative blood loss and early postoperative recovery.

Methods Retrospective comparative study included 68 patients with extracapsular hip fracture who were divided into dalteparin and reviparin group. Medical records were used to obtain demographic data, laboratory parameters, haemoglobin and haematocrit levels, platelet count, mortality rate and medical complications.

Results Out of total 68 patients, 31 were in reviparin and 37 in dalteparin group. Mean age of patients was 70.5 (± 14.4) and 76.8 (± 8.4) years in reviparin and dalteparin group, respectively ($p=0.071$). Median values of haemoglobin levels on the first postoperative day were lower in dalteparin group compared to reviparin group ($p=0.012$). On the first postoperative day haematocrit values were also lower in dalteparin than in reviparin group ($p=0.015$). Both groups showed an increase in platelet count on the first postoperative day, but without significant difference ($p=0.084$). There was no statistically significant difference in intrahospital mortality between the groups (6.4% vs. 2.7%; $p=0.588$). One case of pulmonary embolism was detected in the dalteparin group.

Conclusion Low-molecular-weight heparin is the drug of choice in patients with hip fractures for thromboprophylaxis. Due to non-antithrombin-mediated actions, reviparin and dalteparin could have different effects on perioperative blood loss. Both dalteparin and reviparin are safe and effective agents for thromboprophylaxis in patients with proximal femur fractures.

Key words: anticoagulants, femur, haemorrhage

Corresponding author:

Mirza Sivo

Department of Orthopaedics and Traumatology, Canton Hospital Zenica
Crkvice 67, 72000 Zenica,
Bosnia and Herzegovina

Phone: +387 32 447 401;

Fax: +387 32 226 576;

E-mail: mirzars4@gmail.com

ORCID ID: <https://orcid.org/0000-0003-2986-4470>

Original submission:

10 August 2022;

Revised submission:

30 September 2022;

Accepted:

20 October 2022

doi: 10.17392/1526-22

INTRODUCTION

Proximal femur fractures are the most frequently operated fracture type in orthopaedic surgery. Due to high cost of care and postoperative fatality rate they have raised intense interest globally (1). Mortality rate in the first year after the hip fracture is 30% and has been unchanged throughout the years (2). It is estimated that the number of hip fractures occurring worldwide will double to 2.6 million by the year 2025, and 4.5 million by the year 2050, because of the increase in life expectancy (3).

Extracapsular hip fractures are associated with low-energy trauma in older age patients and high-energy trauma in young patients, resulting in similar fracture patterns. For pertrochanteric fractures minimally invasive osteosynthesis with short intramedullary nail is the treatment of choice and may be associated with shorter operation time and less blood loss (4). This method allows early post-operative weight bearing, which is associated with shorter hospital stay and fewer medical complications (5).

Fractures of the hip and lower extremity have been noted to increase the risk of thrombosis (1). Low-molecular-weight heparin (LMWH) is the drug of choice for thromboprophylaxis in patients with hip fracture. It has not been shown that dose adjustment has influence on anticoagulation effectiveness, but different LMWHs can have pharmacokinetic and pharmacodynamic differences due to molecular structures, half-lives, antithrombin- and non-antithrombin-mediated actions, anti-factor Xa:anti-factor IIa ratio (6). Thus, they can have different effects on perioperative blood loss, especially in patients who are treated with intramedullary implants, since surgeons do not have much influence on haemostasis (7). Reviparin sodium is a LMWH with a mean peak molecular weight of 3900 daltons. It is characterised by a narrow molecular weight distribution profile, with an anti-factor Xa:anti-factor IIa ratio of ≥ 3.6 (8). Dalteparin sodium has the mean molecular weight of 6000 daltons, the antifactor Xa to anti-factor IIa ratio for dalteparin is about 2.7 (6).

Anaemia is a strong negative prognostic factor in patients with hip fracture (7). It is associated with increased postoperative mortality, poor physical performance, increased length of hospitalisation

(9). In order to decrease blood loss in patients with intertrochanteric fractures, effects of tranexamic acid were investigated (10,11). Different factors that can affect perioperative blood loss were analysed such as wound drainage (12) and fracture fixation methods (13,14).

According to available data most studies which analyse different LMWHs are focused on the frequency of venous thromboembolism (VTE) (15,16). Very few studies compare the effects of different LMWHs on blood loss (17).

The aim of this study was to determine differences between reviparin and dalteparin in patients with extracapsular hip fracture treated with intramedullary nailing and their effects on perioperative blood loss and early postoperative recovery.

PATIENTS AND METHODS

Patients and study design

A retrospective comparative study including 68 patients with extracapsular hip fractures who were treated operatively at the Department of Orthopaedics and Traumatology in Canton Hospital Zenica during the years 2019 and 2021 was conducted. Before 2020 at our department LMWH reviparin was used for thromboprophylaxis of hospitalised patients with hip fractures. During the Covid 19 pandemic in 2020 our institution switched to dalteparin.

Medical records in 2019 and 2021 were used to collect data, patients were divided into two groups. A total of 31 and 37 patients met all inclusion criteria in reviparin and dalteparin group, respectively. Inclusion criteria were: fractures of proximal femur type 31.A1 and 31.A2 according to the Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association classification (18), injury less than two weeks old, patients without previous anaemia. Exclusion criteria were previous operations of the ipsilateral hip, associated fractures, pathologic fractures, coagulation disorders, oncologic patients.

Methods

In the preoperative assessment of patients the American Society of Anaesthesiology Scale was used (19). All operations were performed in general or spinal anaesthesia and all patients received 2 g of cefazolin as a prophylactic antibiotic

half an hour before the incision and for two days postoperatively twice daily. In all cases short third generation Gamma-nail was used for osteosynthesis. Patients in the reviparin group received reviparin sodium 0.6 mL or 3436 IU subcutaneously once daily; patients in the dalteparin group received 5000 IU of dalteparin- sodium subcutaneously once daily as thromboprophylactic agent. Perioperatively both agents were administered 12 hours before and 12 hours after the operative procedure.

Medical records from 2019 and 2021 were used to collect preoperative haemoglobin and haematocrit levels and platelet count; the same data were recorded <24 hours after the surgery as the first postoperative day, and on the second postoperative day. Pre-surgical length of hospital days, as well as the duration of postoperative hospitalisation (in days) were also collected.

All patients were evaluated for early complications and mortality rate. A follow-up was done until discharge from the Department. In 15 patients in the reviparin group and 25 in the dalteparin group haemoglobin, haematocrit levels and platelet count were not collected on the second postoperative day due to administration of blood transfusions or because data were missing; however, the number of blood transfusions in neither of the groups was recorded.

Statistical analysis

Demographic characteristics of patients were evaluated using descriptive statistics. χ^2 test or Fisher exact test were used to compare differences between categorical variables. Independent two sided Student t-test was used for continuous variables with normal distribution. Nonparametric Mann-U-Whitney test was used in cases without normal distribution. Statistical significance was set at $p < 0.05$.

RESULTS

Out of 68 patients included in the study, 31 were in reviparin and 37 in the dalteparin group. There were 26 males and 42 females ($p = 0.565$). Mean age of patients was 70.5 (± 14.4) and 76.8 (± 8.4) years in reviparin and dalteparin group, respectively. Patients who received dalteparin were older than patients who received reviparin ($p = 0.071$) (Table 1).

Table 1. Demographic characteristics of patients

Variables	Reviparin (31)	Dalteparin (37)	p
Gender (No)			0.565
Males	13	13	
Females	18	24	
Age (mean $\pm$ SD)	70.5 (± 14.4)	76.8 (± 8.4)	0.071
Hospital stay (days)(CI 95%)			
Time to surgical intervention	8.23 (CI: 7.01 – 9.44)	5.76 (CI: 5.02-6.50)	0.001
Postoperative stay	11.16 (CI: 10.20-12.12)	8.38 (CI: 7.48-9.28)	0.000

Patients in the dalteparin group had shorter time to surgical intervention than patients in the reviparin group, 5.76 (CI: 5.02-6.50) and 8.23 (CI: 7.01–9.44) days, respectively ($p = 0.001$). Duration of postoperative hospitalisation was also shorter in dalteparin than in the reviparin group, 8.38 (CI: 7.48-9.28) and 11.16 (CI: 10.20-12.12) days, respectively ($p = 0.000$).

There were no statistically significant differences in preoperative haemoglobin level between groups ($p = 0.118$). The values of haemoglobin showed a linear decrease on the first and second postoperative day. Median values of haemoglobin level on the first postoperative day were lower in dalteparin compared to the reviparin group, 103.189 (± 12.2901) g/L and 110.861 (± 12.1049) g/L, respectively ($p = 0.012$) (Table 2). The median level of haemoglobin on the second postoperative day in the reviparin group was not statistically different compared to the dalteparin group ($p = 0.871$).

Table 2. Difference between haemoglobin, haematocrit values and platelet counts across groups

Variable	LMWH	No of patients	Mean (SD)	p
Hg (g/L)				
pre-op	Reviparin	31	128.103 (14.1823)	0.118
	Dalteparin	37	122.946 (12.6687)	
post-op day 1	Reviparin	31	110.861 (12.1049)	0.012
	Dalteparin	37	103.189 (12.2901)	
post-op day 2	Reviparin	16	106.000 (8.0944)	0.871
	Dalteparin	12	106.583 (10.7065)	
Hc (L/L)				
pre-op	Reviparin	31	0.3848 (0.04249)	0.091
	Dalteparin	37	0.3676 (0.04030)	
post-op day 1	Reviparin	31	0.3313 (0.03640)	0.015
	Dalteparin	37	0.3086 (67.735)	
post-op day 2	Reviparin	16	0.3156 (0.02607)	0.861
	Dalteparin	12	0.3175 (0.02989)	
Platelet count (x109/L)				
pre-op	Reviparin	31	238.48 (67.735)	0.760
	Dalteparin	37	244.11 (80.890)	
post-op day 1	Reviparin	31	309.32 (99.013)	0.084
	Dalteparin	37	269.30 (88.928)	
post-op day 2	Reviparin	16	307.13 (98.782)	0.177
	Dalteparin	12	259.25 (77.108)	

LMWH, low-molecular-weight heparin; Hg, haemoglobin; Hc, haematocrit

Haematocrit values were not statistically different between the groups preoperatively ($p=0.091$). On the first postoperative day haematocrit values were $0.3086 (\pm 0.03824)$ L/L in the dalteparin group and $0.3313 (\pm 0.03640)$ L/L in the reviparin group ($p=0.015$) (Table 2). Haematocrit values were not statistically different between the groups on the second postoperative day ($p=0.861$).

There was no statistically significant difference in the platelet count value between the groups preoperatively ($p=0.760$). Both groups showed an increase in the platelet count on the first postoperative day which was lower in the dalteparin group than in the reviparin group $269.30 (\pm 88.928) \times 10^9/L$ and $309.32 (\pm 99.013) \times 10^9/L$, respectively ($p=0.084$) (Table 2).

Intrahospital mortality rate in the reviparin group of patients was 6.4% and in the dalteparin group 2.7% ($p=0.588$). There were no medical complications in the reviparin group; one case of pulmonary embolism was detected in the dalteparin group.

DISCUSSION

Demographic characteristics of patients in this study are similar to other studies. Proximal femur fractures mostly occur in patients above the age of 70 years (20). The prevalence of this injury is 2–3 times higher in females than in males (21). In our study the mean age of patients was $70.5 (\pm 14.4)$ years and $76.8 (\pm 8.4)$ years in the reviparin and dalteparin group, respectively; there were 42 females and 26 males. Although males less frequently sustained fractures of proximal femur than females, osteoporosis in males is one of the risk factors that is underestimated, since older males are also affected with hip fracture and state that male osteoporosis is underscreened, underdiagnosed and undertreated, both in primary and secondary prevention of fragility fractures (22,23).

The length of postoperative hospital stay in our study was shorter in the dalteparin group of patients than in the reviparin group; however, shorter postoperative hospital stay in the dalteparin group was probably due to the adaptation of the Department and fewer beds during Covid 19 pandemic in 2021.

Time to surgical intervention was shorter in the dalteparin group, compared to the reviparin group. Ronga et al. state that relation between time-to-surgery and blood loss is poorly studied; they

found that lower blood loss was observed when surgery was performed 24 hours after admission (8). However, another study showed that surgery performed 48 hours after admission can result in a longer hospital stay (24).

Postoperative haemoglobin analysis is essential for monitoring blood loss after surgery in orthopaedic patients. Analysing haemoglobin level preoperatively and five consecutive days postoperatively Nagra et al. found a linear decrease, which was the lowest on the second postoperative day (25). We also found a linear decrease in haemoglobin levels, which were also the lowest on the second postoperative day. However, haemoglobin levels in our study were recorded for only two postoperative days, and data were collected for 16 patients in reviparin and for 12 patients in the dalteparin group on the second postoperative day. Further studies are necessary in order to standardise postoperative haemoglobin monitoring.

In a randomised prospective study of the clinical effectiveness of dalteparin and enoxaparin, Bilawicz et al. did not find statistical difference between haemoglobin level on the first postoperative day, however, more patients in enoxaparin group received more red cell transfusions (26). They also noted a decrease in the platelet count on the first postoperative day. In our study haemoglobin levels on the first postoperative day were lower in dalteparin than in the reviparin group. Also, unlike in the study of Bilawicz et al. we found an increase in the platelet count on the first postoperative day.

Current literature reports one-year mortality rate after hip fracture between 26 to 33% (6). Intrahospital mortality rate in reviparin group of patients was 6.4% and in the dalteparin group 2.7%. A longer follow-up is required to evaluate long-term mortality differences between groups.

We recorded one case of pulmonary embolism which occurred in the dalteparin group on the fifth postoperative day. According to the literature VTE can occur early after injury (27). In a study of Miano et al. most cases of VTE after trauma occurred by the fifth postoperative day (16).

Planès et al. compared the efficacy and safety of reviparin and enoxaparin in patients undergoing total hip replacement. They found that the two treatment groups were clinically equivalent in

efficacy. The reviparin-treated patients had fewer haematomas, bruising and higher red cell counts and lower haemoglobin levels than the enoxaparin-treated patients (28). To our knowledge there are no studies in the literature which compare reviparin and dalteparin in patients with proximal femur fractures.

The limitations of study are retrospective nature and short follow-up of patients.

Based on our results there are some differences in laboratory parameters postoperatively between

the patients who received dalteparin and reviparin, however, both LMWHs remain safe and effective agents for thromboprophylaxis in patients with extracapsular hip fractures. A longer follow-up is required to determine long-term complications and differences between the groups.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

1. Tornetta III P, Ricci MW, Ostrum FR, McQueen MM, McKee M, eds. *Rockwood and Green's Fractures in Adults*. 9th ed. Philadelphia: Wolters Kluwer Health, 2019.
2. Vestergaard P, Rejnmark L, Mosekilde L. Has mortality after a hip fracture increased? *J Am Geriatr Soc* 2007; 55:1720-6.
3. Dhanwal KD, Dennison ME, Harvey CN, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. *Indian J Orthop* 2011; 45:15-22.
4. Buckley RE, Moran CG, Apivatthakakul T, eds. *AO Principles of Fracture Management*. 3th ed. Davos: Georg Thieme Verlag, 2017.
5. Sanchez ME, Lozano HB, Velarde-Garrido DV, Alarma BL, Sanchez-Mayoral VT, Romera OP, Lopez PC. Key factors influencing clinical and functional outcomes in extracapsular proximal femur fractures: the role of early weight-bearing - one-year follow-up cohort of 495 patients. *Med Glas* 2021; 18:280-6.
6. Racine E. Differentiation of the low-molecular-weight heparins. *Pharmacotherapy* 2001; 21:62-70.
7. Ronga M, Bonzini D, Valoroso M, La Barbera G, Tamini J, Cherubino M, Cherubino P. Blood loss in trochanteric fractures: multivariate analysis comparing dynamic hip screw and Gamma nail. *Injury* 2017; 48 (Suppl 3):44-7.
8. Hao C, Sun M, Wang H, Zhang L, Wang W. Low molecular weight heparins and their clinical applications. *Prog Mol Biol Transl Sci* 2019; 163:21-39.
9. Foss NB, Kristensen MT, Kehlet H. Anaemia impedes functional mobility after hip fracture surgery. *Age Ageing* 2008; 37:173-8.
10. Tian S, Shen Z, Liu Y, Zhang Y, Peng A. The effect of tranexamic acid on hidden bleeding in older intertrochanteric fracture patients treated with PFNA. *Injury* 2018; 49:680-4.
11. Schiavone A, Bisaccia M, Inkov I, Rinonapoli G, Manni M, Rollo G, Meccariello L, Vicente IC, Ceccarini P, Ruggiero C, Carraffa A. Tranexamic acid in petrochanteric femoral fracture: Is it a safe drug or not? *Folia Med (Plovdiv)* 2018; 60:67-78.
12. Chang HM, Lu WY, Kuan FC, Su WR, Chen PY, Su PF, Hsu KL. Wound drainage after proximal femoral nail antirotation (PFNA) fixation may negatively affect the patients with intertrochanteric fractures: A prospective randomized controlled trial. *Injury* 2021; 52:575-81.
13. Lanzetti RM, Caraffa A, Lupariello D, Ceccarini P, Gambaracci G, Meccariello L, Manfreda F, Maiettini D, Vicente CI, Scialpi M, Bisaccia O, Rinonapoli G, Bisaccia M. Comparison between locked and unlocked intramedullary nails in intertrochanteric fractures. *Eur J Orthop Surg Traumatol* 2018; 28:649-58.
14. David GG, Michele B, Umberto R, Cioanca F, Andrea S, Alfonso C, Cristina IV, Maria ML, Antonio HJ, Giuseppe R, Luigi M. Metabolic Shock in Elderly Pertrochanteric or Intertrochanteric Surgery. Comparison of three surgical methods. Is there a much safer? *Rom J Anaesth Intensive Care* 2020; 27:17-26.
15. Okoye OT, Gelbard R, Inaba K, Esparza M, Belzberg H, Talving P, Teixeira PG, Chan LS, Demetriades D. Dalteparin versus Enoxaparin for the prevention of venous thromboembolic events in trauma patients. *Eur J Trauma Emerg Surg* 2014; 40:183-9.
16. Miano TA, Cuker A, Christie JD, Martin N, Smith B, Makley AT, Guo W, Hennessy S. Comparative Effectiveness of enoxaparin vs dalteparin for thromboprophylaxis after traumatic injury. *Chest* 2018; 153:133-42.
17. Begatin J, Carević V, Begatin K. Jesu li svi niskomolekularni heparini jednaki? (Are all low molecular weight heparins the same?) [in Croatian]. *Medicus* 2010; 19:191-6.
18. Müller ME, Koch P, Nzarian S, Schatzker J. *The Comprehensive Classification of Fractures of Long Bones*. Berlin Heidelberg: Springer, 1990.
19. Mayhew D, Mendonca V, Murthy BVS. A review of ASA physical status – historical perspectives and modern developments. *Anaesthesia* 2019; 74:373-9.
20. Li L, Bennett-Brown K, Morgan C, Dattani R. Hip fractures. *Br J Hosp Med* 2020; 2:1-10.
21. Zuckerman JD. Hip fracture. *N Engl J Med* 1996; 334:1519-25.
22. Rinonapoli G, Ruggiero C, Meccariello L, Bisaccia M, Ceccarini P, Caraffa A. Osteoporosis in men: a review of an underestimated bone condition. *Int J Mol Sci* 2021; 22:2105.
23. Bisaccia M, Rinonapoli G, Meccariello L, Ripani U, Pace V, Rollo G, Vicente CI, Bisaccia O, Gómez GD, Guijarro LS, De Masi De Luca A, Caraffa A. Osteoporosis in male patients: epidemiology, clinical aspects and DEXA Scan assessment. *Clin Cases Miner Bone Metab* 2019; 16:31-5.

24. Seong YJ, Shin WC, Moon NH, Suh KT. Timing of Hip-fracture Surgery in Elderly Patients: Literature Review and Recommendations. *Hip Pelvis* 2020; 32:11-6.
25. Nagra NS, van Popta D, Whiteside S, Holt EM. An analysis of postoperative hemoglobin levels in patients with a fractured neck of femur. *Acta Orthop Traumatol Turc* 2016; 50:507-13.
26. Biławicz J, Lipa M, Wielgos M. Comparison of low-molecular-weight heparins in thromboprophylaxis of major orthopaedic surgery - randomized, prospective pilot study. *Open Med* 2020; 15:1048-53.
27. Owings JT, Kraut E, Battistella F, Cornelius JT, O'Malley R. Timing of the occurrence of pulmonary embolism in trauma patients. *Arch Surg* 1997; 132:862-7.
28. Planès A, Vochelle N, Fagola M, Bellaud M. Comparison of two low-molecular-weight heparins for the prevention of postoperative venous thromboembolism after elective hip surgery. *Blood Coagul Fibrinolysis* 1998; 9:499-505.

Comparison of dexmedetomidine alone or with other sedatives for paediatric sedation during magnetic resonance imaging: a systematic review

Rudy Vitraludyono¹, Arie Utariani², Elizeus Hanindito²

¹Department of Anaesthesiology and Reanimation, ²Consultant of Paediatric Anaesthesia, Department of Anaesthesiology and Reanimation; Faculty of Medicine, Airlangga University/ Dr. Soetomo General Hospital, Surabaya, Indonesia

ABSTRACT

Aim To compare the outcome of sole dexmedetomidine or with other sedative drugs in paediatric patients during magnetic resonance imaging (MRI).

Methods Literature was obtained from PubMed and Science-Direct from 2010-2020 using key words: sedation, paediatric, dexmedetomidine, ambulatory, MRI, ketamine, propofol, midazolam. The literature selection was based on Participant, Intervention, Comparators, Outcomes (PICO) analysis. All English full-text and peer-reviewed articles were included. The primary outcome was hemodynamic stability, respiratory compromise, and recovery time. The risk of bias analysis was assessed using Cochrane collaboration Risk of Bias (RoB 2.0).

Result Of 106 studies, 17 studies were included with a total 3.430 paediatric patients undergoing MRI. Dexmedetomidine alone provides a more stable hemodynamic but longer recovery time than ketamine, propofol or midazolam. The combination of dexmedetomidine and ketamine provides more stable hemodynamics, especially in the incidence of hypotension and bradycardia, and does not significantly reduce airway configuration more than sole dexmedetomidine or ketamine. Intranasal dexmedetomidine is more recommended than its combination with midazolam. Combining dexmedetomidine with ketamine, propofol or midazolam provides a shorter recovery time.

Conclusion A combination of dexmedetomidine with other sedatives such as ketamine, propofol and midazolam is better than sole dexmedetomidine for paediatric sedation during magnetic resonance imaging.

Key words: anaesthesia, ketamine, midazolam, propofol

Corresponding author:

Rudy Vitraludyono

Department of Anaesthesiology and Reanimation, Faculty of Medicine, Airlangga University/Dr. Soetomo General Hospital

Jl. Jaks Agung Suprpto no.2 Malang, Surabaya, East Java, Indonesia

Phone: +62 85 2313 97 700;

E-mail: dinoanestesi@ub.ac.id

ORCID ID: <https://orcid.org/0000-0002-3783-7029>

Original submission:

26 August 2022;

Revised submission:

19 September 2022;

Accepted:

20 October 2022

doi: 10.17392/1532-22

Med Glas (Zenica) 2023; 20(1): 7-14

INTRODUCTION

In paediatrics discomfort is mainly felt during invasive and non-invasive medical procedures. Pain becomes the main complaint in an emergency condition. Because of that, sedation has become essential in paediatric management. Sedation is also commonly used in imaging, such as magnetic resonance imaging (MRI), computed tomography or echocardiography to ensure patients remain calm and still (1-3).

MRI is a diagnostic tool often used to visualize precise tissue differentiation using a magnetic field (4). The patients movement must be under control to provide a good quality image. In paediatrics this procedure is challenging because sometimes paediatric patients cannot cooperate (3). The American College of Emergency Physicians (ACEP) has defined Procedural Sedation and Analgesia (PSA) as a technique in administering sedative or dissociative agents with or without analgesic to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function (5). The aim of this procedure is different in adults because, in paediatrics this procedure controls the behaviour and keeps the patient cooperative during the procedure. Sedation also aims to provide patient safety, minimize discomfort, anxiety and physiological trauma (6). However, in cooperative paediatric patients, non-pharmacological modality might help reduce the need for sedatives (5). Before sedation, it needs to be considered whether the procedure will provoke pain or not. If the pain is not adequately managed, the physiological and behavioural response will affect long-term nociceptive developments in paediatric patients (7).

There are several sedation modalities for MRI. The most common sedation includes inhalation and intravenous sedation. Some intravenous sedatives are often used such as propofol, ketamine, chloral hydrate and dexmedetomidine. Sevoflurane is commonly used in inhalation sedation (8). In 2005 studies related to dexmedetomidine as premedication in paediatrics during MRI emerged. Dexmedetomidine is less frequently used causing respiratory depression. However, dexmedetomidine potentially causes cardiovascular depression and must be put into consid-

eration. Dexmedetomidine dose-dependent potentially lowers blood pressure through adrenergic alpha-2 receptor agonists in the sympathetic ganglion. Besides, dexmedetomidine also needs more prolonged onset (9).

The aim of this study was to compare the outcome of sole dexmedetomidine and a combination of dexmedetomidine with other sedative drugs in paediatrics during magnetic resonance imaging (MRI).

MATERIALS AND METHODS

Materials and study design

This systematic review was done in the Department of Anaesthesiology and Reanimation, Faculty of Medicine, Airlangga University /Dr. Soetomo Hospital Surabaya, Indonesia, in the period December 2021-January 2022. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) method was used to analyse current evidence from studies comparing the sedative effect of dexmedetomidine versus the combination of dexmedetomidine with ketamine, propofol, midazolam in paediatric patients undergoing magnetic resonance imaging (MRI). Article searches were conducted on PubMed and ScienceDirect, using key words sedation, pediatric, dexmedetomidine, ambulatory, MRI, ketamine, propofol and midazolam.

Methods

The selection criteria used the Participant, Intervention, Comparators, Outcomes (PICO) framework. Participants: research subjects were paediatric patients aged 1 day – 18 years who underwent a magnetic resonance imaging (MRI) procedure with sedation. Intervention: subjects received sedation between dexmedetomidine and dexmedetomidine combined with ketamine, propofol and midazolam. Comparator: paediatric patients undergoing MRI using sedative sole dexmedetomidine compared with subjects sedated with a combination of dexmedetomidine with ketamine, propofol, midazolam. Outcome: paediatric hemodynamics (blood pressure and pulse rate), the occurrence of respiratory depression, recovery time. All full-text peer-reviewed studies comparing sedation outcomes using dexmedetomidine and other sedatives in paediatric patients

age 1 day – 18-year were included. The articles were only in English. Abstracts and conference proceedings were excluded. Research articles that met the inclusion criteria for evaluation were determined based on the evidence-based level on categories from the National Health and Medical Research Council (NHMRC). For RCT research, quality and risk of bias were assessed using the Cochrane Collaboration Risk of Bias (RoB 2.0) (10). The final assessment was scored as follows: low risk of bias, moderate risk of bias/multiple considerations and high risk of bias, as described in the Cochrane manual (10). For case studies with a control group, quality and risk assessments were done using guidelines from The National Institutes of Health (NIH) quality assessment tool for case-series studies (Interventional) (11), while case studies without comparisons for control groups used guidelines from The National Institutes of Health (NIH) quality assessment tool for before-after (pre-post) study with no control group (11). The final assessment was scored as good, moderate and poor. For case reports, there are no guidelines for assessing quality reports.

Articles were managed using the Mendeley reference processor (version 1083). The articles were identified based on the evaluation of titles and abstracts. After screening for duplicate articles, the full text of the articles was finalized for eligibility for inclusion in the study. After screening, feasibility, quality assessment and risk of bias, data extraction from all selected articles was carried out, and important findings from the article were written based on the data extraction process. Data extraction includes: general characteristics of the study design and level of evidence according to NHMRC, study group, type of surgery, number of samples and baseline characteristics of the study samples; quality and risk of bias from research articles; assessment of the outcomes - hemodynamics (blood pressure and pulse rate of paediatric patients), the occurrence of respiratory depression, recovery time.

RESULTS

From the flow chart of systematic review, 106 potential studies were obtained. After the screening of duplicate articles, titles and abstracts, 66 studies were excluded due to duplication and did not meet the inclusion criteria. From the rest of

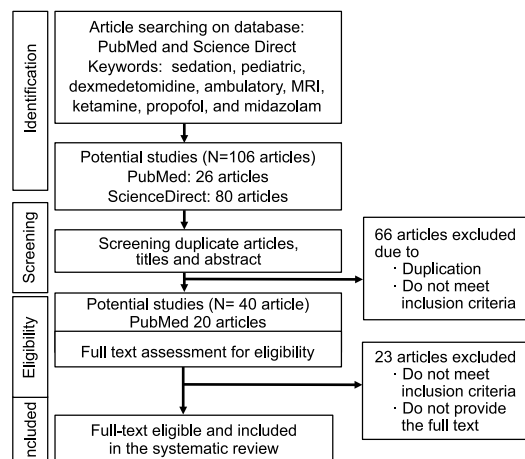


Figure 1. PRISMA diagram of systematic review

potential studies (N=40), full text screening found that 23 studies did not meet the inclusion criteria and did not provide full text. Therefore, 17 studies met the criteria and were further investigated with the total number of research subjects, 3,430 paediatric patients (Figure 1). The studies consisted of retrospective studies, retrospective reviews, systematic reviews, prospective studies, randomized controlled studies, and non-randomized controlled studies.

Olgun et al. (12), showed that the success rate of sedation using intranasal dexmedetomidine was 96.2%. The median effective dose (ED50) of intranasal dexmedetomidine increases with age for the first three years of life. Intranasal dexmedetomidine and intravenous ketamine may be the best choices as sedative agents in children with risk factors for alpha-mannosidosis (12). There have been several comparative studies between dexmedetomidine and its combination with other sedatives. Intranasal dexmedetomidine is better at reducing anxiety and produces a higher level of sedation at the time of induction than intranasal midazolam (13). However, a retrospective review of 244 paediatric patients showed that intranasal dexmedetomidine combined with midazolam was an effective regimen for sedation (14). Buccal dexmedetomidine with or without midazolam provides adequate sedation with minimal side effects but has a failure rate of almost 20% (15). Low-dose dexmedetomidine bolus (0.5 mcg/kg) can be used as an adjuvant to reduce the need for propofol in sedation (16). Combination of dexmedetomidine and ketamine superior to ketamine and dexmedetomidine alone (17).

Several studies discussed the hemodynamic changes in using different sedatives in paediatric patients who underwent MRI. In general, dexmedetomidine is better in maintaining hemodynamics than other sedatives. Abulebda et al. (18) stated that dexmedetomidine has more stable hemodynamics than propofol. However, dexmedetomidine has a longer recovery time (19). Research by Eldeek et

al. (20) and Tammam et al. (17) stated that dexmedetomidine provides adequate sedation in most children without hemodynamic disturbances compared to ketamine. Meanwhile, the combination of ketamine and dexmedetomidine did not cause significant hemodynamic changes (21) (Table 1).

The use of dexmedetomidine alone or in combination with other sedatives did not cause significant

Table 1. The sedative effect of dexmedetomidine compared to the combination of dexmedetomidine with ketamine, propofol and midazolam on blood pressure and pulse rate

References	Research design, sample size, variables, statistical analysis	Outcome			
		Dose	Airway configuration	Hemodynamic	Recovery time
Abulebda et al. (18)	Design: Retrospective review Sample: 105 paediatric patients (Group D 56 subjects, Group P 49 subjects) Variables: demographics, hemodynamic changes, sedation time Statistical analysis: T-test, Wilcoxon test, ANOVA	IV Propofol 1 mg/kg (maximum of 50 mg), followed by continuous infusion of 83 mcg/kg/min IV Dexmedetomidine 2 mcg/kg 10 minutes followed by maintenance infusion of 1 mcg/kg/h	NA	Dexmedetomidine is better in maintaining stable hemodynamics than propofol	NA
Mylavarapu et al.(21)	Design: a prospective study Sample: 25 paediatric patients Variables: demographic characteristics, hemodynamics, outcomes Statistical analysis: paired t-test, Wilcoxon signed-rank test, descriptive statistics, linear mixed-effect models	IV Dexmedetomidine 2 mcg for 10 min followed by dexmedetomidine infusion 2 mcg/kg/h IV Ketamine 2 mg/kg	Ketamine after dexmedetomidine did not significantly decrease upper airway configuration compared to dexmedetomidine alone.	No hemodynamic changes	NA
Ahmed et al.(19)	Design: a retrospective review Sample: 966 patients (Group D 544 patients received dexmedetomidine) group P 452 patients received propofol) Variables: heart rate, respiration rate, blood pressure, oxygen saturation Statistical analysis: Student t-test, Mann-Whitney rank-sum test, Fisher exact test	IV Dexmedetomidine 2 mcg/kg over 10 minutes followed by infusion of 1 mcg/kg/h IV Propofol 2 mg/kg over 2 minutes followed by infusion of 83 mcg/kg/minutes	NA	Dexmedetomidine provides stable hemodynamics	Dexmedetomidine has longer recovery time Propofol has a faster onset and recovery time.
Gupta et al.(26)	Design: a double-randomized prospective study Sample: 60 paediatric patients (Group D 30 subjects, Group M 30 subjects) Variables: demographics, parental separation, hemodynamics, sedation level, median sedation Statistical analysis: unpaired t-test, paired t-test, χ^2	IN Dexmedetomidine 1 mcg/kg IN Midazolam 0.2 mg/kg	NA	Intranasal dexmedetomidine maintains better hemodynamics	NA
Eldeek et al. (20)	Design: Randomized prospective trial Sample: 110 paediatric patients (group D 55 subjects, group K 55 subjects) Variables: sedative, hemodynamic, respiratory effects, and complications. Statistical analysis: one-tailed test, ANOVA, t-test χ^2 test	IV Dexmedetomidine 1 mcg/kg followed by continuous infusion of 0.5-0.75 mcg/kg/h IV Ketamine 1mg/kg followed by continuous infusion 10-15 mcg/kg/min	Dexmedetomidine provide no respiratory compromise	Dexmedetomidine provide no hemodynamics change	NA
Tammam et al. (17)	Design: a blinded randomized comparison study Sample: 162 children (group D 54 subjects, group K 54, group DK 54 subjects) Variables: section onset, sedation failure rate, hemodynamic stability Statistical analysis: One-way ANOVA, Pearson, and χ^2 tests	IM Dexmedetomidine 3 mcg/kg IM Ketamine 4 mg/kg Dexmedetomidine 1.5 mcg/kg + ketamine 2 mg/kg	NA	Dexmedetomidine and ketamine combination has more stable hemodynamics than ketamine or dexmedetomidine alone	NA

NA, not applicable; IV, intravenous; IM, intramuscular; IN, intranasal

Table 1. (continued) The sedative effect of dexmedetomidine compared to the combination of dexmedetomidine with ketamine, propofol and midazolam on blood pressure and pulse rate

References	Research design, sample size, variables, statistical analysis	Outcome			
		Dose	Airway configuration	Hemo-dynamic	Recovery time
Mahmoud et al. (22)	Design: a prospective, single-blind, controlled comparative study Sample: 60 patients (Dex group 30, Prop group 30) Variable: Airway morphology Analysis: Wilcoxon sum-rank test, two-sample t-test, Wilcoxon test, ANOVA	IV Dexmedetomidine Low 1 mcg/kg/h; High 3 mcg/kg/h	Both Dexmedetomidine and Propofol have no significant change in airway dimensions	NA	NA
		IV Propofol Low 100 mcg/kg/min. High 200 mcg/kg/min			
Watt et al. (23)	Design: Randomized controlled blind study Sample: 40 children Variables: demographics, procedure time, cine measurements, anaesthetic level, spoiled chart airway volume measurements diet (SPGR) Analysis: Paired and unpaired t-test, Wilcoxon test, Mann Whitney test, ANOVA test	IV Dexmedetomidine 1 mcg/kg 10 minutes followed by infusion of 0.1 mg/kg midazolam (IV), then dexmedetomidine infusion 1 mcg/kg/h continued	There was no difference in airway collapse between sedation with dexmedetomidine and propofol after sevoflurane induction.	NA	NA
		IV Propofol 300 mcg/kg/min for 10 minutes, reduced to 250 mcg/kg/min			
Tang et al. (24)	Design: a systematic review Sample: 6 randomized controlled trials (415 paediatric patients) Variables: recovery time, patient discharge time, failure of sedation, desaturation, Pediatric Anesthesia Emergence Delirium scale (PAED) Statistical analysis: PRISMA	Propofol 300 mcg/kg/min – 3 mg/kg IV Dexmedetomidine 0.3 – 2 mcg/kg	NA	NA	Propofol has a shorter recovery time and faster induction of sedation than dexmedetomidine
		IV Propofol 3 mg/kg initial dose followed by 100 mcg/kg/min continuous infusion of mean dose 97.9 mcg/kg/h 2 mg/kg and followed by continuous infusion of 200 mcg/kg/min a single dose of 1 mg/kg infusion at 300 ug/kg/min for 10 mins and reduced to 250 mcg/kg/min 1 mg/kg bolus followed by continuous infusion of 100 ug/kg/min			
Zhou et al. (25)	Design: a systematic review Sample: 6 studies with 368 subjects Variables: sedation onset, recovery time, sedation time, MRI time, MRI quality, PAED Statistical analysis: PRISMA and meta-analysis	IV Dexmedetomidine. 1 mcg/kg initial dose followed by continuous infusion of 0.5 ug/kg/h continuous infusion of mean dose 1.8 ug/kg/h 2 mcg/kg followed by continuous infusion of 2 mcg/kg/h single dose of 0.3 mcg/kg 1 mcg/kg followed by 1 mcg/kg/h infusion 2 mcg/kg for 10min followed by continuous infusion of 1 mcg/kg/h	NA	NA	Propofol has faster onset and recovery time than dexmedetomidine
Balasubramanian et al. (13)	Design: Non-randomized controlled study Sample: 88 patients received initiation, 35 patients received dexmedetomidine, 38 patients received propofol, 15 did not receive the drug Variables: Demographics, the success rate of MRI, quality of MRI, continuity of MRI, side effects, recovery time, and duration of treatment Statistical analysis: χ^2 test, ANOVA, unpaired t-test, Kruskal-Wallis, and Mann Whitney	IV Dexmedetomidine 1 mcg/kg for 10 minutes IV ketamine 1 mg/kg IV propofol 1 mg/kg	NA	NA	Propofol has faster recovery time than dexmedetomidine and ketamine

NA, not applicable; IV, intravenous; IM, intramuscular; IN, intranasal

changes in airway configuration. Mylavarapu et al. (21) found that adding ketamine after dexmedetomidine did not significantly decrease the airway configuration compared to dexmedetomidine alone. Mahmoud et al. study (22) also stated that the use of dexmedetomidine or propofol did not cause changes in airway configuration in patients with history of obstructive sleep apnoea (OSA). The study of Watt et al. (23) stated no difference in airway between sedation using dexmedetomidine and propofol after sevoflurane induction (Table 1, 2).

Propofol has a shorter recovery time than dexmedetomidine or ketamine. Ahmed et al. (19) found that propofol has a faster onset and recovery time than dexmedetomidine. Tang et al. (24) and Balasubramanian et al. (13) found that trial sequential analysis (TSA) recommended propofol over dexmedetomidine because of shorter recovery time and faster onset. Propofol is recommended for paediatric patients undergoing MRI because it has a better sedative effect, faster onset and recovery time, also lower side effects of delirium than dexmedetomidine (25) (Table 1).

An analysis of potential bias found that no articles had potential bias on selective reporting points, incomplete outcome data and blinding of outcome assessment. More than 75% of the studies did not have the potential for bias on the points of allocation concealment and blinding of participants and personnel. As many as 50% of the studies had no potential for random sequence generation bias, and 12.5% had a high potential for bias (Figure 2). The limitation of this study is that there was no meta-analysis of the outcome. Further meta-analyses might be done as the continuity of this study.

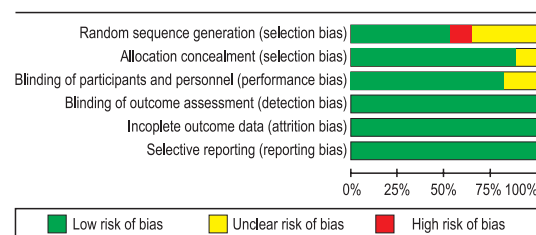


Figure 2. Risk of bias: review of authors' judgements about each bias risk item presented as percentages across all included studies

DISCUSSION

Procedural sedation and analgesia (PSA) as premedication in paediatrics before undergoing MRI examination has several side effects and risks.

Monitoring is needed, especially in hemodynamic stability, respiratory depression and recovery time. Several sedatives prescribed for PSA include propofol, ketamine, chloralhydrate, and dexmedetomidine in paediatrics (16).

In this systematic review, dexmedetomidine was able to maintain hemodynamic stability in paediatric patients. Studies conducted by Abulebda et al. (18) and Ahmed et al. (19) stated that dexmedetomidine could maintain hemodynamic stability better than propofol. A retrospective review by Ahmed et al. (19) found that hypotension and bradycardia were more common in the propofol group.

There was no significant difference in hemodynamics between dexmedetomidine and midazolam (24). The level of sedation of intranasal dexmedetomidine is higher than midazolam, thus giving the patient more peace when separated from their parents; 80% of patients in the dexmedetomidine group achieved satisfactory sedation (OAA/S score > 4) (26).

The use of ketamine provokes some adverse events, including nausea, vomiting and dysphoria (18). However, the combination of dexmedetomidine (1.5 mg/kg) and ketamine (2 mg/kg) intramuscularly gives better results in terms of hemodynamic stability (16). Based on the result, dexmedetomidine is the best choice over propofol, midazolam and ketamine in terms of hemodynamic stability (16-18, 24).

Intravenous dexmedetomidine administration has a high incidence of hemodynamic instability and a high rate of sedation failures, also requires additional supplemental sedation (IV midazolam titration 0.05mg/kg every 4 minutes) (16). The intramuscular administration has been shown to provide better hemodynamic stability even though the onset of sedation is lower than the intravascular administration (16). Intranasal administration can be used as an alternative to MRI premedication because it does not significantly affect hemodynamics. In addition, intranasal sedation is non-invasive and easy to perform (26) and can be used as an option for sedation in paediatrics with alpha-mannosidosis (27). The median effective dose (ED50) of intranasal dexmedetomidine includes: 0.4 mg/kg in children 1-6 months of age, 0.5 mg/kg at 7-12 months of age, 0.9 mg/kg at 13-24 months of age, and 1.0 mg/kg in children aged 24-

36 months (28). Meanwhile, according to Sulton et al. (14) a dose of 3 mg/kg intranasal dexmedetomidine is recommended for paediatric patients aged 14 months, and the study of Olgun and Ali (12) stated that at a dose of 4 mg/kg dexmedetomidine is effective in paediatric patients under one year of age. In school-aged children, the buccal route is preferred over the intranasal route. Dexmedetomidine given by the buccal route with or without the addition of oral midazolam does not cause serious adverse events, but the percentage of failure reaches 20% (15).

There is no significant respiratory depression in paediatric patients who receive propofol or dexmedetomidine who were previously given inhaled sevoflurane (20). In obstructive sleep apnoea patients undergoing sedation using dexmedetomidine or propofol, upper airway morphology did not experience significant changes. However, Mahmoud et al. (22) showed that 23% of paediatric patients in the propofol group required additional airway support. The administration of dexmedetomidine alone or the combination of dexmedetomidine and ketamine in paediatric patients undergoing general anaesthesia did not cause a significant difference in the upper airway diameter (19).

The comparison of dexmedetomidine and propofol shows that propofol has a faster onset than dexmedetomidine (22). Ahmed et al. (19) also showed that dexmedetomidine onset was longer (13.6 ± 4.58 minutes) than propofol (2.0 ± 0.00 minutes). Dexmedetomidine needs a longer induction duration due to the slow infusion rate (more than 10 minutes) to avoid unwanted hemodynamic impairment. Dexmedetomidine has a longer discharge time (92 minutes) than the propofol group (37 minutes).

REFERENCES

1. Tervonen M, Pokka T, Kallio M, Peltoniemi O. Systematic review and meta-analysis found that intranasal dexmedetomidine was a safe and effective sedative drug during paediatric procedural sedation. *Acta Paediatr Int J Paediatr* 2020; 109:2008–16.
2. Ramalho CE, Bretas PMC, Schvartsman C, Reis AG. Sedation and analgesia for procedures in the pediatric. *J Pediatr (Rio J)* 2017; 93:2–18.
3. Jung SM. Drug selection for sedation and general anesthesia in children undergoing ambulatory magnetic resonance imaging. *Yeungnam Univ J Med* 2020; 37:159–68.
4. Blüml S, Panigrahy A. *MR Spectroscopy of Pediatric Brain Disorders*. New York: Springer, 2012.
5. Godwin SA, Caro DA, Wolf SJ, Jagoda AS, Charles R, Marett BE, Moore J, American College of Emergency Physicians. Clinical policy: procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 2005; 45:177–96.
6. Côté CJ, Wilson S, Casamassimo P, Crumrine P, Gorman RL, Hegenbarth M, & American Academy of Pediatric Dentistry. Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: An update. *Pediatrics* 2006;118:2587–602.

A study of Gupta et al. (26) stated that the onset of midazolam (5-15 minutes) was better than dexmedetomidine (10-20 minutes). However, the sedation level of dexmedetomidine was better than midazolam. A study conducted by Sulton et al. (14) showed that intranasal dexmedetomidine combined with midazolam was an effective pre-medication regimen prior to MRI examination.

Overall, studies in this systematic review have a low risk of bias. However, there are two studies by Balasubramanian et al. (13) and Boriosi et al. (15), which have a high risk of bias in random sequence generation ($n=12.5\%$). Balasubramanian et al. (13) study was a non-randomized control study. The recruited subjects had their history reviewed. Boriosi et al. (15) did not mention the study's recruitment method. In addition, the design used was a retrospective review by reviewing the patient's medical record so that the sample selection may not have been done randomly.

Limitations of this study is in terms of heterogeneity analysis which was not carried out to assess heterogeneity between the analysed studies.

In conclusion, a combination of dexmedetomidine and ketamine provides better hemodynamic stabilization, it does not provoke airway depression and provides a shorter recovery time. Dexmedetomidine alone requires a longer recovery time than other sedatives. The combination of dexmedetomidine with ketamine, propofol or midazolam shortens recovery time compared to sole dexmedetomidine.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

7. Mahajan C, Dash HH. Procedural sedation and analgesia in pediatric patients. *J Pediatr Neurosci* 2014; 9:1–6.
8. Miller AL, Theodore D, Widrich J. *Inhalational Anesthetic*. Treasure Island: StatPearls Publishing, 2021.
9. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. *Clin Pharmacokinet* 2017; 56:893–913.
10. Cochrane Denmark & Centre for Evidence-Based Medicine Odense. Cochrane Methods Bias. <https://methods.cochrane.org/bias/> (10 October 2022)
11. Ma LL, Wang YY, Yang ZH, Huang D, Weng H, Zeng XT. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? *Military Med Res* 2020; 7:1–11.
12. Olgun G, Ali MH. Use of intranasal dexmedetomidine as a solo sedative for MRI of infants. *Hosp Pediatr* 2018; 8:68–71.
13. Balasubramanian, B, Kulkarni SB. A non-randomized controlled study of total intravenous anesthesia regimens for magnetic resonance imaging studies in children. *J Anaesthesiol Clin Pharmacol* 2019; 35:379–85.
14. Sulton C, Kamat P, Mallory M, Reynolds J. The Use of intranasal dexmedetomidine and midazolam for sedated magnetic resonance imaging in children: a report from the Pediatric Sedation Research Consortium. *Pediatr Emerg Care* 2020; 36:138–42.
15. Boriosi JP, Eickhoff JC, Hollman GA. Safety and efficacy of buccal dexmedetomidine for MRI sedation in school-aged children. *Hosp Pediatr* 2019; 9:348–54.
16. Nagoshi M, Reddy S, Bell M, Cresencia A, Margolis R, Wetzel R, Ross P. Low-dose dexmedetomidine as an adjuvant to propofol infusion for children in MRI: a double-cohort study. *Paediatr Anaesth*. 2018; 28:639–46.
17. Tammam TF. Comparison of the efficacy of dexmedetomidine, ketamine, and a mixture of both for pediatric MRI sedation. *Egypt J Anaesth* 2013; 29:241–6.
18. Abulebda K, Louer R, Lutfi R, Ahmed SS. A Comparison of safety and efficacy of dexmedetomidine and propofol in children with autism and autism spectrum disorders undergoing magnetic resonance imaging. *J Autism Dev Disord* 2018; 48:3127–32.
19. Ahmed S, Unland T, Slaven J, Nitu M. Dexmedetomidine versus propofol: is one better than the other for MRI sedation in children? *J Pediatr Intensive Care* 2016; 6:117–22.
20. Eldeek AM, Elfawal SM, Allam MG. Sedation in children undergoing magnetic resonance imaging comparative study between dexmedetomidine and ketamine. *Egypt J Anaesth* 2016; 32:263–8.
21. Mylavarapu G, Fleck RJ, Ok MS, Ding L, Kandil A, Amin RS, Das B, Mahmoud M. Effects on the upper airway morphology with intravenous addition of ketamine after dexmedetomidine administration in normal children. *J Clin Med* 2020; 9:1–14.
22. Mahmoud M, Jung D, Salisbury S, McAuliffe J, Gunter J, Patio M, Donnelly LF, Fleck R. Effect of increasing depth of dexmedetomidine and propofol anesthesia on upper airway morphology in children and adolescents with obstructive sleep apnea. *J Clin Anesth* 2013; 25:529–41.
23. Watt S, Sabouri S, Hegazy R, Gupta P, Heard C. Does dexmedetomidine cause less airway collapse than propofol when used for deep sedation. *J Clin Anesth* 2016; 35:259–67.
24. Tang Y, Meng J, Zhang X, Li J, Zhou Q. Comparison of dexmedetomidine with propofol as sedatives for pediatric patients undergoing magnetic resonance imaging: a meta-analysis of randomized controlled trials with trial sequential analysis. *Exp Ther Med* 2019; 1775–85.
25. Zhou Q, Shen L, Zhang X, Li J, Tang Y. Dexmedetomidine versus propofol on the sedation of pediatric patients during magnetic resonance imaging (MRI) scanning: a meta-analysis of current studies. *Oncotarget* 2017; 8:102468–73.
26. Gupta A, Dalvi NP, Tendolkar BA. Comparison between intranasal dexmedetomidine and intranasal midazolam as premedication for brain magnetic resonance imaging in pediatric patients: a prospective randomized double blind trial. *J Anaesthesiol Clin Pharmacol* 2017; 33:236–40.
27. Trevisan M, Romano S, Barbi E, Bruno I, Murru FM, Cozzi G. Intranasal dexmedetomidine and intravenous ketamine for procedural sedation in a child with alpha-mannosidosis: a magic bullet? *Ital J Pediatr* 2019; 45:1–6.
28. Zhang W, Fan Y, Zhao T, Chen J, Zhang G, Song X. Median effective dose of intranasal dexmedetomidine for rescue sedation in pediatric patients undergoing magnetic resonance imaging. *Anesthesiology* 2016; 125:1130–5.

***Clitorea ternatea* flower extract induces platelet-derived growth factor (PDGF) and GPx gene overexpression in ultraviolet (UV) B irradiation-induced collagen loss**

Rizka Sofyanti Putri¹, Agung Putra^{2,4}, Chodidjah³, Dewi Masyitah Darlan^{5,6}, Setyo Trisnadi³, Siti Thomas³, Nur Dina Amalina^{2,7}, Rizky Candra Irawan²

¹Postgraduate Biomedical Sciences Program, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, ²Stem Cell and Cancer Research Indonesia, ³Department of Postgraduate Biomedical Sciences, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, ⁴Departement of Pathology, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, ⁵Department of Parasitology, Faculty of Medicine, Universitas Sumatera Utara, Medan, ⁶Pusat Unggulan Tissue Engineering, Faculty of Medicine, Universitas Islam Sultan Agung, Semarang, ⁷Pharmacy Study Program, Faculty of Mathematics and Natural Sciences, Universitas Negeri Semarang, Semarang; Indonesia

ABSTRACT

Aim To determine the effect of *Clitorea ternatea* flower extract (CTFE) in the gel dosage form on the expression of GPx and platelet-derived growth factor (PDGF) in ultraviolet (UV) - B irradiation-induced collagen loss rat model.

Methods This is experimental research with post-test control group design. Twenty healthy male Wistar rats were divided into four treatment groups: a sham group, UVB control group, two treatment groups with gel of CTFE 5% and gel of CTFE 10%, respectively. Each group was treated with UVB at 302 nm with a MED of 160 mJ/cm² for 5 days, whereas the sham group did not receive UVB. In the treatment groups CTFE 5% and CTFE 10% gel were given on the 6th to the 14th day. On day 14 all treatment groups were terminated, and GPx and PDGF gene expression were analysed using qRT-PCR.

Results In the group of gel of CTFE 10%, there was a significant increase in GPx gene expression (9.51±1.83) and PDGF (4.36±1.18) compared to the UVB control group which had GPx and PDGF gene expression of 4.90±1.64) and 0.032±0.01, respectively.

Conclusion The administration of CTFE gel showed an increase of the expression of GPx and PDGF genes on UVB irradiation-induced collagen loss rat model.

Key words: *clitorea ternatea* flower extract, collagen loss, GPx, PDGF

Corresponding author:

Agung Putra
Faculty of Medicine,
Universitas Islam Sultan Agung
Jl. Kaligawe Raya KM.4, Terboyo Kulon,
Kota Semarang, Jawa Tengah, Indonesia
Phone: +62 826 4251646;
E-mail: dr.agungptr@gmail.com
Rizka Sofyanti Putri ORCID ID: <https://orcid.org/0000-0003-3509-2155>

Original submission:

25 August 2022;

Revised submission:

12 November 2022;

Accepted:

20 December 2022

doi: 10.17392/1530-22

Med Glas (Zenica) 2023; 20(1): 15-21

INTRODUCTION

Collagen loss is initiated by the ultraviolet-B (UVB) radiation-induced overproduction of reactive oxygen species (ROS) (1) ROS overexpression induced diacylglycerol (DAG) and arachidonate acid secretion leading to activation of protein kinase C-3 (PKC3), thereby triggering proinflammatory cytokine and inhibiting growth factor including platelet-derived growth factor (PDGF) (2). On the other hand, inhibition of collagen synthesis is also affected by an oxidant/antioxidant imbalance such as glutathione peroxidase (GPx) obstruction (2–4). Recently, retinol is the first line therapy for collagen loss inhibition (5). However, retinol increases the risk of UV-induced skin damage including skin cancer (6). Studies showed that butterfly pea flower (*Clitoria ternatea*) is a source of anthocyanins and other flavonoids, which may have antioxidant activity (7,8). Unfortunately, no evidence supports a favourable role of *Clitoria ternatea* flower extract (CTFE) in the regulation of PDGF and GPx expression in the UVB irradiation-induced collagen loss.

Recent findings indicate that the induction of antioxidant enzyme such as GPx and improvement of PDGF level could be achieved by application of natural antioxidant (9–11). Flavonoid causes a reduction in postprandial inflammatory response such as high-sensitivity C-reactive protein and interleukin-6 (IL-6) with a concomitant increase in antioxidant capacity (12). Furthermore, flavonoid significantly induces several growth factors such as transforming growth factor- β (TGF- β) and PDGF through activation of p38 mitogen-activated protein kinases (MAPKs) pathway (13,14). Therefore, treatment with flavonoid may be a potential strategy for inhibiting collagen loss.

Clitoria ternatea flower contains several phytochemical compounds, such as flavonoids and phenolic acids (7,8). A previous study reported that *Clitoria ternatea* flower extract inhibited oxidative damage to bovine serum albumin in vitro (15). Anthocyanins in *Clitoria ternatea* inhibits the activity of proinflammatory cytokine including IL-6 and TNF- α by blocking ROS expression (16). The polyacrylate anthocyanins and flavanol glycosides as major constituents of CTFE inhibit UV-induced oxidative stress on skin cells (17). Furthermore, CTFE significantly

inhibited the collagen density by inhibiting the MMP-1 expression.

Nevertheless, the effect of CTFE on the regulation of PDGF and GPx gene expression in the UVB irradiation-induced collagen loss has never been investigated.

The aim of this study was to evaluate the effect of CTFE on the regulation of PDGF and GPx gene expression in the UVB irradiation-induced collagen loss rat models.

MATERIAL AND METHODS

Material and study design

This post-test only control group study design was conducted in Stem Cell and Cancer Research (SCCR) Laboratory, Faculty of Medicine, Sultan Agung Islamic University, Semarang, Indonesia, from June – August 2022.

The study was approved by the Ethic Committee of Sultan Agung Islamic University (No. 306/VIII/2022/Komisi Bioetik).

Methods

Extraction of *Clitoria ternatea* flower extract. *Clitoria ternatea* flowers were collected from Tawangmangu in Central Java Indonesia in May 2022 (Latitude -7.665158 and Longitude 111.129500). They were rinsed with tap water followed by distilled water to remove the dirt on the surface. The dried *Clitoria ternatea* flower was blended until small pieces and sieved with a mesh size of 120 mesh. 50 g of *Clitoria ternatea* flower were extracted in a maceration apparatus with 500 mL 98% ethanol for 24 h. The filtrate was then evaporated under rotary vacuum evaporator (IKA) and the crude extract was kept in refrigerator 4 (18,19). CTFE (5% and 10%) was dissolved in gel bases (Katechu, USA). The formulations were stored at 4 until further analysis.

Phytochemical screening of *Clitoria ternatea* flower extract. The crude CTFE was tested for the presence of flavonoids, alkaloids, tannins, steroids, terpenoids and saponins. The qualitative results are expressed as (+) for the presence and (–) for the absence of phytochemicals. The flavonoids were tested using Wilstater's test according to Femanda et al. (20). Briefly, 2 mg of CTFE was mixed with HCl 500 μ L and 0.02 mg magnesium. The presence of flavonoids is characterized

by the occurrence of discoloration. The presence of alkaloids indicated with a brown coloured precipitate that were determined under Wagner's test, 15 mg of CTFE was stirred with 1% HCl (6 mL) on water bath for 5 minutes and filtered. The filtrate was added with a few drops of Wagner solution (2 grams of potassium iodide and 1.27 g of Iodine in 95 mL of distilled water) (21). Furthermore, tannins content was analysed in the CTFE with 1% ferric chloride, black or blue coloration was taken as a positive result of tannins (22). Liebermann-Burchard test was used to determine the presence of steroids and terpenoids, briefly 100 mg of CTFE was shaken with chloroform and a few drops of acetic anhydride were added to the test tube and boiled in a water bath and rapidly cooled in iced water. Concentrated H_2SO_4 (2 mL) was added alongside of the test tube. The formation of a brown ring at the junction of two layers and turning the upper layer to green shows the presence of steroids, while the formation of deep red colour indicates the presence of triterpenoids (23). The saponin presence was analysed under Forth's test, 500 mg of CTFE was shaken with 10 mL of distilled water. The formation of frothing, which persists on warming in a water bath for 5 min, shows the presence of saponins (23).

Total flavonoid content of *Clitorea ternatea* flower extract. Total flavonoid content was determined using the aluminum colorimetric method (24) with some modifications using gallic acid as a standard. A calibration curve of gallic acid was prepared in the range of 200 - 700 μ g/mL. Briefly, extract (0.5 mL) and standard (0.5 mL) were placed in different test tubes and to each 10% aluminum chloride (0.1 mL), 1 M potassium acetate (0.1 mL), 80% methanol (1.5 mL) and distilled water (2.8 mL) were added and mixed. A blank was prepared in the same manner where 0.5 mL of distilled water was used instead of the sample or standard, and the amount of aluminum chloride was also replaced by distilled water. All tubes were incubated at room temperature for 30 min. The absorbance was taken at 415 nm. The concentration of flavonoid was expressed as mg gallic acid equivalent (GE) per gram of extract.

Collagen loss animal model. Twenty healthy male Wistar rats (250 $\pm$ 25 g) CV=10% were fed ad libitum and reared at 28 °C and a photoperiod of 12 hours. After a week of acclimatization, rats

were randomly divided into the following five groups: Sham/Untreated, UVB irradiation, UVB irradiation and 5% gel of CTFE and UVB irradiation and 10% CTFE gel. Each group consisted of five rats. This study used UVB light (broadband with peak emission at 302 nm CL-100M, UVP, USA). Rats were exposed to UVB light of 160 mJ/cm² for 30 minutes for 5 consecutive days according to a previous study with a slight modification (25). The 200 mg of CTFE gels were administered topically on the dorsal rat skin daily for up to 14 days. UVB group rats did not receive any treatment. On day 15, all rats were terminated, and skin tissue was isolated for further analysis.

Collagen analysis. The tissue paraffin block was cut using a microtome to a thickness of 5 μ m then stained with Masson Trichrome (Bio optica, catalog #04010802) and observed under the light microscope (Olympus CX21, Tokyo, Japan). The percentage of collagen density was calculated from the area of collagenous tissue formed on each slide using ImageJ.

GPx and PDGF gene expression by qRT-PCR. Total RNA from rat skin tissue was extracted with TRIzol (Invitrogen, Shanghai, China) according to the manufacturer's protocol. Briefly, first-stranded cDNA was synthesized with 1 g of total RNA using Super-Script II (Invitrogen, Massachusetts, USA). SYBR No ROX Green I dye (SMOBIO Technology Inc, Hsinchu, Taiwan) was used for reverse-transcription in a real-time PCR instrument (PCR max Eco 48), and mRNA levels of the PDGF and GPx genes were measured using the respective primers (Table 1). The used thermocycler conditions were as follows: initial step at 95°C for 10 minutes, followed by 50 cycles at 95°C for 15 seconds, and 60°C for 1 minute. The gene expression was recorded as the Cycles threshold (Ct). Data were obtained using Eco Softwa-

Table 1. Primer sequences for GPx, PDGF and GAPDH genes

Gene symbol	Primer sequence 5'→3'
GPx	Forward GPx 5'
	- AGTTCGGACATCAGGAGAATGGCA-3'
	Reverse GPx 5'
PDGF	- TCACCATTACCTCGCACTTCTCA-3'
	Forward PDGF 5'
	- GAGCTAGCG AGA ATC CCA AAA GCC TCAA-3'
GAPDH	Reverse PDGF 5'
	- CTCTCGAGG CGG GGT TGC AGA AGT GT-3'
	Forward GAPDH 5'
GAPDH	- GTCTCCTCTGACTTCAACAGCG-3'
	Reverse GAPDH 5'
	- ACCACCCTGTTGCTGTAGCCAA-3'

re v5.0 (Illumina Inc, San Diego, CA, USA). All reactions were performed in triplicate, and data analysis used the $2^{-\Delta\Delta}$ Ct method (Livak method).

Statistical analysis

All data are presented as mean $\pm$ standard deviation (SD). Data analysis used one-way ANOVA and continued with the Least Significant Difference (LSD) test with $p < 0.05$.

RESULTS

The phytochemical screening of crude ethanolic extract of *Clitoria ternatea* flower revealed the presence of some secondary metabolites such as alkaloid, saponin, tannin, and flavonoid (Table 2). The total flavonoid content of CTFE was 682.02 ± 9.48 mg GE/g. These values are higher than total flavonoid content of the same family with methanol solvent (26).

Table 2. Phytochemical screening of secondary metabolites from *Clitoria ternatea* flower extract

Chemical component	Name of the test	CTFE
Alkaloids	Wagner test	++
Flavonoids	Wilstater test	+++
Tannins	Braemer's test	+
Saponins	Forth test	+
Steroids	Lieberman Burchardt test	-
Terpenoids	Lieberman Burchardt test	+

CTFE, *Clitoria ternatea* flower extract

In this study, we validate the collagen loss induced-UVB under Masson Trichrome staining. Based on the results of histological observations, the collagen content in the dermal tissue induced by UVB significantly decreased, as indicated by the turquoise colour on the Masson Trichrome staining (Figure 1). These data indicated that the UVB irradiation successfully inhibit collagen synthesis leading to collagen loss condition.

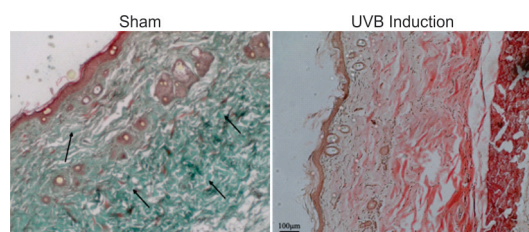


Figure 1. Collagen expression in all study groups, sham and UVB induction group. Histological view of skin tissue with specific Masson Trichrome staining that is sensitive to collagen in green (100x magnification)

A significant increase of CTFE gels of GPx gene expression in doses-dependent manner was found (Figure 2). In the control group, naturally in-

duced GPx gene expression was 4.90 ± 1.64 - fold greater than in the sham group. The 5% and 10% of CTFE groups had significantly increased GPx gene expression of 6.01 ± 1.25 and 9.51 ± 1.83 , respectively, - fold greater than the sham group.

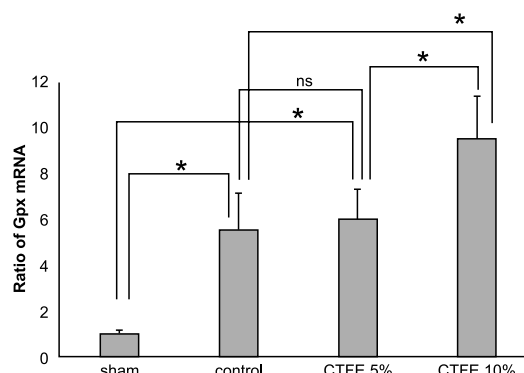


Figure 2. The effect of *Clitoria ternatea* flower extract (CTFE) on GPx expression on UVB irradiation-induced collagen loss rat models. Data are presented as fold change in gene expression relative to UVB unexposed group

* $p < 0.05$; ns, non-significant

CTFE gels significantly increased PDGF gene expression in doses-dependent manner (Figure 3). In the control group, PDGF gene expression was depleted until 0.032 ± 0.01 -fold greater than the sham group. The 5% and 10% of CTFE groups had significantly increased PDGF gene expression 0.44 ± 0.15 and 4.36 ± 1.18 , respectively, - fold greater than the sham group.

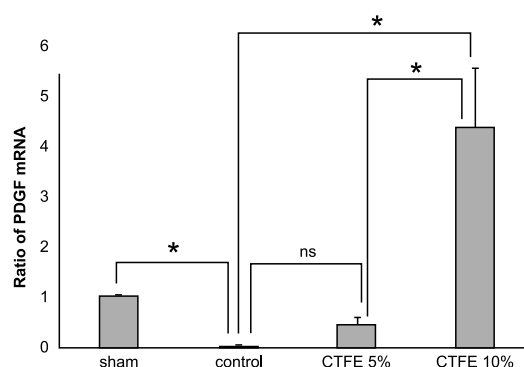


Figure 3. The effect of *Clitoria ternatea* flower extract (CTFE) on platelet-derived growth factor (PDGF) expression on UVB irradiation-induced collagen loss rat models. Data are presented as fold change in gene expression relative to UVB unexposed group

* $p > 0.05$

DISCUSSION

In this study the detected phytochemical compounds are known to have medicinal importance including antioxidant, anticancer, antiinflammation, and antibacterial activity. A previous study

also reported that flavonoids compound has antioxidant functions and inhibiting a high scavenging activity of harmful ROS, including UVB irradiation (27). Furthermore, in this study we evaluated the effect of CTFE on the GPx and PDGF gene expression on the UVB irradiation-induced collagen loss rat models.

The key point for a limiting oxidative stress and preventing UVB-induced damage to the skin is a removal or detoxification of reactive oxygen species (ROS). This is accomplished in large part by antioxidant enzymes. A number of enzymes have been identified that are involved in this process including the ROS scavengers including glutathione peroxidase (GPx) (28). UVB-induced oxidative stress has been reported to be associated with transient decreases in GPx activity in mouse skin (27-28). Reduced expression of SOD and GPx activity has also been described in human keratinocytes treated with UVB *in vitro* (29-31). Flavonoids scavenge free radicals effectively by forming semiquinone radicals, which bind to free radicals to form a stable quinone structure (32). In addition, previous study supported the previous study that flavonoid compounds such as quercetin form hydrogen bonds with Ser212 through the 3'-OH group, thereby inhibiting the activity of kinase protein (MEK1) (33). Quercetin also inhibits the activation of phosphoinositide 3-kinase (PI3K) and activates protein kinase (MAPK) to induce the expression of antioxidant enzymes (29). The ability of flavonoid compounds as antioxidants has been shown to reduce oxidative stress conditions by increasing the GPx enzyme (27,31,34). In this study we also evaluated the effect of CTFE on the PDGF gene expression.

UVB irradiation suppressed PDGF expression leading to inhibition of TGF- β expression on the collagen synthesis pathway (35,36). TGF- β is a prototypical fibrogenic cytokine, which increases the

expression of extracellular matrix (ECM) genes and regulates the downregulation of matrix-degrading enzymes through the SMAD pathway, mainly associated with collagen synthesis (37-39).

Previous studies reported that the C-6 structure of flavonoids inhibited the expression of the TGF- β /Smad and PI3K/mTOR signalling pathways. This structure also inhibited the α -SMA expression and collagen synthesis (40). Flavonoid also induced the expression of PDGF through MAPK pathway (41). The flavonoid chrysoeriol induced PDGF-induced ERK1/2 activation (42). A previous study reported that PDGF mediated collagen synthesis through the stimulation of type III collagen production (43). The B ring structure of flavonoids also acts as a scavenger of hydroxyl free radicals, so the ROS produced due to UVB rays can be suppressed (44). If ROS overexpression is not established, the growth factor activation pathway is unaffected, and collagen synthesis can occur normally (45).

In conclusion, the CPTE may inhibit UVB irradiation-induced collagen loss through elevation GPx and PDGF gene expression. CPTE might accelerate the restoration of UVB irradiation-induced collagen loss.

ACKNOWLEDGMENT

We would like to thank the Stem Cell and Cancer Research (SCCR) Laboratory, the Medical Faculty at Sultan Agung Islamic University (UNISSULA), Semarang, Indonesia, and all who contributed to this research.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interest: None to declare

REFERENCES

1. Subedi L, Lee TH, Wahedi HM, Baek SH, Kim SY. Resveratrol-enriched rice attenuates UVB-ROS-induced skin aging via downregulation of inflammatory cascades. *Oxid Med Cell Longev* 2017; 2017.
2. Mandal JP, Shiue CN, Chen YC, Lee MC, Yang HH, Chang HH, Hu CT, Liao PC, Hui LC, You RI, Wu WS. PKC δ mediates mitochondrial ROS generation and oxidation of HSP60 to relieve RKIP inhibition on MAPK pathway for HCC progression. *Free Radic Biol Med* 2021; 163:69-87.
3. Lim JY, Kim OK, Lee J, Lee MJ, Kang N, Hwang JK. Protective effect of the standardized green tea seed extract on UVB-induced skin photoaging in hairless mice. *Nutr Res Pract* 2014; 8:398-403.
4. Rong J, Shan C, Liu S, Zheng H, Liu C, Liu M, Jin F, Wang L. Skin resistance to UVB-induced oxidative stress and hyperpigmentation by the topical use of *Lactobacillus helveticus* NS8-fermented milk supernatant. *J Appl Microbiol* 2017; 123:511-23.

5. Zasada M, Budzisz E. Retinoids: active molecules influencing skin structure formation in cosmetic and dermatological treatments. *Postepy Dermatolog Alergol* 2019; 36:392–7.
6. Hada M, Mondul AM, Weinstein SJ, Albanes D. Serum retinol and risk of overall and site-specific cancer in the ATBC study. *Am J Epidemiol* 2020; 189:532–42.
7. Iamsaard S, Burawat J, Kanla P, Arun S, Sukhorum W, Sripanidkulchai B, Uabundit N, Wattathorn J, Hipkiao W, Fongmoon D, Kondo H. Antioxidant activity and protective effect of *Clitoria ternatea* flower extract on testicular damage induced by ketoconazole in rats. *J Zhejiang Univ Sci B* 2014; 15:548–55.
8. Vidana Gamage GC, Lim YY, Choo WS. Anthocyanins From *Clitoria ternatea* Flower: Biosynthesis, Extraction, Stability, Antioxidant Activity, and Applications. *Front Plant Sci* 12:792303.
9. Ungur RA, Borda IM, Codea RA, Ciortea VM, Năsu BA, Muste S, Sarpataky O, Filip M, Irsay L, Crăciun EC, Căinap S. A flavonoid-rich extract of *Sambucus nigra* L. reduced lipid peroxidation in a rat experimental model of gentamicin nephrotoxicity. *Materials* 2022; 15:772–9.
10. Lei L, Chen Y, Ou L, Xu Y, Yu X. Aqueous root extract of *Asparagus cochinchinensis* (Lour.) Merr. Has antioxidant activity in D-galactose-induced aging mice. *BMC Complement Altern Med* 2017; 17:1–7.
11. Ighodaro OM, Akinloye OA. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): their fundamental role in the entire antioxidant defence grid. *Alexandria Journal of Medicine* 2018; 54:287–93.
12. Leyva-López N, Gutierrez-Grijalva EP, Ambríz-Pérez DL, Basilio Heredia J. Flavonoids as cytokine modulators: a possible therapy for inflammation-related diseases. *Int J Mol Sci* 2016; 17: 921–30.
13. Seo J, Lee HS, Ryoo S, Seo JH, Min BS, Lee JH. Tangeretin, a citrus flavonoid, inhibits PGDF-BB-induced proliferation and migration of aortic smooth muscle cells by blocking AKT activation. *Eur J Pharmacol* 2011; 673:56–64.
14. Xu B, Wang X, Wu C, Zhu L, Chen O, Wang X. Flavonoid compound icariin enhances BMP-2 induced differentiation and signalling by targeting to connective tissue growth factor (CTGF) in SAMP6 osteoblasts. *PLoS One* 2018; 13.
15. Thilavech T, Adisakwattana S, Channuwong P, Rada-rit K, Jantarapat K, Ngewlai K, Sonprasan N, Chusak C. *Clitoria ternatea* flower extract attenuates postprandial lipemia and increases plasma antioxidant status responses to a high-fat meal challenge in overweight and obese participants. *Biology* 2021; 10:975–82.
16. Nugraha AP, Rahmadhani D, Puspitaningrum MS, Rizqianti Y, Kharisma V, Ernawati DS. Molecular docking of anthocyanins and ternatin in *Clitoria ternatea* as coronavirus disease oral manifestation therapy. *J Adv Pharm Technol Res* 2021; 12:362–7.
17. Zakaria NNA, Okello EJ, Howes MJ, Birch-Machin MA, Bowman A. *In vitro* protective effects of an aqueous extract of *Clitoria ternatea* L. flower against hydrogen peroxide-induced cytotoxicity and UV-induced mtDNA damage in human keratinocytes. *Phytotherapy Research* 2018; 32:1064–72.
18. Amalina ND, Wahyuni S, Harjito. Cytotoxic effects of the synthesized *Citrus aurantium* peels extract nanoparticles against MDA-MB-231 breast cancer cells. *J Phys Conf Ser* 2021; 1918(3).
19. Suzery M, Cahyono B, Amalina ND. Antiproliferative and apoptosis effect of hyptolide from *Hyptis pectinata* (L.) Poit on human breast cancer cells. *Journal of Applied Pharmaceutical Science* 2020; 10:1–6.
20. Fernanda MAHF, Andriani RD, Estulenggani Z, Kusumo GG. Identification and determination of total flavonoids in ethanol extract of old and young ang-sana leaves (*Pterocarpus indicus* Willd.) using visible spectrophotometry. In *Scitepress* 2019; 541–4.
21. Y R, Y I, M.S I. Comparative phyto-constituents analysis from the root bark and root core extractives of *Cassia ferruginea* (Schrad D. C) plant. *Scholars Journal of Agriculture and Veterinary Sciences* 2016; 3:275–83.
22. Sri Sulasmi E, Saptasari M, Mawaddah K, Ama Zulfia F. Tannin identification of 4 species pteridophyta from baluran national park. In: *Journal of Physics: Conference Series*. Institute of Physics Publishing. 2019.
23. Adu JK, Amengor CDK, Kabiri N, Orman E, Patamia SAG, Okrah BK. Validation of a simple and robust Liebermann-Burchard colorimetric method for the assay of cholesterol in selected milk products in Ghana. *Int J Food Sci*. 2019; 2019.
24. Pękal A, Pyrzyńska K. Evaluation of aluminium complexation reaction for flavonoid content assay. *Food Anal Methods* 2014; 7:1776–82.
25. Wise LM, Stuart GS, Real NC, Fleming SB, Mercer AA. VEGF receptor-2 activation mediated by VEGF-E limits scar tissue formation following cutaneous injury. *Adv Wound Care* 2018; 7:283–97.
26. Putra A, Alif I, Hamra N, Santosa O, Kustiyah AR, Muhar AM, Lukman K. MSC-released TGF- β regulate α -SMA expression of myofibroblast during wound healing. *J Stem Cells Regen Med* 2020; 16:73–9.
27. Hao J, Lou P, Han Y, Zheng L, Lu J, Chen Z, Ni J, Yang Y, Xu M. Ultraviolet-B irradiation increases antioxidant capacity of Pakchoi (*Brassica rapa* L.) by inducing flavonoid biosynthesis. *Plants* 2022; 11:776.
28. Polefka TG, Meyer TA, Agin PP, Bianchini RJ. Effects of solar radiation on the skin. *J Cosmet Dermatol* 2012; 11:134–43.
29. Brunetti C, Di Ferdinando M, Fini A, Pollastri S, Tattini M. Flavonoids as antioxidants and developmental regulators: relative significance in plants and humans. *Int J Mol Sci* 2013; 14: 3540–55.
30. Hasanuzzaman M, Bhuyan MHMB, Zulfiqar F, Raza A, Mohsin SM, al Mahmud J, Mujita M, Fotoluos V. Reactive oxygen species and antioxidant defense in plants under abiotic stress: Revisiting the crucial role of a universal defense regulator. *Antioxidants* 2020; 9:1–52.
31. Bajpai VK, Baek KH, Kang SC. Antioxidant and free radical scavenging activities of taxoquinone, a diterpenoid isolated from *Metasequoia glyptostroboides*. *S Afr J Bot* 2017; 111:93–8.
32. Sungkar T, Putra A, Lindarto D, Sembiring RJ. Intravenous umbilical cord-derived mesenchymal stem cells transplantation regulates hyaluronic acid and interleukin-10 secretion producing low-grade liver fibrosis in experimental rat. *Med Arch* 2020; 17:177–82.

33. Baby B, Antony P, Al Halabi W, Al Homedi Z, Vijayan R. Structural insights into the polypharmacological activity of quercetin on serine/threonine kinases. *Drug Des Devel Ther* 2016; 10:3109.
34. Addison R, Weatherhead SC, Pawitri A, Smith GR, Rider A, Grantham HJ, Cockell SJ, Reynolds NJ. Therapeutic wavelengths of ultraviolet B radiation activate apoptotic, circadian rhythm, redox signalling and key canonical pathways in psoriatic epidermis. *Redox Biol* 2021; 41:101924.
35. Karamichos D. Regulation of corneal fibroblast morphology and collagen. *Journal Tissue Viability* 2009; 33:1–15.
36. Al-Qattan MM, Abd-Elwahed MM, Hawary K, Arafa MM, Shier MK. Myofibroblast expression in skin wounds is enhanced by collagen III suppression. *Bio-med Res Int* 2015; 2015.
37. Lin PS, Chang HH, Yeh CY, Chang MC, Chan CP, Kuo HY, Liu HC, Liao WC, Jeng PY, Yeung SY, Jeng JH. Transforming growth factor beta 1 increases collagen content, and stimulates procollagen I and tissue inhibitor of metalloproteinase-1 production of dental pulp cells: Role of MEK/ERK and activin receptor-like kinase-5/Smad signaling. *J Formos Med Assoc* 2017; 116:351–8.
38. Hamra NF, Putra A, Tjipta A, Amalina ND, Nasihun T. Hypoxia mesenchymal stem cells accelerate wound closure improvement by controlling α -smooth muscle actin expression in the full-thickness animal model. *Open Access Maced J Med Sci* 2021; 9:35–41.
39. Drawina P, Putra A, Nasihun T, Prajoko YW, Dirja BT, Amalina ND. Increased serial levels of platelet-derived growth factor using hypoxic mesenchymal stem cell-conditioned medium to promote closure acceleration in a full-thickness wound. *Indones J Biotechnol* 2022; 27:36–42.
40. Luo Y, Ren Z, Du B, Xing S, Huang S, Li Y, Lei Z, Li D, Chen H, Huang Y, Wei G. Structure identification of viceninii extracted from *Dendrobium officinale* and the reversal of TGF- β 1-induced epithelial–mesenchymal transition in lung adenocarcinoma cells through TGF- β /Smad and PI3K/Akt/mTOR signaling pathways. *Molecules* 2019; 24:144–152.
41. Putra A, Rosdiana I, Darlan DM, Alif I, Hayuningtyas F, Wijaya I, Aryanti R, Makarim FR, Antari AD. Intravenous administration is the best route of mesenchymal stem cells migration in improving liver function enzyme of acute liver failure. *Folia Med* 2020; 62:52–8.
42. Cha BY, Shi WL, Yonezawa T, Teruya T, Nagai K, Woo JT. An inhibitory effect of chrysoeriol on platelet-derived growth factor (PDGF)-induced proliferation and PDGF receptor signaling in human aortic smooth muscle cells. *J Pharmacol Sci* 2009; 110:105–10.
43. Amalina ND, Suzery M, Cahyono B. Cytotoxic activity of *Hyptis pectinate* extracts on MCF-7 human breast cancer cells. *Indonesian Journal of Cancer Chemoprevention* 2020; 11:1–6.
44. Masyithah Darlan D, Munir D, Karmila Jusuf N, Putra A, Ikhsan R, Alif I. In vitro regulation of IL-6 and TGF- β by mesenchymal stem cells in systemic lupus erythematosus patients. Vol. 17, *Med Glas (Zenica)*. 2020; p. 408–413.
45. Restimulia L, Ilyas S, Munir D, Putra A, Madiadipoe-ra T, Farhat F, Sembiring RJ, Ichwan M, Amalina ND, Alif I. The CD4⁺ CD25⁺ FoxP3⁺ regulatory T cells regulated by MSCs suppress plasma cells in a mouse model of allergic rhinitis. *Med Arch* 2021; 75:256.

Relation between thyroid hormonal status, neutrophil-lymphocyte ratio and left ventricular systolic function in patients with acute coronary syndrome

Mirela Halilčević¹, Edin Begić^{2,3}, Amela Džubur⁴, Alen Džubur¹, Buena Aziri³, Azra Durak-Nalbantić¹, Alden Begić¹, Ammar Brkić⁵, Ena Gogić⁶, Orhan Lepara⁷

¹ Department of Cardiology, Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Centre University of Sarajevo, ² Department of Cardiology, General Hospital "Prim. Dr. Abdulah Nakaš", ³ Department of Pharmacology, Sarajevo Medical School, Sarajevo School of Science and Technology, ⁴ Department of Public Health, Faculty of Medicine, University of Sarajevo; Sarajevo, ⁵ Internal Medicine Clinic, University Clinical Centre of Tuzla, Tuzla, ⁶ Department of Physical Medicine and Rehabilitation, Medical Institute Gata, Bihać, ⁷ Department of Human Physiology, School of Medicine, University of Sarajevo, Sarajevo; Bosnia and Herzegovina

ABSTRACT

Aim To examine a relation of thyroid function, neutrophil-lymphocyte ratio (NLR) with left ventricular function measured through the left ventricular ejection fraction (LVEF) in patients with acute myocardial infarction treated with percutaneous coronary intervention (PCI).

Methods This prospective research involved 160 consecutive patients with acute myocardial infarction. Patients were divided into those with normal thyroid hormone status (n=80) and those with hypothyroidism (newly diagnosed) (n=80). Inflammatory parameters and parameters of hormonal status were taken for analysis: thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), free thyroxine (FT4), and free triiodothyronine (FT3). All patients underwent transthoracic echocardiographic examination (TTE) five days upon admission, and left ventricular ejection fraction (LVEF) was analysed.

Results Significant difference between the two groups was verified in values of T3, T4, erythrocytes, haemoglobin, haematocrit, neutrophil, lymphocytes, NLR, C-reactive protein (CRP) and sedimentation rate. Patients with euthyroidism had a higher frequency of coronary single-vessel disease (p=0.035) and a significantly lower frequency of triple vessel disease (p=0.046), as well as a higher median value of LVEF (p=0.003). There was a significant correlation between LVEF with haemoglobin values (p=0.002), NLR (p=0.001), and CRP (p=0.001).

Conclusion The altered status of the thyroid gland in acute myocardial infarction is associated with the severity of the coronary blood vessel lesion, LVEF and correlates with inflammatory response.

Key words: myocardial infarction, prognosis, risk

Corresponding author:

Mirela Halilčević
Department of Cardiology,
Clinic for Heart, Blood Vessel and
Rheumatic Diseases Clinical Centre
University of Sarajevo
Bolnička 25, 71000 Sarajevo,
Bosnia and Herzegovina
Phone: +387 33 297 521;
Fax: +387 33 297 805;
E-mail: mirela_hh@hotmail.co.uk
ORCID ID: <https://orcid.org/0000-0002-0025-4835>

Original submission:

15 September 2022;

Revised submission:

22 September 2022;

Accepted:

26 October 2022

doi: 10.17392/1543-22

Med Glas (Zenica) 2023; 20(1): 22-27

INTRODUCTION

Ischemic heart disease is differentiated in two directions, as a chronic form (stable angina pectoris) and as an acute form (acute coronary syndrome - ACS) (1). The term ACS refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) (2). In 2018, the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction defined myocardial infarction, either STEMI or NSTEMI, as the presence of an acute myocardial injury, verified by elevated levels of myocardial necrosis enzymes, as a consequence of acute myocardial ischemia (the most severe forms of myocardial ischemia, if they are not quite short-term, can lead to myocardial infarction, which occurs distal to the site of critical narrowing of the coronary artery) (2). NSTEMI and STEMI are characterized as an increase in troponin above the >99th percentile of reference values (3). Poor therapeutic adherence is an important barrier to achieving optimal treatment goals and is associated with increased rate of major adverse cardiac events (MACE). Delayed follow-up of patients after acute myocardial infarction (AMI) results in a poorer short-term and long-term drug treatment (4,5).

Despite progress in the treatment of myocardial infarction, damage to the myocardium and subsequent remodelling of the left ventricle remain the main serious problems that affect the prognosis of patients, and in modern cardiology, the focus is on the prediction of a new cardiovascular incident, that is, on its primary and secondary prevention (4,5). For the functioning of the cardiovascular system, maintaining thyroid hormone homeostasis is of great importance (6). Triiodothyronine (T3) is a regulator of inotropic and lusitropic (relaxation) properties of the heart, thanks to its influence on myosin isoforms and especially on proteins that manage calcium (6). Thyroid hormones have a positive effect on oxidative stress after myocardial infarction. T3 and tetraiodothyronine or thyroxine (T4) reduce the levels of reactive oxygen species (ROS) induced

by myocardial infarction (6). Hypothyroidism is linked to diastolic hypertension, dyslipidaemia, atherosclerotic plaque progression and instability and endothelial dysfunction (7). Also, in an acute incident, there are variations in thyroid plasma concentration, which themselves can affect the patient's prognosis as follows: inhibition of the 5'-deiodination of T4, resulting in increased plasma reverse T3 and decreased plasma T3 values, and in a lower metabolic clearance of T4; increased secretion of TSH (provoked by the lower T3 levels) resulting in increased thyroidal secretion of T4 and T3, which is then switched off by the negative feedback of thyroid hormones on the pituitary (8). In the experimental application of T3 and T4 in rats that suffered a myocardial infarction, there was a normalization of cardiac redox status and prevention of lipid peroxidation, which was associated with the alleviation of cardiac remodelling after ischemic injury (9) suggesting that oxidative stress may play an important role in the cardioprotective effect of T3 and T4.

The potential impact of hormonal status on the course of myocardial infarction and heart failure may significantly impact future research on the individualization of myocardial infarction and heart failure treatment, depending on the patient's thyroid status. Considering the importance of thyroid hormones in the metabolism, the question arises whether their values can be important for the stratification of patients regarding the outcome and occurrence of MACE during and after AMI. There were no similar investigations in Bosnia and Herzegovina.

The aim of the study was to examine the association of thyroid function, neutrophil-lymphocyte ratio (NLR) with left ventricular function measured through ejection fraction of left ventricle (EFLV) in a patient with acute myocardial infarction treated with percutaneous coronary intervention (PCI).

PATIENTS AND METHODS

Patients and study design

This prospective research involved 160 consecutive patients with ACS that were hospitalized in the Clinic for Heart, Blood Vessel and Rheumatic Diseases, Clinical Centre of the University of Sarajevo during the period January-July 2022. The pa-

tients were divided into those with normal thyroid hormone status (n=80) and those with hypothyroidism (newly diagnosed) (n=80). Inclusion criteria were: age over 18 years, patients with ACS (STEMI or NSTEMI), elevated cardio specific enzymes for myocardial necrosis (creatin kinase (CK), creatine kinase-MB (CK-MB), cardiac troponin I), percutaneous coronary intervention (PCI) performed during hospitalization, and newly discovered hyper or hypothyroidism. Exclusion criteria were previous myocardial infarction, previous PCI or myocardial revascularization, primary cardiomyopathy, previous hypothyroidism or hyperthyroidism, diabetes mellitus, patients with chronic renal failure and creatinine >2.0 mg/dL (176.8 μmol/L) and patients on a chronic haemodialysis program, pregnancy, malignant disease, treatment with amiodarone, patients with psychiatric diagnoses, patients who were not motivated to perform an interventional procedure.

An informed consent was obtained from all patients following an explanation of the purpose of the study. An ethical approval was obtained from the Ethical Committee of the Clinical Centre of the University of Sarajevo.

Methods

Inflammatory parameters (sedimentation rate, leukocytes, platelets, haemoglobin, haematocrit, neutrophils, lymphocytes, neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), and fibrinogen) were measured at admission and 24-48 hours after the PCI procedure. Parameters of hormonal status, thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), free thyroxine (FT4), and free triiodothyronine (FT3)) were taken within 24 hours of admission. The maximum values of inflammatory parameters were analysed. Reference ranges for evaluated laboratory parameters were: erythrocytes $4.34-5.72 \times 10^{12}/L$ and $3.86-5.08 \times 10^{12}/L$ for males and females respectively; leukocytes $3.4-9.7 \times 10^9/L$; haemoglobin 137-175 g/L in males and 119-157 g/L in females; haematocrit 0.41-0.53 % in males and 0.35-0.47% in females; platelets $158-424 \times 10^9/L$ for males and females; neutrophil granulocytes 44-72%; lymphocytes 20-46%; fibrinogen 2.0-4.0 g/L; sedimentation 0 to 22 mm/h for males and 0 to 29 mm/hr for females; CRP up to 5.0 mg/L; T4 66-181 nmol/L; T3 1.3-3.1 nmol/L;

TSH 0.27-4.20 μmol/mL; FT4 12.0-22.0 pmol/L; FT3 3.1-6.8 pmol/L.

Intrahospital complications were recorded (ventricular heart rhythm disorders, atrial tachyarrhythmias, acute heart failure and intrahospital death).

All patients underwent transthoracic echocardiographic examination (TTE) after five days of admission, and LVEF was measured by the Simpson method (10).

Statistical analysis

Tests of descriptive statistics were performed, with the display of measures of central tendency and dispersion. Each variable was tested for belonging to a normal distribution using the Kolmogorov-Smirnov test. Quantitative variables were compared by t-test with a correction for unequal variances where they were normally distributed. The Kruskal-Wallis test was used for the non-parametric analysis of the comparison of average values. Categorical variables were analysed with the χ^2 -test, with Yates's correction for continuity for 2x2 tables, or with Fisher's test for analyses in which cells were less than 5. A relative risk determination was calculated using the usual methodology with 2x2 tables. A statistical level of 95% ($p < 0.05$) was taken as significant.

RESULTS

The average age of patients was 61 ± 11 years; in the group of patients with hypothyroidism it was 64 ± 10 and in patients with euthyroidism 58 ± 11 years ($p < 0.001$). There were males predominated in the total sample, 111 (69.4%) ($p = 0.002$), as well as in the group with euthyroidism, 65 (81.3%), in comparison with the group of patients with hypothyroidism, 46 (57.5%). A significant difference was verified in monitored parameters (T3, T4, erythrocytes, haemoglobin, haematocrit, neutrophil, lymphocytes, NLR, CRP, sedimentation). In accordance with coronary angiography, patients with euthyroidism were more frequently without the presence of coronary disease ($p = 0.01$) and single-vessel disease ($p = 0.035$), and less frequently with triple vessel disease ($p = 0.046$). No statistically significant difference was verified between the groups in two-vessel and multivessel coronary disease occurrence. In both groups, two (2.5%) patients were diagnosed with myocardial infarction

with non-obstructive coronary arteries (MINOCA). A total of 58 (72.5%) patients with euthyroidism achieved complete resolution of the ST segment compared to 44 (55%) of those with hypothyroidism ($p=0.02$). Patients with hypothyroidism had a 38.9% higher relative risk for incomplete or absent ST-segment resolution after PCI.

The median value of LVEF in the group of patients with hypothyroidism was 40% (36-45%), while in the group with euthyroid hormone level it was 44% (40-48%) (patients with euthyroid hormone level had a higher median value LVEF) ($p=0.003$).

An indication for coronary artery bypass graft (CABG) during hospitalization was significantly more frequent ($p=0.045$) in the group of patients with hypothyroidism, 21 (26.3%), compared to euthyroid patients, 10 (12.5%).

The total number of in-hospital complications was significantly higher ($p<0.001$) within the group of patients with hypothyroidism, 42 (52.5%), in comparison with patients with euthyroid hormone level, 17 (21.3%).

Atrial tachyarrhythmia was also significantly more frequent ($p=0.002$) in the group with hypothyroidism, 15 (18.8%), than in the euthyroid group, two (2.5%). There was a significant correlation between EFLV with haemoglobin values ($p=0.002$), NLR ($p=0.001$), and CRP ($p=0.001$) (Table 1).

Table 1. Monitored parameters in two group of patients

Parameter	Euthyroidism (Mean $\pm$ SD) (n=80)	Hypothyroidism (Mean $\pm$ SD) (n=80)	p
Triiodothyronine (T3) (nmol/L)	1.96 $\pm$ 0.55	1.21 $\pm$ 0.31	<0.001
Thyroxine (T4) (nmol/L)	111.40 $\pm$ 20.83	103.82 $\pm$ 24.0	0.034
Free triiodothyronine (T3) (pmol/L)	4.58 $\pm$ 0.66	4.20 $\pm$ 1.99	0.112
Free thyroxine (T4) (pmol/L)	16.82 $\pm$ 2.69	16.28 $\pm$ 4.08	0.325
Erythrocytes (x10 ¹² /L)	5.02 $\pm$ 0.48	4.73 $\pm$ 0.48	<0.001
Leucocytes (x10 ⁹ /L)	9.67 $\pm$ 1.98	9.55 $\pm$ 2.56	0.732
Platelets (x10 ⁹ /L)	225.35 $\pm$ 68.56	240.65 $\pm$ 67.56	0.157
Haemoglobin (g/L)	152.61 $\pm$ 14.95	144.04 $\pm$ 17.00	0.001
Haematocrit (%)	45.32 $\pm$ 4.50	43.35 $\pm$ 5.37	0.013
Neutrophils %	4.57 $\pm$ 1.37	6.94 $\pm$ 1.48	<0.001
Lymphocytes (%)	1.26 $\pm$ 0.60	1.08 $\pm$ 0.38	0.021
Neutrophil/lymphocyte ratio	4.10 $\pm$ 1.47	6.76 $\pm$ 1.65	<0.001
C-reactive protein (mg/L)	10.85 $\pm$ 10.58	19.34 $\pm$ 19.52	0.001
Fibrinogen (g/L)	4.62 $\pm$ 2.46	4.55 $\pm$ 2.20	0.858
Sedimentation (mm/h)	9.01 $\pm$ 7.30	23.24 $\pm$ 14.84	<0.001

SD, standard deviation;

DISCUSSION

In patients with decreased thyroid hormone values, CRP and sedimentation values were elevated, indicating that these patients have an increased inflammatory response. In addition, haemoglobin, haematocrit and erythrocyte values were decreased. The number of intrahospital complications in patients with hypothyroidism was higher, and the LVEF itself was lower. Our data revealed that there was a significant correlation between LVEF with haemoglobin, NLR and CRP values. Research indicates CRP levels are elevated during progressive thyroid failure, which could be an additional risk factor for coronary heart disease in hypothyroid patients (11). Interestingly, assessing CRP and troponin levels, a prospective multicentre observational study by Jabbar et al. indicated a twofold higher risk of mortality in AMI patients with low serum T3 levels (though not on other forms of thyroid dysfunction), implying a potential therapeutic modality for this group of patients (12). However, in a study conducted by Wang et al. it was observed that, in STEMI patients, CRP levels were negatively correlated with FT3 but positively correlated with cardiac injury biomarkers, suggesting that the link between AMI and a decreased thyroid function profile could be well mediated by an inflammatory response (13). In our study, euthyroid patients were more frequently without the presence of coronary disease on coronary angiography, as well as with single-vessel disease; patients with hypothyroidism had a significantly higher relative risk for incomplete or absent ST-segment resolution after PCI. Wang et al. indicated that in AMI patients, there was an increased risk of revascularization and heart failure due to hypothyroid status, which was therefore considered to be an independent prognostic factor for major adverse cardiovascular events (14). Our study found that the patients with euthyroid hormone level had a higher median value of LVEF. Interestingly, in the study of patients with subclinical hypothyroidism and AMI it was suggested that thyroid replacement therapy did not substantially improve left ventricular ejection fraction (LVEF) during the follow-up period, thus not favouring the idea that patients with AMI should be treated for subclinical hypothyroidism (15). Moreover, in our study, the total number of in-hospital com-

plications was significantly more frequent within the group of patients with hypothyroidism. In particular, an indication for CABG during hospitalization was significantly more frequent in the group of patients with hypothyroidism. Similarly, an observational study evaluating the TSH and FT4 level of STEMI patients with previously unknown and untreated subclinical hypothyroidism (SCH), who underwent primary PCI, reported poor in-hospital outcomes compared to euthyroid patients; also, patients with SCH were more likely to have lower LVEF (equal to or less than 40%) level, contributing to short-term and long-term mortality (16,17). These findings in patients with hypothyroid status could be attributed to decreased nitric oxide availability, which may contribute to endothelial dysfunction, hampering flow-mediated vasodilation, as well as mitochondrial oxidative stress caused by elevated plasma inflammatory markers or by impaired left ventricular systolic function (16,18).

Furthermore, Li et al. found that, compared to euthyroid patients, STEMI patients with subclinical hyperthyroidism at admission, and those with low baseline T3 level, had a worse prognosis and an increased risk of in-hospital mortality (19).

Limitations of this study include the observational study design and a relatively small sample

size. However, one of the study's strengths is that it evaluated relevant variables affecting thyroid function. Moreover, the prospective nature of our study allowed for the systematic collection of all pertinent data. The paper indicates the importance of thyroid hormone in the evaluation of the inflammatory process during AMI and indicates importance of thyroid hormone in MACE prediction.

In conclusion, the cardiovascular system is considerably and adversely impacted by the role of TSH, its absence, as well as alterations in thyroid hormone concentrations. In ACS patients, routine thyroid function testing before performing PCI should be done. The altered status of the thyroid gland in acute myocardial infarction is associated with the severity of the coronary blood vessel lesion, LVEF and correlates with inflammatory response. Routine analysis of the hormonal status of the thyroid gland along with other risk factors enables better screening of patients with a higher probability of developing in-hospital complications and a worse outcome in acute myocardial infarction.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

REFERENCES

1. Sirajuddin A, Mirmomen SM, Kligerman SJ, Groves DW, Burke AP, Kureshi F, White CS, Arai AE. Ischemic heart disease: noninvasive imaging techniques and findings. *Radiographics* 2021; 41:990-1021.
2. Bhatt DL, Lopes RD, Harrington RA. Diagnosis and treatment of acute coronary syndromes: a review. *JAMA* 2022; 327:662-75.
3. Begic E, Obradovic S, Jankovic S, Romanovic R, Djenic N, Dzudovic B, Jovic Z, Malovic D, Subota V, Stavric M, Ljuca F, Kusljagic Z. Increased C-reactive protein is associated with major adverse cardiovascular events after STEMI. *Erciyes Med J* 2020; 42:276-80.
4. Obradovic S, Begic E, Jankovic S, Romanovic R, Djenic N, Dzudovic B, Jovic Z, Malovic D, Subota V, Stavric M, Ljuca F, Kusljagic Z. Association of PC and AT levels in the early phase of STEMI treated with pPCI with LV systolic function and 6-month MACE. *Acta Clin Belg* 2020; 76:1-7.
5. Arambam P, Kaul U, Ranjan P, Janardhanan R. Prognostic implications of thyroid hormone alterations in acute coronary syndrome - a systematic review. *Indian Heart J* 2021; 73:143-8.
6. Klein I, Danzi S. Thyroid disease and the heart. *Circulation* 2007; 116:1725-35.
7. Wiersinga WM, Lie KI, Touber JL. Thyroid hormones in acute myocardial infarction. *Clin Endocrinol (Oxf)* 1981; 14:367-74.
8. Ojamaa K, Kenessey A, Shenoy R, Klein I. Thyroid hormone metabolism and cardiac gene expression after acute myocardial infarction in the rat. *Am J Physiol Endocrinol Metab* 2000; 279:E1319-24.
9. Gray L, Chen F, Teeter EG, Kolarczyk LM, Smeltz AM. Evaluation of the Simpson's method to determine left ventricular ejection fraction using the transgastric two-chamber view. *Semin Cardiothorac Vasc Anesth* 2022; 26: 195-9.
10. Christ-Crain M, Meier C, Guglielmetti M, Huber PR, Riesen W, Staub JJ, Müller B. Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. *Atherosclerosis* 2003; 166:379-86.
11. Jabbar A, Ingole L, Thomas H, Carey P, Junejo S, Addison C, Vernazza J, Austin D, Greenwood JP, Zaman A, Razvi S. Prevalence, predictors and outcomes of thyroid dysfunction in patients with acute myocardial infarction: the ThyAMI-1 study. *J Endocrinol Invest* 2021; 44:1209-18.

12. Wang WY, Tang YD, Yang M, Cui C, Mu M, Qian J, Yang YJ. Free triiodothyronine level indicates the degree of myocardial injury in patients with acute ST-elevation myocardial infarction. *Chin Med J (Engl)* 2013; 126:3926-9.
13. Wang W, Wang S, Zhang K, Chen J, Zhang X, Shao C, Li P, Tang YD. Hypothyroidism is associated with clinical outcomes in patients with acute myocardial infarction: subgroup analysis of China PEACE study. *Endocrine* 2021; 74:128-37.
14. Jabbar A, Ingoe L, Junejo S, Carey P, Addison C, Thomas H, Parikh JD, Austin D, Hollingsworth KG, Stocken DD, Pearce SHS, Greenwood JP, Zaman A, Razvi S. Effect of levothyroxine on left ventricular ejection fraction in patients with subclinical hypothyroidism and acute myocardial infarction: a randomized clinical trial. *JAMA* 2020; 324:249-58.
15. Izhakov E, Zahler D, Rozenfeld KL, Ravid D, Bannai S, Topilsky Y, Stern N, Greenman Y, Shacham Y. Unknown subclinical hypothyroidism and in-hospital outcomes and short- and long-term all-cause mortality among ST segment elevation myocardial infarction patients undergoing percutaneous coronary intervention. *J Clin Med* 2020; 9: 3829.
16. Manolis AA, Manolis TA, Melita H, Manolis AS. Subclinical thyroid dysfunction and cardiovascular consequences: An alarming wake-up call? *Trends Cardiovasc Med* 2020; 30:57-69.
17. Ertugrul O, Ahmet U, Asim E, Gulcin HE, Burak A, Murat A, Sezai YS, Biter HI, Hakan DM. Prevalence of subclinical hypothyroidism among patients with acute myocardial infarction. *Int Sch Res Notices* 2011; 2011:810251.
18. Li MF, Wei ZT, Li S, Feng QM, Li JB. Association of mild thyroid dysfunction and adverse prognosis among Chinese patients with acute ST segment elevation myocardial infarction. *Front Endocrinol (Lausanne)* 2022; 13:879443.

Trends in stroke thrombolysis rate in Bosnia and Herzegovina: a hospital-based observation study

Marija Bender¹, Stjepan Čović², Matea Baranik¹, Sandra Lakičević¹, Inge Klupka-Sarić¹

¹Department of Neurology, University Hospital Mostar, ²School of Medicine, University of Mostar; Mostar, Bosnia and Herzegovina

Corresponding author:

Matea Baranik
Department of Neurology,
University Hospital Mostar
88000 Mostar, Bosnia and Herzegovina
Phone/fax: +387 36 336-352;
Fax +387 36 336 352;
E-mail: matea.baranik@hotmail.com
Marija Bender ORCID ID: <http://www.orcid.org/0000-0001-5672-9712>

ABSTRACT

Aim To assess trends in thrombolysis rates and door-to-needle times in University Hospital Mostar.

Methods Data from the University Hospital Mostar Registry were used. Information on the number of ischaemic stroke patients, intravenous thrombolysis rates and „door-to-needle times“ (DNT) were collected between January 2013 and December 2021.

Results Out of the total of 3100 ischaemic stroke patients, alteplase was given to 130 patients giving a thrombolysis rate of 4.2%. The mean hospital thrombolysis rate increased from 2.4% in 2013 to 10.6% in 2021.

Conclusion Although the hospital thrombolysis rate more than quadrupled, there is still a low proportion of acute ischaemic stroke patients who received intravenous thrombolysis therapy. Education and interventions indicating the importance of recognition and treatment of acute ischemic stroke are necessary for all physicians.

Key words: alteplase, developing country, door-to-needle times, ischaemic stroke

Original submission:

23 May 2022;

Revised submission:

23 July 2022;

Accepted:

30 August 2022

doi: 10.17392/1504-22

Med Glas (Zenica) 2023; 20(1): 28-31

INTRODUCTION

Intravenous thrombolytic therapy (IVT) after ischaemic stroke significantly improves functional outcomes, reduces mortality and it has been the first-line treatment worldwide since 1996 (1). Despite the revolutionary development of the treatment, stroke remains the second leading cause of death and the third leading cause of disability worldwide (2,3). During the last three decades, the burden of stroke increased substantially, with the bulk of the global stroke burden residing in low-income and middle-income countries (LMICs) (3,4). Also, a greater increase in stroke incidence, mortality and disability has been proven in LMICs comparing to high-income countries (HICs). However, stroke occurs about 15 years earlier among individuals in LMICs than in HICs (5). Additionally, quality of stroke care in developing countries is generally poor (6). Low stroke thrombolysis rates persist for years and in-hospital treatments they are delayed (7).

In Bosnia and Herzegovina (B&H) there are no studies relating to thrombolysis rate for stroke.

The aim of this study was to assess trends in thrombolysis rates and door-to-needle times, and whether there have been improvements in treatment rates and therapy delays over years.

This study should be of great significance to help further improvement of stroke care in developing countries.

PATIENTS AND METHODS

Patients and study design

This cross-sectional study included all patients admitted to University Hospital Mostar, B&H, with a diagnosis of acute ischemic stroke between January 2013 and December 2021. Acute ischemic stroke is defined by the International Classification of Diseases (8).

Methods

Data for the analysis were used from the University Hospital Mostar Registry. Information on the number of ischaemic stroke patients, numbers of acute ischemic stroke (AIS) patients treated with recombinant tissue plasminogen activator (rt-PA) and „door-to-needle times“ (DNT) were collected. The rate of IVT was defined as the number of

AIS patients receiving IVT divided by the number of all patients with a diagnosis of AIS.

Statistical analysis

The Kolmogorov-Smirnov test was used to assess the data normality of continuous variables. Categorical variables are presented as numbers and percentages. Mann-Whitney tests and chi-squared tests were performed for continuous variables and categorical variables, respectively. Statistical significance was set at $p < 0.05$.

RESULTS

From January 2013 to December 2021, 3743 patients with a diagnosis of stroke were admitted to the University Hospital Mostar. Of these, there were 3100 (83%) ischemic strokes. Intravenous thrombolytic therapy was administered to 130 (4.2%) patients of all ischemic stroke (IS) patients.

The proportion of patients treated with thrombolysis substantially increased over time from 0.76% in 2015 to 10.6% in 2021 ($p < 0.05$) (Figure 1).

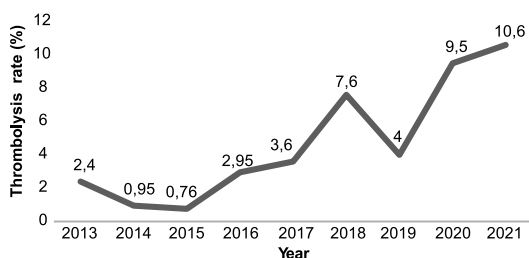


Figure 1. Thrombolysis rate during the period 2013–2021

Data on DNT were provided for all patients who received thrombolytic therapy. The initial median DNT in 2016 was 113 minutes and the final in 2021 was 81 minutes (Figure 2) ($p < 0.05$). DNT < 20 , < 45 , and < 60 minutes were achieved in 0%, 4%, and 8.5% patients, respectively.

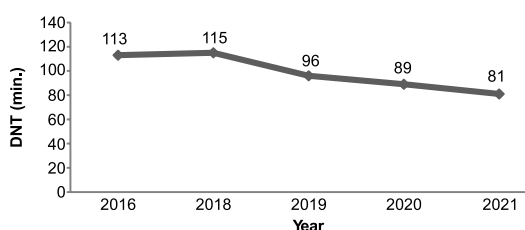


Figure 2. Door-to-needle time (DNT) during the period 2016–2021

DISCUSSION

We have managed to achieve a thrombolysis rate of almost 11% and demonstrated a significant

increase in thrombolytic rates over the period of 9 years. To our knowledge, this is the first study that shows the thrombolysis rate for stroke in B&H. Thrombolysis rate in other studies varied from 3.8% to 24.4%. The highest thrombolysis rate was reported in the Czech Republic (23.5%), Austria (16.8%), and The Netherlands (21.7%), while the thrombolysis rate in developing countries remains low (below 4%) (9-13). However, the majority of these studies were population-based (unlike ours), which enabled comparison with our hospital-based study. Nevertheless, we showed significant improvement in thrombolytic treatment over years, and it is reasonable to expect that we will reach the thrombolytic rate of over 15% before 2030 as defined by the Stroke Action Plan for Europe (14).

Although we managed to achieve a reduction in DNT over 5 years, our results are significantly below the target set in 2018 by the American Heart Association stating that 50% of patients should achieve DNT in less than 45 minutes (15). Long DNT in our study is probably a reflection of the poor intrahospital organization and lack of prenotification system and urgent stroke protocols for patients who are candidates for reperfusion therapy. These findings are not unusual for developing countries where stroke strategies lack in general (7).

Recent studies from the Czech Republic (8) and The Netherlands (15) showed that it was possible to dramatically decrease DNT after the implementation of evidence-based guidelines in routine medical practice. These studies demonstrated

that thrombolytic treatment can be initiated for the majority of patients within 20 or 25 minutes in the Czech Republic and The Netherlands respectively, and in this way, they established a new benchmark for DNT (9,16).

According to the Global Burden of Disease B&H belongs to the regions with the highest estimated lifetime risk of stroke, 1 of 3 people older than 25 will have stroke during their life (17). If the current trends continue, by 2050 we can expect 200 million stroke survivors and over 30 million new strokes each year, much of this burden will probably remain in developing countries if we do not take necessary actions.

The improvement in the management of stroke after the implementation of evidence-based guidelines in routine medical practice has significantly lowered the burden of stroke in HICs (18).

In conclusion, we emphasize the need for the development of national stroke strategies in Bosnia and Herzegovina, which would include, among other things, the implementation of a pre-notification system and in-hospital urgent stroke protocols for patients who are candidates for reperfusion therapy. Also, efforts should be made to raise public awareness of stroke and in this way improve stroke recognition.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

REFERENCES

1. National Institute of Neurological D, Stroke rt PA-SSG. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333:1581-7.
2. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlathshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Eyckborst KJ, Silver FL, Shuaib A, Tampeieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia J, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts S, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015; 372:1019-30.
3. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJH, Waldervreen MAA, Staals J, Hofmeijer J, A van Oostayen J, Lycklama a Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, Bruijn SF, C van Dijk L, Kappelle LJ, Lo RH, Dijk EJ, Vries J, Kort PM, Rooij JJJ, Berg JSP, Hasselt BAAM, Aerden LAM, Dallinga RJ, Visser MC, Bot JCJ, Vroomen PC, Eshghi O, Schreuder THCM, Heijboer RJJ, Keizer K, Tielbeek AV, Hertog HM, Gerrits DG, Berg-Vos RM, Karas GB, Steyerberg EW, Flach H, Marquering HA, Jenninkens SFM, Beenen LFM, Berg R, Koudstaal PJ, Zwam WH, Roos Y, Lugt A, Oostenbrugge R, Majoie C, Dipper D. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; 372:11-20.
4. Collaborators GBDS. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 2021; 20:795-820.
5. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009; 8:355-69.

6. Kim J, Thayabaranathan T, Donnan GA, Howard G, Howard VJ, Rothwell PM, Feigin V, Norrving B, Owolabi M, Pandian J, Liu L, Cadilhac DA, Thrift AG. Global stroke statistics 2019. *Int J Stroke* 2020; 15:819-3.
7. Yaria J, Gil A, Makanjuola A, Oguntoye R, Miranda JJ, Lazo-Porras M, Zhang P, Tao X, Ahlgren JA, Bernabe-Oritz A, Moscoso-Porras M, Malaga G, Svyato I, Osundina M, Gianella C, Bello O, Lawal A, Temitope A, Adebayo O, Lakkhanaloet M, Brainin M, Johnson W, Thrift AG, Phromjai J, Mueller-Stierlin A, Perone SA, Varghese C, Feigin V. Quality of stroke guidelines in low- and middle-income countries: a systematic review. *Bull World Health Organ* 2021; 99:640-52E.
8. Krawczyk P, Swiecicki L. ICD-11 vs. ICD-10 - a review of updates and novelties introduced in the latest version of the WHO International Classification of Diseases. *Psychiatr Pol* 2020; 54:7-20.
9. Mikulik R, Bar M, Cernik D, Herzig R, Jura R, Jurak L, Neumann J, Sanak D, Ostry S, Sevic P, Skoda O, Skoloudin D, Vaclavik D, Tomek A. Stroke 20 20: Implementation goals for intravenous thrombolysis. *Eur Stroke J* 2021; 6:151-9.
10. Nilanont Y, Nidhinandana S, Suwanwela NC, Hanchaiphiboolkul S, Pimpak T, Tatsanavivat P, Saposnik G, Pongvarin N. Quality of acute ischemic stroke care in Thailand: a prospective multicenter countrywide cohort study. *J Stroke Cerebrovasc Dis* 2014; 23:213-9.
11. Zakaria MF, Aref H, Abd ElNasser A, Fahmy N, Tork MA, Fouad MM, ElBlok A, Roushdy T, ElFaramawy S, El-Shiekh MA, Moustafa RR. Egyptian experience in increasing utilization of reperfusion therapies in acute ischemic stroke. *Int J Stroke*. 2018; 13:525-9.
12. Phan HT, Gall SL, Blizzard CL, Lannin NA, Thrift AG, Anderson CS, Kim J, Grimlex R, Castlex HC, Hand P, Cadilhac D. Sex Differences in Care and Long-Term Mortality After Stroke: Australian Stroke Clinical Registry. *J Womens Health (Larchmt)* 2019; 28:712-20.
13. Willeit J, Geley T, Schoch J, Rinner H, Tur A, Kreuzer H, Thiemann N, Knoflach M, Toell T, Pechlaner R, Willeit K, Klingler N, Praxmarer S, Baubin M, Beck G, Berek K, Dengg C, Engekhardt K, Erlacher T, Fluckinger T, Grander W, Grossman J, Kathrein H, Kaiser N, Matosevic B, Matzak H, Mayr M, Perfler R, Poewe W, Rauter A, Schoenherr G, Schoenherr HR, Schinnerl A, Spiss H, Thurner T, Vergeiner G, Werner P, Woll E, Willeit P, Kiechl S. Thrombolysis and clinical outcome in patients with stroke after implementation of the Tyrol Stroke Pathway: a retrospective observational study. *Lancet Neurol* 2015; 14:48-56.
14. Norrving B, Barrick J, Davalos A, Dichgans M, Cordonnier C, Guekht A, Kutluk K, Mikulik R, Wardlaw J, Richard E, Nabavi D, Molina C, Bath PM, Stibrant Sunnerhagen K, Rudd A, Drummond A, Planas A, Caso V. Action Plan for Stroke in Europe 2018-2030. *Eur Stroke J* 2018; 3:309-36.
15. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2018; 49:e46-e110.
16. Kuhrij LS, Wouters MW, van den Berg-Vos RM, de Leeuw FE, Nederkoorn PJ. The Dutch Acute Stroke Audit: Benchmarking acute stroke care in the Netherlands. *Eur Stroke J* 2018; 3:361-8.
17. Collaborators GBDM. Global, regional, and national age-sex-specific mortality and life expectancy, 1950-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392:1684-735.
18. Li L, Scott CA, Rothwell PM, Oxford Vascular S. Trends in stroke incidence in high-income countries in the 21st century: population-based study and systematic review. *Stroke*. 2020; 51:1372-80.

Can laboratory and clinical parameters predict the occurrence of acute arterial occlusion in COVID-19 patients?

Kristian Karlović¹, Gojko Bogdan¹, Pejana Rastović², Martin Kajić²

¹Department of Radiology, ²Department of Surgery; University Clinical Hospital Mostar, Mostar, Bosnia and Herzegovina

ABSTRACT

Aim To determine radiologic, clinic and laboratory characteristics of COVID-19 positive patients with acute arterial occlusion and compare them with post COVID-19 and non-COVID-19 patients.

Methods In this retrospective study, 53 patients with acute occlusion of peripheral arteries admitted to the University Clinical Hospital Mostar in the period between 29 February 2020 and 30 September 2021 were involved. The first group was made of COVID-19 positive patients, the second group were post COVID-19 patients and a control group were non-COVID-19 patients.

Results Most patients were males, 37 (69.8%). The average age of COVID positive patients was 66.09±11.25 years, post COVID-19 patients 71.33±5.22 years and COVID-19 negative patients 69.82±1.99 years. Lower extremities were most affected, 38 (71.6%), without significant alteration in the coagulogram. Acute arterial occlusion occurred about 2 weeks after the beginning of COVID-19 or at the time of the first appearance of symptoms.

Conclusion We have to take special care about patients with risk factors for developing acute arterial occlusion due to thromboembolism or thrombosis 10 days after the beginning of the disease. We also recommend the use of low molecular weight heparin (LMWH) and monitoring coagulation state due to anti Xa and thromboelastometry.

Key words: angiography, coronavirus, heparin, thromboembolism

Corresponding author:

Kristian Karlović

¹Department of Radiology,

University Clinical Hospital Mostar

Bijeli brijeg bb 88000 Mostar,

Bosnia and Herzegovina

Phone: +387 63 247 825;

Fax: +387 36 341 966;

E-mail: kristiankarlovic@live.com

ORCID ID: [https://orcid.org/0000-0002-](https://orcid.org/0000-0002-4149-6773)

4149-6773

Original submission:

26 July 2022;

Revised submission:

11 August 2022;

Accepted:

10 December 2022

doi: 10.17392/1520-22

Med Glas (Zenica) 2023; 20(1): 32-37

INTRODUCTION

The clinical feature of the COVID-19 infection is dominated by bilateral pneumonia, often with a severe form and the development of respiratory failure, sometimes dependent on mechanical support (1). The disease has been named COVID-19 according to the World Health Organisation (WHO) (2). Except for pneumonia, SARS-CoV-2 has been associated with procoagulation incidents, especially in patients with severe COVID-19. The venous system is more frequently affected than arterial, but both systems are atypical for developing such complications after the infection with some respiratory virus (3). Most patients who died of COVID-19 had elevated D-dimers and fulfilled the criteria for diagnosing disseminated intravascular coagulopathy. Because of that, soon after the coagulation disorder had been noticed and connected with COVID-19, a need for some therapeutic solutions and diagnostic management occurred (4). COVID-19, among others, provokes inflammatory reaction which, along with complex mechanisms, affects blood coagulation, even due to prothrombotic state in some cases (5). This coagulopathy results in numerous pulmonary embolisms (PE), deep venous thromboses (DVT), and acute arterial occlusions because of thrombosis or thromboembolism (5,6). In the Klock et al. study among 184 patients with COVID-19 in the Intensive Care Unit (ICU), 57 (31%) had some thrombotic or thromboembolic incident, in which pulmonary embolism predominated; also, all patients were on high doses of heparin (6). A new entity has been described as COVID-19 associated coagulopathy (CAC), which is different from other kinds of coagulopathies, sepsis-induced coagulopathy (SIC) or disseminated intravascular coagulopathy (DIC); it is indicative by elevated D-dimers, while other parameters of coagulation are mildly disturbed (7). Understanding pathophysiology, monitoring and modification of coagulation is necessary for therapeutic purposes in order to maintain homeostasis (8). It has been shown that the use of low molecular weight heparin (LMWH) has positive impact in the treatment of COVID-19 patients, which significantly reduces mortality and thromboembolic incidents (9). In a study by Tang et al, severe clinical form patients with COVID-19 were examined and divided by sepsis-induced coagulopathy (SIC) score; further analysis showed

that those who had received heparin in any form had lower mortality rates contrary to those who had not received heparin (9).

By identifying patients with COVID-19 who are at risk of thrombosis or thromboembolism, we could take timely diagnostic and therapeutic action, thereby reducing morbidity and mortality. The aim of this study was to determine clinical and laboratory characteristics of COVID-19 patients with arterial thrombosis or thromboembolism and to evaluate whether the obtained results can be used to predict the occurrence of such an incident.

PATIENTS AND METHODS

Patients and study design

In total, 53 patients from the University Hospital Centre (UHC) Mostar participated in this study. All patients were admitted in the period between 29 February 2020 and 30 September 2021, and all had acute occlusions of peripheral arteries caused by thrombosis or thromboembolism, confirmed with multi-slice computed tomography (MSCT) angiography.

An informed consent was obtained from all patients. The Ethical Committee of the UHC Mostar approved this study.

The patients were divided in three groups: COVID positive patients - those who had positive PCR test and active COVID-19, post COVID-19 patients - those who had overcome COVID-19 and COVID-19 negative patients – those without proof of active COVID-19.

Methods

Clinical data, general data, days since the start of the COVID-19 disease, when thromboembolism appeared and laboratory parameters were taken for every patient from the day when thromboembolism appeared. Laboratory results included a count of platelets (reference value $158-454 \times 10^9/L$), prothrombin time (PT) (reference value 7.7-9.7 s), thrombin time (TT) (reference value 14-21 s), activated thromboplastin time (aPTT) (reference value 23-32 s), international normalised ratio (INR) (reference value 0-1.1), fibrinogen concentration (reference value 1.8-3.5 g/L), and D-dimers concentration (reference value $<0.50 \text{ mg/L}$). Blood tests were analysed in the Institute for Laboratory Diagnostics of UHC Mostar.

Statistical analysis

Data were presented as mean and standard deviation, mean and interquartile range, number and percentage. Student T test, χ^2 , ANOVA and Kruskal Wallis test were used. A $p < 0.05$ was considered statistically significant.

RESULTS

Most patients were males, 37 (69.8%), and 16 (30.2%) were females ($p = 0.004$).

Out of all 53 examined patients, 22 (41.5%) were SARS-CoV-2 positive and had active COVID-19, nine (17%) were post-COVID patients with overcoming disease, and 22 (41%) without proof of active COVID-19 considered as COVID-19 negative.

There were statistically more male than female patients in the group of COVID-19 positive patients, 20 (91%) versus two (9%), respectively ($p = 0.009$).

The average age of COVID-19 positive patients was 66.09 ± 11.25 years, post COVID-9 patients 71.33 ± 5.22 years and COVID-19 negative patients 69.82 ± 1.99 years ($p = 0.687$). Females in the COVID-19 positive group were slightly older than males ($p = 0.072$).

The highest number of patients had thromboembolism of lower extremities, although in the group

up of COVID-19 positive there was a noticeable thromboembolism of upper extremities, but without statistical significance ($p = 0.343$) (Table 1).

In the group of COVID-19 positive patients, thromboembolism occurred after 13 ± 2 days of the disease (in average); the earliest incident was recorded 9 days after the disease and the latest one after 18 days.

In the group of post COVID-19 patients, thromboembolism occurred after 65 days (in average) with outstanding variability: the earliest incident happened after 19 days from the beginning of the disease and the latest one 180 days after the beginning of COVID-19.

Most patients had atherosclerosis according to the radiology diagnostic, 40 (75.5%) ($p < 0.001$).

Regarding the therapy that affects blood clotting, patients with COVID-19 and post COVID-19 were mostly under therapy at the time of the thromboembolic incident for a longer period of time in contrast to patients without COVID-19 (Table 1).

Frequency of the intake of some medicines, which affect blood clotting and also the distribution and comparison regarding to the groups, showed that 14 (out of 22) COVID positive patients received LMWH in the therapy ($p = 0.000$) (Table 3).

Table 1. Localization of thromboembolism and intake of drugs which affects blood clotting in the moment of thromboembolism with regard to group participation

Variable	No (%) of patients in the group			
	COVID positive	Post COVID	COVID negative	Total
Localization				
Upper limb	8 (15.09)	2 (3.77)	4 (7.54)	14 (26.41)
Lower limb	13 (24.52)	7 (13.2)	18 (33.96)	38 (71.69)
Visceral branch of aorta	1 (1.88)	0	0	1 (1.88)
Therapy				
YES	16 (30.18)	6 (11.32)	7 (13.2)	29 (54.7)
NO	6 (11.32)	3 (5.66)	15 (28.3)	22 (41.5)
Total	22 (41.5)	9 (16.9)	22 (41.5)	53 (100)

Table 2. Intake of some drugs which affect blood clotting in the moment of thromboembolism in standard doses once per day

Drug	YES/NO	No (%) of patients in the group			P
		COVID Positive (22)	Post COVID (9)	COVID Negative (22)	
Acetyl salicylic acid 100 mg	YES	8 (15.09)	2 (3.77)	6 (11.32)	0.685
	NO	14 (26.4)	7 (13.2)	16 (30.18)	
Rivaroxaban 20 mg	YES	1 (1.88)	3 (5.66)	0	0.005
	NO	21 (39.62)	6 (11.32)	22 (41.5)	
Clopidogrel 75 mg	YES	0	1 (1.88)	0	0.083
	NO	22 (41.5)	8 (15.09)	22 (41.5)	
LMWH 0.6 mL	YES	14 (26.4)	3 (5.66)	1 (1.88)	0.000
	NO	8 (15.09)	6 (11.32)	21 (39.62)	

LMWH, Low molecule weight heparin;

Table 3. Average laboratory values of platelets, fibrinogen, D-dimers and coagulogram with regard to the group

Variable	Reference value	Mean $\pm$ standard deviation			P
		COVID 19 positive	Post COVID 19	COVID 19 negative	
Platelet ($\times 10^9$ /L)	158-454	221.09 ± 94.23	236.78 ± 68.71	246.55 ± 92.60	0.655
D-dimers mg/L	< 0.50	3.39 ± 1.56	2.82 ± 1.46	3.27 ± 1.20	0.428
Fibrinogen (g/L)	1.8-3.5	3.88 ± 1.33	4.24 ± 1.76	4.22 ± 0.94	0.689
aPTT (seconds)	23-32	29.98 ± 3.96	27.78 ± 4.24	28.30 ± 3.84	0.306
PT (seconds)	7.7-9.7	10.37 ± 1.66	10.30 ± 0.95	9.15 ± 0.66	0.005
TT (seconds)	14-21	17.87 ± 6.34	17.48 ± 2.08	20.09 ± 15.63	0.799
INR (ratio)	0-1.1	1.21 ± 0.19	1.19 ± 0.10	1.07 ± 0.08	0.010

aPTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; INR, international normalized ratio;

The lowest values of TT were in the group of COVID-19 negative, and highest were in the group of COVID-19 positive patients. The highest INR was in the group of COVID-19 positive patients, and the lowest in the group of COVID-19 negative patients (Table 4).

Table 4. Average values of coagulation parameters between the groups of COVID-19 positive and post COVID-19 according to the low molecular weight heparin (LMWH) intake

Variable (Reference value)	COVID status	Mean±standard deviation		p
		LMWH intake	Without LMWH intake	
Platelet (x109 /L) (158-454)	COVID positive	192.36±82.75	271.38±96.85	0.05
	Post COVID	185.67±73.11	262.33±55.37	0.11
D-dimers (mg/L) (<0.50)	COVID positive	3.07±1.83	3.85±1.02	0.32
	Post COVID	3.51±0.92	1.78±1.81	0.23
Fibrinogen (g/L) (1.8-3.5)	COVID positive	4.06±1.36	3.61±1.32	0.50
	Post COVID	3.43±2.88	4.65±1.51	0.36
aPTT (seconds) (23-32)	COVID positive	30.21±3.75	29.65±4.52	0.78
	Post COVID	27.86±3.65	27.75±4.85	0.97
PT (seconds) (7.7-9.7)	COVID positive	10.59±1.85	10.08±1.42	0.53
	Post COVID	10.60±1.01	10.15±0.98	0.54
TT (seconds) (14-21)	COVID positive	15.1±6.91	21.04±4.03	0.06
	Post COVID	18.76±3.26	16.72±0.59	0.20
INR (ratio)	COVID positive	1.22±0.21	1.19±0.16	0.73
	Post COVID	1.21±0.12	1.18±0.1	0.71

aPTT, activated partial thromboplastin time; PT, prothrombin time;
TT, thrombin time; INR, international normalized ratio,

DISCUSSION

According to this study, predomination of males is noticeable, especially in groups linked to COVID-19, while in the group without COVID-19 there was no difference in gender distribution. These results are similar with other studies (6, 10-12). Therefore, male gender can be considered a risk factor for developing procoagulation state in COVID-19 positive patients and consequent development of thromboembolism (10-12).

Although SARS-CoV-2 can infect people regardless of their age, the development of COVID-19, severity of clinical picture and presence of complications are linked to older age (12). In the context of thromboembolism, older age has shown to be an unfavourable factor (13). The main reasons are, among others, the weakness of the immune system, and often comorbidities such as atherosclerosis, hypertension, diabetes mellitus, etc. (12-14). The average age of our patients with active COVID-19 was 64.25 years, which is very close to the results of our neighbour Italy, where the average age was 66 years, and also male gender was more frequent (14).

Because of the appearance of procoagulation state in COVID-19 positive patients, acute thrombosis and thromboembolisms are very common despite of the use of different medicines that influence blood clot forming such as LMWH (15). Pulmonary emboli predominate as complications in up to 30% of cases, followed by venous thrombosis (16). Di Minno et al. reported the prevalence of venous thromboembolism 24.3-39.2%, whereas the prevalence of arterial thrombosis was 4.4% (16). The prevalence of patients with arterial incidents was low, but the total infected population was not negligible because of high mortality (15,16).

In the beginning, arterial thromboembolisms were presented as case reports, especially because of unusual localizations (17), but as time went on, they began to be considered as expected complication of COVID-19. The appearance of arterial thromboembolism in COVID-19 patients is, unfortunately, a sign predicting lethal outcome (17,18).

Perhaps the most significant result of our study is the identification of the period when thromboembolic incident most often occurred: in the group of COVID-19 positive patients, arterial thromboembolism occurred about 13 days from the beginning of the disease, and earliest at day 9. Gonzalez-Fajardo et al. (18) stated that arterial thromboembolism appears (in average) after 15.77 days of hospitalization, which is similar to our results. This fact implicates that one should be very alert in the period of 2 weeks from the beginning of COVID-19 and pay attention to clinical signs of circulatory insufficiency and according to the findings, make prompt diagnostics. The patients with COVID-19 in the intensive care unit (ICU) with impaired consciousness are the primary vulnerable group that happens due to the severity of the underlying disease, which is also due to the inability to communicate and be timely alert of the symptoms (18). Despite the recovery of COVID-19, the risk of thromboembolic incidents does not subside. Although not as high in incidence as during the disease, thromboembolic incidents threaten for up to several months after the negative test. They also occur despite the prophylaxis used (19).

Although more than half of the patients with COVID-19 and post COVID-19 from our study were taking a drug that affects blood clotting, in con-

trast to COVID-19 negative patients, thromboembolic incidents certainly occurred, and blood clotting monitoring parameters were not significantly altered (20).

Platelets were significantly lowered in the group of COVID-19 positive patients, and two-thirds of patients were on a therapeutic dose of LMWH for a long period. In this case, maybe we can talk about an impact of LMWH on platelets. However, if we want to discuss heparin induced thrombocytopenia (HIT) as an entity which can be responsible for paradox appearance of clots, we point out that literature adverts to such incidents in a low percentage (21). In addition, the occurrence of HIT has been associated with the use of unfractionated heparin, while in this study everyone received LWMH (22).

Only slightly modified values of PT and INR were found, which are known as measures of extrinsic pathway, and their elevated values should manifest reduced coagulability of blood. However, this finding is also possible because of the consumption of coagulation factors, and they were measured on the day when the thromboembolic incident happened (20). D-dimers were elevated in every of the three examined groups, in the group of COVID-19 positive patients, the lowest values were recorded in comparison with the other two. We have obtained similar results with fibrinogen, too. In a meta-analysis of Bao et al. who investigated differences in laboratory findings between severe and non-severe patients

with COVID-19, there were disorders in coagulogram that were obvious in the first examined group; the author claimed that some disturbances in laboratory findings can predict the progress of COVID-19 (20).

Therefore, the coagulation findings obtained in this study, especially with the administration of therapy, do not indicate the risk of thromboembolic incidents. Administered medicines, though, do not change the coagulogram significantly, so for monitoring of coagulation, measurements which can represent the effect of LMWH, such as anti-Xa or rotational thromboelastometry should be introduced (23,24).

In conclusion, attention should be paid to COVID-19 patients, especially hospitalized in the ICU about 10 days from the onset of the disease in terms of early detection and the treatment of thrombosis and thromboembolism. For this purpose, we suggest the use of thromboelastometry parameters, as well as faster radiological diagnostic tool, such as colour doppler ultrasound. Early diagnosis, as well as the treatment of these incidents, may increase the overall survival of COVID-19 positive patients.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflicts of interest: None to declare.

REFERENCES

- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395:497-506.
- World Health Organization. Coronavirus Disease 2019 (COVID-19) Situation Report– 26, February 15, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200215-sitrep-26-covid-19.pdf?sfvrsn=a4cc6787_2. (28 March 2020).
- Kunutsor SK, Laukkanen JA. Incidence of venous and arterial thromboembolic complications in COVID-19: A systematic review and meta-analysis. *Thromb Res* 2020; 196:27-30.
- Lippi G, Favaloro EJ. D-dimer is associated with severity of coronavirus disease 2020: a pooled analysis. *ThrombHaemost* 2020; 120:876-8.
- Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. *Int J Hematol* 2021; 113:45-57.
- Klok FA, Kruip MJHA, van der Meer NJM, Arboius MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020; 191:145-7.
- Pawlowski C, Wagner T, Puranik A, Murugadoss K, Loscalzo L, Venkatakrishnan AJ, Pruthi RK, Houghton DE, O'Horo JC, Morice WG 2nd, Williams AW, Gores GJ, Halamka J, Badley AD, Barnathan ES, Makimura H, Khan N, Soundararajan V. Inference from longitudinal laboratory tests characterizes temporal evolution of COVID-19-associated coagulopathy (CAC). *Elife* 2020; 9:e59209.
- Levy JH, Koster A, Quinones QJ, Milling TJ, Key NS. Antifibrinolytic therapy and perioperative considerations. *Anesthesiology* 2018; 128:657-70.

9. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J ThrombHaemost* 2020; 18:1094-9.
10. Naqvi IH, Alam MT, Rehan M, Mahmood K, Aurangzeb M, Talib A. COVID-19-associated coagulopathy and thromboembolism: determination of their patterns and risk factors as predictors of mortality among severe COVID-19 patients. *Curr Vasc Pharmacol* 2022; 20:77-86.
11. Su W, Qiu Z, Zhou L, Hou J, Wang Y, Huang F, Zhang Y, Jia Y, Zhou J, Liu D, Xia Z, Xia ZY, Lei S. Sex differences in clinical characteristics and risk factors for mortality among severe patients with COVID-19: a retrospective study. *Aging (Albany NY)* 2020; 12:18833-43.
12. Ya'qoub L, Elgendy IY, Pepine CJ. Sex and gender differences in COVID-19: More to be learned! *Am Heart J Plus* 2021; 3:100011.
13. Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? *Aging (Albany NY)* 2020; 12:9959-81.
14. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt JD, Sacco C, Bertuzzi A, Sandri MT, Barco S; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res* 2020; 191:9-14.
15. Cheruiyot I, Kipkorir V, Ngure B, Misiani M, Munguti J, Ogeng'o J. Arterial Thrombosis in Coronavirus Disease 2019 Patients: A rapid systematic review. *Ann Vasc Surg* 2021; 70:273-81.
16. Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and venous thromboembolism: a meta-analysis of literature studies. *Semin Thromb Hemost* 2020; 46:763-71.
17. Garg K, Barfield ME, Pezold ML, Sadek M, Cayne NS, Lugo J, Maldonado TS, Berland TL, Rockman CB, Jacobowitz GR. Arterial thromboembolism associated with COVID-19 and elevated D-dimer levels. *J VascSurg Cases Innov Tech* 2020; 6:348-51.
18. Gonzalez-Fajardo JA, Ansuategui M, Romero C, Comanges A, Gómez-Arbeláez D, Ibarra G, Garcia-Gutierrez A. Mortality of covid-19 patients with vascular thrombotic complications. *Med Clin (Barc)* 2021; 156:112-17.
19. Zuin M, Rigatelli G, Zuliani G, Roncon L. The risk of thrombosis after acute-COVID-19 infection. *QJM* 2021; 114:619-20.
20. Bao J, Li C, Zhang K, Kang H, Chen W, Gu B. Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19. *Clin Chim Acta* 2020; 509:180-94.
21. Lovecchio F. Heparin-induced thrombocytopenia. *ClinToxicol (Phila)* 2014; 52:579-83.
22. Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients. *Cochrane Database Syst Rev* 2017; 4:CD007557.
23. Brown W, Lunati M, Maceroli M, Ernst A, Staley C, Johnson R, Schenker M. Ability of thromboelastography to detect hypercoagulability: a systematic review and meta-analysis. *J Orthop Trauma* 2020; 34:278-86.
24. Kunutsor SK, Laukkanen JA. Incidence of venous and arterial thromboembolic complications in COVID-19: a systematic review and meta-analysis. *Thromb Res* 2020; 196:27-30.

Minimally invasive mini-thoracotomy access as a surgical method in state-of-the-art treatment of single-vessel coronary heart disease

Edin Kabil^{1,2}, Nermir Granov^{1,2}, Ilirijana Haxibeqiri-Karabdić^{1,3}, Sanja Grabovica^{1,3}, Ermina Mujičić^{1,3}, Slavenka Štraus^{1,2}, Bedrudin Banjanović^{1,2}, Muhamed Djedović^{1,2}

¹Clinic for Cardiovascular Surgery, University Clinical Center of Sarajevo, ²School of Medicine, University of Sarajevo, ³Sarajevo Medical School, Sarajevo School of Science and Technology; Sarajevo, Bosnia and Herzegovina

ABSTRACT

Aim To compare outcomes of two different surgical techniques of coronary artery bypass grafting (CABG) for treating isolated left anterior descending (LAD) coronary artery disease by full median sternotomy technique vs. minimally invasive approach via left anterior mini-thoracotomy.

Methods This retrospective, observational study, which included 61 elective patients, was conducted at the Clinic for Cardiovascular Surgery of the Clinical Centre of the University of Sarajevo in the period from June 2019 to January 2022. Patients were divided in two groups according to the operative technique used, the sternotomy CABG group of 30 patients where the access considered full median sternotomy, and the minimally invasive CABG group where left anterior mini-thoracotomy was performed. The groups were compared by previously defined primary and secondary clinical postoperative outcomes.

Results Out of 61 patients, the majority was males, 50 (82%). The analysis of the outcomes of the minimally invasive CABG surgery showed significantly shorter operative times ($p=0.001$), less postoperative drainage ($p=0.001$) and transfusion requirements, shorter mechanical ventilation duration ($p=0.0001$), low major adverse cardiac and cerebrovascular events rates, as well as shorter Intensive Care Unit stay days with mean of 3.3 ± 1.442 days ($p=0.025$), but no total hospital stay days with mean of 6.7 ± 1.832 days ($p=0.075$) compared to sternotomy CABG group.

Conclusion Minimally invasive approach for CABG surgery in treating isolated single vessel LAD disease, together with the fast-track protocol, offers a reasonable alternative to full median sternotomy, leading to faster patients' overall recovery and improving the quality of life.

Key words: anaesthesia, revascularization, cardiac surgery

Corresponding author:

Edin Kabil

Clinic for Cardiovascular Surgery,
University Clinical Centre of Sarajevo

Bolnička 25, Sarajevo,

Bosnia and Herzegovina

Phone: +387 33 297 941;

Fax: +387 33 298 522;

E-mail: edin.kabil@kcus.ba

ORCID ID: <https://orcid.org/0000-0001-7023-6244>

Original submission:

03 June 2022;

Revised submission:

10 August 2022;

Accepted:

07 November 2022

doi: 10.17392/1506-22

Med Glas (Zenica) 2023; 20(1): 38-44

INTRODUCTION

The growing incidence of coronary artery disease (CAD) in the global population has placed coronary artery bypass surgery (CABG) in one of the most commonly performed surgical procedures worldwide (1-2). The CABG is considered as a gold standard for treatment of one-or-multivessel ischemic heart disease intended to relieve symptoms of the cardiovascular disease and to enhance patient's life expectancy (3). Although the opinion is widely accepted that surgical revascularization improves the survival, it still carries the risk of postoperative complications (4). Despite the ever-aging population and increased risk scores of the patients, postoperative outcomes have improved over time, due to the surgical technique advancements and more accurate patient selection, together with the optimization of anaesthesia and intensive care fast track protocol, leading to a decline of mortality and major morbidity (1,4).

In the past decades, different surgical techniques for CABG have evolved to minimize the surgical trauma and postoperative morbidity (1-4). Calafiore et al. popularized the technique of minimally invasive direct coronary artery bypass grafting (MIDCAB) for treating isolated coronary artery disease (5). New technological improvements establish the role of minimally invasive approaches via a small 5 to 10 cm incision of left anterior thoracotomy instead of sternotomy, mainly for isolated LIMA to LAD bypass grafting (4-6). Nowadays, the MIDCAB is among cardiac surgeons adopted as a patient-friendly technique due its reduced invasiveness, but it also gives respectable results comparable to other CABG techniques in treating single vessel ischemic disease (6,7). Minimally invasive approaches for CABG offer a reasonable alternative to sternotomy because of less surgical trauma, less wound infection rates, decreased blood loss and transfusion rates, decreased ventilation times and hospital stay, but also cosmetic advantages, leading to faster patient's overall recovery and the improvement of quality of life (3,6,7). While several meta-analyses of large multicentre studies of outcomes of conventional CABG and MIDCAB have been published (6,7), regional centres in developing countries are still lacking comprehensive analytical studies of MIDCAB outcomes.

The aim of the study was to compare clinical outcomes of two different operative techniques for

treating isolated LAD coronary artery disease, by the standard CABG surgery through the median full sternotomy technique vs. minimally invasive approach by left anterior mini-thoracotomy.

PATIENTS AND METHODS

Patients and study design

This retrospective, comparative, observational study was conducted at the Clinic for Cardiovascular Surgery of the University Clinical Centre of Sarajevo in the period from June 2019 to January 2022. A total of 61 non-randomized, elective patients treated for isolated LAD artery disease were included in the study. The patients, 50 males and 11 females, at the age between 43 and 85 years, were categorized according to a surgeon's choice of a technique for isolated CABG in two different groups: sternotomy CABG group (n=30) and minimally invasive CABG group (n=31). Exclusion criteria were: multi vessel coronary artery disease, combined valvular and coronary artery surgery and urgent surgery. There was no significant difference in either group in the number of comorbidities and age.

The study was conducted in accordance with the Helsinki Declaration. The Institutional Ethical Committee approved the study and a written patient consent for the surgery was obtained.

Methods

Anesthesia and surgical technique. The preoperative assessment was conducted by standard institutional protocol. Following the induction of anaesthesia, the patients were intubated with a single lumen endotracheal tube. Mechanical ventilation was adjusted to the protective ventilation technique. General anaesthesia was maintained by fast-track protocols to facilitate early extubation. The hemodynamics was monitored by standard invasive hemodynamic monitoring. To minimize the risk of bleeding antifibrinolytics were used in both patient groups. The heparinization was accomplished by standard doses of heparin. The surgical technique of the sternotomy CABG group assumed full median sternotomy, while in the minimally invasive CABG group the surgical approach was through a small up to 6 cm incision at the level of the left anterolateral 4th or 5th intercostal space depending on patients' ana-

tomy. Cell saver was used to minimize the risk of blood transfusions. After chest tubes placement and skin closure the patients were admitted to the Intensive Care Unit (ICU).

Postoperative outcome. Hemodynamics of the patients was continuously monitored postoperatively. Postoperative drainage was observed hourly until chest drain removal. Blood transfusions were required in haemoglobin values below 70 g/L. In patients with signs of postoperative bleeding, blood, fresh frozen plasma and platelet transfusions at platelet count (PLT) of $<50.000 \times 10^9/L$ were indicated. Urgent chest revision was performed in the case when the criteria for open chest exploration by institutional protocols were met. Postoperatively, the antiplatelet therapy was administered by the earlier accepted guidelines on the day of surgery.

The primary outcome of the study was to compare the postoperative drainage and transfusion requirements, as well as the duration of surgery and invasive mechanical ventilation, length of ICU stay and total hospital stay, between the patient groups.

The secondary outcome was to compare and measure by the follow-up of infection rate, new onset of arrhythmia or myocardial infarction (AMI), inotropic drugs and mechanical support requirement (intra-aortic balloon pump - IABP), extracorporeal membrane oxygenation - ECMO) needed for surgical chest revision, occurrence of cerebrovascular and endothoracic incidents (pneumo-or haemothorax) and lethal outcome.

Major adverse cardiac and cerebrovascular events (MACCE) were defined as in-hospital, death, acute myocardial infarction (AMI), or acute ischemic stroke, and were evaluated during hospitalisation time.

Statistical analysis

Categorical data were presented as percentage. Continuous data were expressed as mean of numbers. The data were presented in the form of figures and tables. The assessment of normality of data was tested with the Shapiro-Wilk test and Kolmogorov-Smirnov test. Appropriate parametric and non-parametric tests were conducted for different types of variables, Fisher exact test or χ^2 test for categorical data and t-test for continuous data. The statistical significance of the tests was set on $p < 0.05$.

RESULTS

Out of the total of 61 patients, the majority were males, 50 (82%); 27 (44%) were older than 65 years of age, while 34 (56%) were categorized in the age group between 40-65 years.

In the sternotomy CABG group, the mean age was 65.5 ± 10.5 years, while in the minimally invasive CABG group the patients mean age was 63.38 ± 9.48 years ($p = 0.161$).

The mean time of the duration of surgery was 206 ± 77 minutes in both groups, whereas the duration of minimally invasive CABG procedure was significantly shorter than in the sternotomy CABG surgery, 175 ± 65 minutes and 239 ± 76 minutes, respectively ($p = 0.001$).

The analysis of the drainage showed statistically significant differences between compared groups, where the mean amount of the drainage in the postoperative period was greater in the sternotomy CABG group in comparison to minimally invasive CABG group, 1188 ± 620 mL and 704 ± 419 mL, respectively ($p = 0.001$) (Figure 1).

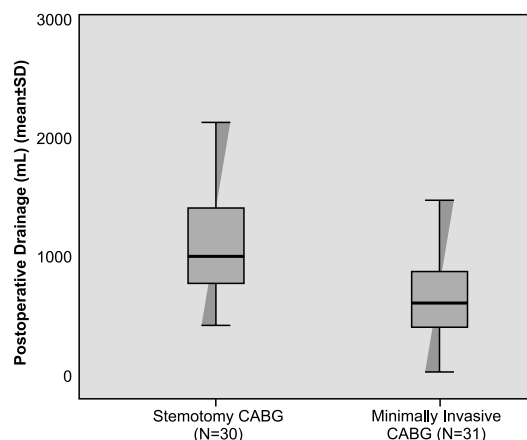


Figure 1. Postoperative drainage (mL) in sternotomy coronary artery bypass grafting (CABG) and minimally invasive CABG group (mean $\pm$ SD)

The minimally invasive CABG group showed less transfusion requirements compared to patients of the sternotomy CABG group, 12 (39%) and 18 (60%), respectively. The analysis of blood derivatives supplementation among the total study population showed that FFP was used in 19 (33%) patients, whereas more frequent demand of FFP was evident in the minimally invasive CABG group compared to the sternotomy CABG group, 13 (42%) and seven (23%), respectively (Table 1).

Table 1. Postoperative patient data during the Intensive Care Unit stay

Variable	Sternotomy CABG (N=30)	Minimally invasive CABG (N=31)	p
MACCE			
AMI (No; %)	1 (3.3)	3 (9.7)	0.671
CVI (No; %)	3 (10)	2 (6.5)	0.614
Death (No; %)	3 (10)	2 (6.5)	0.614
MV duration (minutes) (Mean±SD)	1300±1658	698±1167	0.0001
Endopleura disorders (No; %)	1 (3.3)	2 (6.5)	0.573
Revision (No; %)	2 (6.7)	3 (10)	0.668
Transfusion requirements (%)			
Blood transfusion	60	39	
FFP	23	42	
Infection (No; %)	2 (6.7)	1 (3.2)	0.612
LOS (days) (Mean±SD)	4.3±2.963	3.3±1.442	0.025
Hospital stay (days) (Mean±SD)	8±3.833	6.7±1.832	0.075

CABG, coronary artery bypass grafting; MACCE, major adverse cardiac and cerebrovascular events; AMI, acute myocardial infarction; MV, mechanical ventilation; SD, standard deviation; FFP- Fresh frozen plasma;

Postoperative chest revision was indicated in five (8%) patients. The revision was done in three (10%) in the minimally invasive CABG group and in two (6.7%) patients in the sternotomy CABG group ($p=0.668$) (Table 1).

In the ICU period of stay a significant difference in the duration of mechanical ventilation between selected groups was found, with shorter mean ventilation time in the minimally invasive CABG group, 698 ± 1167 minutes, compared to 1300 ± 1658 minutes in sternotomy CABG group ($p=0.0001$) (Figure 2).

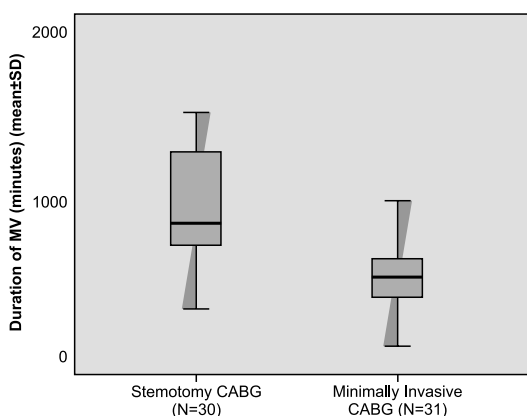


Figure 2. Duration of mechanical ventilation (MV), postoperatively in sternotomy coronary artery bypass grafting (CABG) group compared to minimally invasive CABG group

In the analysis of ICU length of stays (LOS) statistically significant differences were observed between the groups, with shorter mean of ICU

days in the minimally invasive CABG group (3.3 ± 1.442 days vs. 4.3 ± 2.963 days; $p=0.025$), while the total hospital stay days did not significantly differ between the compared patient groups (6.7 ± 1.832 days for minimally invasive CABG group, vs. 8 ± 3.833 days for sternotomy CABG group; $p=0.075$) (Table 1).

Regarding major adverse cardiac and cerebrovascular events (MACCE), postoperative ischemic incidents in the early postoperative period during hospitalization were presented in five (out of 61; 8%) patients; three patients in the sternotomy CABG group and two patients in the minimally invasive CABG group. A slightly higher frequency of cerebrovascular insults in the sternotomy CABG group was noticed ($p=0.614$). Postoperative acute myocardial infarction (AMI) was slightly more frequent in the minimally invasive CABG group compared to the sternotomy CABG group, three (9.7%) and one (3.3%), respectively ($p=0.671$). None of the patients required the support of IABP or ECMO.

The infection rate did not show a significant difference between selected patient groups, although it was slightly lower in the minimally invasive CABG group than in sternotomy CABG group, one (3.2%) and two (6.7%), respectively ($p=0.612$). There was no significant difference in the occurrence of endopleural disorders like pneumo-or haemothorax ($p=0.73$). The postoperative overall lethal outcome was noticed in 5 (8.2%) patients; 3 patients in the sternotomy CABG group and 2 patients in the minimally invasive CABG group ($p=0.614$) (Table 1).

DISCUSSION

The aim of our study was to present the minimally invasive surgical approach to the single-vessel (LAD) coronary disease treatment as a plausible alternative to open surgery by comparing clinical outcomes in the early postoperative period. Several recent studies were published to present potential benefits of the minimally invasive surgery (2,6,7). With the growing recognition of potential benefits of minimally invasive surgery, the interest in MIDCAB surgery among cardiac surgeons is continuously raising. This observational study conducted in a regional cardiac surgery centre, also showed significant advantages in faster overall recovery and return to daily activities after

minimally invasive approaches together with the ICU fast track protocol, especially in the high-risk population.

Since the population is aging and expressing high risk comorbidities, cardiac surgeons all over the world strive for various techniques to reduce the risk associated with conventional CABG surgery (4). The term minimally invasive still remains not well specified, since it can be defined as avoidance of the cardiopulmonary bypass due to its adverse systemic effects, as well as a sternal sparing technique requiring special endoscopic instruments and advanced equipment to access the LAD through the 4th or 5th intercostal space via left anterior mini-thoracotomy (8,9).

A careful patient selection is of crucial importance to accomplish satisfactory results (6-8). Our study population is similar to several large comparative studies such as Kayatta et al. and Diegeler et al. studies, choosing younger male patients between 40 and 65 of age with lower body mass index and favourable chest anatomy characteristics for MIDCAB surgery (7,8). In the pioneer studies of Diegeler et al. reviewing indications and selection factors for minimally invasive surgery, several conditions are considered as unfavourable for MIDCAB, such as diffuse disease, smaller vessel diameters, calcifications, anatomical exposure difficulties, especially in obese women with large breasts (8). On the other hand, Hage et al. presented that older population with multiple comorbidities, especially diabetic disease, may have a greater benefit of sternal bone preservation and lower wound infection risk by minimal invasive cardiac surgery (10). Although our research could not prove statistically significant difference in postoperative infection rate between observed groups, the deep sternal wound infection was more frequently present in the sternotomy CABG group. As there is no sternal heal present, the patients have no mobility restrictions and can quickly return to normal life activities (8). Our study has emphasized a shorter operative time as an additional factor prioritizing the minimal invasive approach by exposing the patient to less surgical stress to avoid the activation of various inflammatory systemic mechanisms associated with higher risk of postoperative complications as presented by Kraft et al. (9).

Similar to results of the meta-analysis of Hage et al. in our single-centre study we have shown that

the mini-thoracic approach led to less postoperative drainage, resulting in significant lower blood transfusion rates in the MIDCAB group compared to sternotomy CABG group (10). The certainly benefit of the MIDCAB surgery to reduce blood loss and transfusion requirements, who carries the risk of transfusion-related complications as TRALI (transfusion-related lung injury) and infection, has been shown in several recommendations for blood management strategies as in the 2017 EACTS guidelines (11-13). The mini-thoracic approach evidently minimizes blood loss by different mechanisms including less tissue trauma by small incisions and tissue retractions and dissections, use of lower systemic heparin dose, standard use of cell salvage and lack of haemodilution and coagulation trauma caused by cardiopulmonary bypass (13). The results of our study regarding the significantly lower postoperative bleeding in the minimally invasive CABG group are comparable with those of the study by Menkis et al. published in the consensus statements of the International Society for Minimally Invasive Cardiothoracic Surgery. Therefore, minimally invasive approach could be an acceptable alternative to conventional surgery due to less bleeding, lower transfusion rates, decreased mechanical ventilation times, as well as less ICU and hospital stay (13). In our study we have shown that the minimally invasive approach ensures early extubation minimizing ventilator-related pulmonary complications in the early postoperative period in accordance to studies underlining the importance of early implementation of enhanced recovery after surgery (ERAS) protocols in cardiac surgery (14-17). In our study ERAS protocols such as the early oral liquids intake, early patient mobilization, could be successfully implemented in the minimally invasive CABG group. Although, our results showing significantly shorter ICU length of stay (LOS) are comparable with other large observational researches such as the Reser et al. study, we could not prove the significant difference regarding the hospital stay days among our patient groups (18).

Cardiovascular complications still remain a major source of mortality and morbidity. The analysis of our research population, consisted of mostly elderly male patients, have shown that the incidence rate of major cerebrovascular events was 8% of the total study population. As the study by Kang et

al. presented, older age (≥ 65 years), male gender, in combination with chronic renal or pulmonary disease and diabetes mellitus, are considered as independent strong predictors of major adverse cardiac and cerebrovascular events (MACCE) and death among CABG patients (19,20).

Our research has some of limitations regarding the small sample size which could have some impacts on statistical measurements and data analysis. Surgeon's experience, the learning curve for minimally invasive procedures and technological capabilities are playing a crucial role in the performance of this type of surgery. Larger prospective studies should be conducted at our centre to provide more accurate results to be comparable with large cardiovascular centres in minimally invasive access in treating coronary artery disease, considering the fact that this method

is implemented in our practice in the past few years.

In conclusion, although technically challenging, the minimally invasive approach through mini-thoracotomy for single-vessel revascularization surgery could be considered in a carefully selected group of patients as an acceptable alternative to full sternotomy technique due its advantages in patient's postoperative recovery and reduction of costs, the highest burden of healthcare system in developing countries.

FUNDING

No specific founding was received for this study.

TRANSPARENCY DECLARATION

Conflicts of interests: Non to declare.

REFERENCES

- Head SJ, Milojevic M, Taggart DP, Puskas JD. Current practice of state-of-the-art surgical coronary revascularization. *Circulation* 2017; 136:1331-45.
- Pattakos G. Minimally invasive direct CABG versus off-pump CABG: can less be more. *Hellenic J Cardiol* 2020; 61:125-6.
- Adams DH, Chikwe J. On-pump CABG in 2018: Still the gold standard. *J Am Coll Cardiol* 2018; 71:992-3.
- Piroze MD, Holzhey DM, Mohr FW. Minimally invasive myocardial revascularization. In: Cohn LH, Adams DH. eds. *Cardiac surgery in the adult*, 5e. McGraw Hill; 2017: 559-74.
- Calafiore AM, Angelini GD. Left anterior small thoracotomy (LAST) for coronary artery revascularisation. *Lancet* 1996; 347:263-4.
- Van Praet KM, Kofler M, Shafit TZN, El Al AA, van Kampen A, Amabile A, Torregrossa G, Kempfert J, Falk V, Balkhy HH, Jacobs S. Minimally invasive coronary revascularisation surgery: a focused review of the available literature. *Interv Cardiol* 2021; 16:e08.
- Kayatta MO, Halkos ME, Narayan P. Minimally invasive coronary artery bypass grafting. *Indian J Thorac Cardiovasc Surg* 2018; 34:302-9.
- Diegeler A, Matin M, Falk V, Battellini R, Walther T, Autschbach R, Mohr FW. Indication and patient selection in minimally invasive and 'off-pump' coronary artery bypass grafting. *Eur J Cardiothoracic Surg* 1999; 16:S79-82.
- Kraft F, Schmidt C, Van Aken H, Zarbock A. Inflammatory response and extracorporeal circulation. *Best Pract Res Clin Anaesthesiol* 2015; 29:113-23.
- Hage A, Hage F, Al-Amodi H, Gupta S, Papatheodorou SI, Hawkins R, Ailawadi G, Mittleman MA, Chu M. Minimally invasive versus sternotomy for mitral surgery in the elderly: a systematic review and meta-analysis. *Innovations (Phila)* 2021; 16:310-16.
- Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA), Boer C, Meesters MI, Milojevic M, I, Benedetto U, Bolliger D, von Heymann C, Jeppsson A, Koster A, Osnabrugge RL, Rannucci M, Ravn HB, Vonk A, Whba A, Pagano D. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. *Eur J Cardiothorac Surg* 2018; 53:79-111.
- de Biasi AR, DeBois WJ, Isom O, Salemi A. Transfusion therapy and blood conservation. In: Cohn LH, Adams DH. eds. *Cardiac surgery in the adult*, 5e. McGraw Hill; 2017: 353.
- Menkis AH, Martin J, Cheng DCH, Fitzgerald DC, Freedman JJ, Gao C, Koster A, Mackenzie GS, Murphy GJ, Spiess B, Ad N. Drug, devices, technologies, and techniques for blood management in minimally invasive and conventional cardiothoracic surgery. A consensus statement from the international society for minimally invasive cardiothoracic surgery (ISMICS) 2011. *Innovations* 2012; 7: 229-41.
- Brindle M, Nelson G, Lobo DN, Ljungqvist O, Gustafsson UO. Recommendations from the ERAS® Society for standards for the development of enhanced recovery after surgery guidelines. *BJS Open* 2020; 4:157-63.
- Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. *JAMA Surg* 2017; 292-98.
- Tiwari KK, Wadhawa V, Jawarkar M, Rathod D, Shah M, Manek P, Doshi C. Total arterial multivessel minimal invasive direct coronary artery bypass grafting via left minithoracotomy. *Gen Thorac Cardiovasc Surg* 2021; 69:8-13.

17. Patil S, Cornett EM, Jesunathades J, Belani K, Fox CJ, Kaye AD, Lambert LA, Urman RD. Implementing enhanced recovery pathways to improve surgical outcomes. *J Anaesthesiol Clin Pharmacol* 2019;35(Suppl 1): S24-8.
18. Reser D, Holubec T, Caliskan E, Guidotti A, Maisano F. Left anterior small thoracotomy for minimally invasive coronary artery bypass grafting. *Multimed Man Cardiothorac Surg* 2015; mmv022.
19. Claessens J, Yilmaz A, Awouters C, Oosterbos H, Thonnissen S, Benit E, Kaya A, Bataille Y. Clinical results after hybrid coronary revascularization with totally endoscopic coronary surgery. *J Cardiothorac Surg* 2022; 17:98.
20. Kang SH, Ahn JM, Lee CH, Lee PH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park DW, Park SJ. Differential event rates and independent predictors of long-term major cardiovascular events and death in 5795 Patients with unprotected left main coronary artery disease treated with stents, bypass surgery, or medication: Insights from a large international multicenter registry. *Circ Cardiovasc Interv* 2017; 10:e004988.

Parameters in predicting the risk of a prolonged hospital stay in patients with acute exacerbation of chronic obstructive pulmonary disease: a single-centre experience

Aida Mujaković^{1,2}, Belma Paralija^{3,4}, Besim Prnjavorac^{2,5,6}, Orhan Lepara⁷, Almir Fajkić⁸, Edin Begić⁹, Avdo Kurtović¹⁰, Midhat Čizmić¹¹, Mirad Odobašić¹²

¹Department of Pulmonology, General Hospital "Prim. dr. Abdulah Nakaš", ²Department of Pathophysiology, School of Medicine, Sarajevo School of Science and Technology, ³Clinic for Pulmonary Diseases and Tuberculosis "Podhrastovi", University of Sarajevo Clinical Centre, ⁴Department of Internal Medicine, School of Medicine, University of Sarajevo; Sarajevo, ⁵Department of Pulmonology, General Hospital Tešanj, Tešanj, ⁶Department of Pathophysiology, School of Medicine, University of Zenica, ⁷Department of Physiology, School of Medicine, University of Sarajevo, ⁸Department of Pathophysiology, School of Medicine, University of Sarajevo, ⁹Department of Cardiology, General Hospital "Prim. dr. Abdulah Nakaš", Sarajevo, ¹⁰Primary Healthcare Centre Gračanica, Gračanica, ¹¹Department of Radiology, General Hospital "Prim. dr. Abdulah Nakaš", ¹²Private Healthcare Institution „Poliklinika dr. Odobašić“, Sarajevo; Bosnia and Herzegovina.

ABSTRACT

Aim To identify clinical and laboratory parameters on admission and/or during a hospital stay that would predict prolonged hospital stay in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Methods A retrospective cross-sectional study was conducted at the Clinic for Pulmonary Diseases and Tuberculosis, Clinical Centre University of Sarajevo for the period 2019-2021 accounting patients admitted due to AECOPD. The need for hospitalization was evaluated according to the current GOLD criteria and certain clinical parameters. Spirometry testing and laboratory analysis were performed for all patients on the day of admission and on the 10th day of hospital stay. Linear regression was used to show the relationship between multiple independent predictor variables and LOS.

Results A total of 50 patients were evaluated during their hospital stay due to AECOPD. Median of LOS was 22.02±1.06, with 90% hospital survival rate. Due to AECOPD the median of LOS in the intensive care unit (ICU) was 4±0.68 days with pH<7.35 in 34% of hospitalized patients. According to spirometry classification on the day of admission, 56% of patients were assigned to group 3 and 16% to group 4 with significant improvement identified on spirometry findings on discharge. Platelets on the day of admission were the only statistically significant positive predictors of the length of hospital stay.

Conclusion Identifying chronic obstructive pulmonary disease patients at risk of frequent exacerbations and appropriate disease management could reduce the disease burden.

Key words: chronic obstructive pulmonary disease, hospitalization, therapeutics

Corresponding author:

Aida Mujaković
General Hospital "Prim. dr. Abdulah Nakaš"
Kranjčevićeva 12, 71000 Sarajevo,
Bosnia and Herzegovina
Phone: +387 33 285 425;
Fax: +387 33 285 370;
E-mail: mujakovic.aida@gmail.com;
ORCID ID: <https://orcid.org/0000-0002-0022-1482>

Original submission:

07 July 2022;

Revised submission:

08 August 2022;

Accepted:

30 August 2022

doi: 10.17392/1514-22

INTRODUCTION

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is defined as acute worsening of respiratory symptoms such as dyspnoea, and/or increased sputum purulence and volume and/or cough which result from increased airway inflammation, mucus production and/or air trapping demanding the use of additional therapeutic modalities (1). Potential risk factors indicating the need for hospital treatment include worsening of resting dyspnoea, high respiratory rate, decrease in peripheral oxygen saturation, acute respiratory failure, depressed mental status, cyanosis and new onset of peripheral oedema, failure of prehospital medical treatment, comorbidities (e.g. heart failure, new onset of cardiac arrhythmias) (1,2). Chronic obstructive pulmonary disease (COPD) exacerbations usually last for 7-10 days, but 20% of patients after eight weeks of follow-up are still recovering from the previous exacerbation state (2). Frequent exacerbations are usual sign of uncontrolled disease and serious disease progression (3). Factors independently associated with poor outcome of AECOPD treatment are comorbidities, older age, low body mass index (BMI), history of frequent COPD exacerbation and long-term oxygen therapy use (4). The number of exacerbations experienced in the prior year remain the strongest predictor of future exacerbation history, along with worsening forced expiratory volume in the first second (FEV1) according to the spirometry findings (5). Exacerbations of COPD are often triggered by viral or bacterial infections presented by an increase in neutrophil and eosinophil count along with increased values of nonspecific inflammatory markers (6). The multiple comorbidities accompanying AECOPD are strongly associated with poor prognosis and worsening of the inpatient costs (1). Therefore, adequate and timely goal-directed treatment according to current guidelines (1) is crucial for AECOPD's favourable outcome with the least possible in-hospital stay.

The aim of this study was to identify both clinical and laboratory parameters on admission and/or during a hospital stay that would predict prolonged hospital stay in patients with AECOPD.

PATIENTS AND METHODS

Patients and study design

A retrospective cross-sectional study was conducted at the Clinic for Pulmonary Diseases and Tuberculosis, Clinical Centre University of Sarajevo for the period 2019-2021 accounting 50 patients admitted due to AECOPD.

Methods

The need for hospitalization was evaluated according to the current GOLD criteria (1) COPD exacerbation was classified as moderate, severe and/or very severe, and the following clinical parameters: smoking status, dyspnoea evaluation according to the modified medical researching council scale (mMRC scale), change in sputum colour and volume, chest pain, signs of upper respiratory tract infection verified at least five days prior admission, increase in body temperature, chest x-ray findings on the day of admission, number of exacerbations in the previous year and comorbidities on admission.

Moderate exacerbation is defined according to the following parameters: $50\% \leq \text{FEV1} < 80\%$, < 3 exacerbation/year, no need for hospitalization during the past one-year period. Severe exacerbation is defined as: $30\% \leq \text{FEV1} < 50\%$, ≥ 3 exacerbation/year, the need for one hospitalization during the past one-year period, ≥ 65 years of age. Very severe exacerbation is defined as $\text{FEV1} < 30\%$, ≥ 3 exacerbation/year, ≥ 2 hospitalizations during the past one-year period, ≥ 65 years of age.

Sputum colour (serous/white/yellow-green/haemoptysis) was evaluated on admission as well as sputum volume appearance, and classified as moderate, increased or not detected.

Modified medical research council scale (mMRC) (7) was used for dyspnoea classification according to the following: mMRC grade 1- dyspnoea only within the strenuous exercise, mMRC grade 2 - walks slower than people of the same age because of dyspnoea or has to stop for breath when walking at own pace, mMRC grade 3 - stops for breath after walking 100 yards (91 meters) or after a few minutes, mMRC grade 4 - too dyspnoeic to leave house or breathless when dressing.

Spirometry testing needed for recordings of forced expiratory volume in the first second (FEV1)

and laboratory analysis including erythrocyte sedimentation rate (ESR), complete (CBC) and differential blood cell count including neutrophils (Neu), lymphocytes (Lym), monocytes (Mono), basophils (Bas) and eosinophils (Eos), C-reactive protein (CRP) and parameters of arterial blood gas analysis (ABG) according to the reference range values were performed for all patients on the day of admission and on the 10th day of hospital stay. The 10th day for the laboratory parameters control was determined as cut-off in concordance to an average time of AECOPD duration according to GOLD criteria (1). Reference ranges for evaluated laboratory parameters were: erythrocytes $4.34 - 5.72 \times 10^{12}/L$ and $3.86 - 5.08 \times 10^{12}/L$ for males and females respectively; leukocytes $3.4 - 9.7 \times 10^9/L$; haemoglobin 137-175 g/L in males and 119-157 g/L in females; haematocrit 0.41-0.53 % in males and 0.35-0.47% in females; platelets $158 - 424 \times 10^9/L$ for males and females; neutrophils 44-72%; lymphocytes 20-46%; monocytes 4-8 %; basophils 0-1 %; eosinophils 2-4 %; CRP up to 5.0 mg/L.

Spirometry findings on admission and discharge related to FEV1 were classified into four different categories: $FEV1 \geq 80\%$ (mild), $50\% \leq FEV1 < 80\%$ (moderate), $30\% \leq FEV1 < 50\%$ (severe); $FEV1 < 30\%$ (very severe) assigned with category 1, 2, 3 and 4, respectively.

On the day of admission physical examination was performed including measurements of vital parameters such as heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) values. Patients were followed during the hospital stay with repeated/daily notification of vital parameters values and timed lab test analysis according to objective clinical improvement or deterioration of the patient's condition.

Statistical analysis

Data were evaluated by standard statistical procedures and presented in tables. The Shapiro-Wilk test was used to evaluate the normal distribution of continuous variables. The results were statistically evaluated and presented as mean value (X) and standard error mean (SEM) for variables. Linear regression was used to show relationship between multiple independent predictor variables and LOS (length of stay). The $p < 0.05$ was considered as statistically significant.

RESULTS

Fifty patients were evaluated during their hospital stay due to AECOPD; 30% were females, and 70% were males. The median of length of hospital stay (LOS) was 22.02 ± 1.06 , with 90% of hospital survival rate. Due to AECOPD the median of LOS in the intensive care unit (ICU) was 4 ± 0.68 days with $pH < 7.35$ in 34% of hospitalized patients. Elevations in partial arterial pressure of CO_2 ($paCO_2$) were identified in only 18% of patients on the day of admission. The majority of patients were passive smokers, 22 (44%), while 18 (36%) were current smokers, and only 1 (2%) was ex-smoker. Twenty-seven (54%) patients did not experience any previous COPD exacerbations, while exacerbations appeared in the last three, six and twelve months in 12 (24%), 7 (14%) and 4 (8%) of patients, respectively. Upper respiratory tract infection was a clinical finding in 27 (54%) of patients. Most patients were classified in groups 2 and 3 according to mMRC on the day of admission, accounting for 14 (28%) and 36 (72%), respectively.

According to spirometry classification on the day of admission, 23 (56%) patients were assigned to group 3, 13 (26%) to group 2 and 8 (16%) to group 4 with significant improvement identified on spirometry findings on discharge, accounting for 22 (44%) in group 1 and 19 (38%) in group 2.

An increase in mean values of nonspecific inflammatory markers such as leukocytes and CRP was noted on admission, accounting for 12.1 ± 0.84 and 73.77 ± 12.95 , respectively. Total leukocyte counts as well as a neutrophil-to-lymphocyte ratio (NLR) and neutrophil count were increased on admission, accounting for 12.1 ± 0.84 , 8.51 ± 1.47 and 80.11 ± 1.71 respectively, with the decrease in number after ten days of hospital stay. However, the eosinophil count was elevated on the 10th day of hospital stay in comparison to the admission result (1.46 ± 0.23 and 1.06 ± 0.29 respectively) (Table 1).

In a univariant linear regression analysis model, by examining independent predictors in patients with acute exacerbation of COPD, parameters such as chest pain, platelets, and eosinophils on the 10th day of hospital stay were identified as statistically significant positive predictors of the length of hospital stay.

The parameters such as elevated body temperature, sputum, sputum volume and respiratory

Table 1. Clinical and laboratory parameters of patients with acute exacerbation of chronic obstructive pulmonary disease (COPD)

Parameter	Value
Length of hospital stay/LOS (days)	22.02±1.06
Hospitalization outcome (death/survival) (%)	10/90
Gender (female/male) (%)	30/70
Smoking status (non-smoker/smoker/passive smoker/ex-smoker) (%)	18/36/44/2
Number of AECOPD (without exacerbation/in last 3 months/in last 6 months/in last 12 months) (%)	54/24/14/8
Upper respiratory tract infection (yes/no) (%)	54/46
Elevated body temperature (<37/37.5/38/38.5 C) (%)	76/2/16/6
mMRC (0/1/2/3/4) (%)	0/0/28/72/0
Sputum (without/serous/white/yellow-green/haemoptysis) (%)	6/38/28/16/10
Sputum volume (without/moderate/increased) (%)	8/6/86
Chest pain (yes/no) (%)	30/70
Spirometry on admission (1/2/3/4) (%)	2/26/56/16
Spirometry on discharge (1/2/3/4) (%)	44/38/18/0
SBP<90mmHg (yes/no) (%)	6/94
paCO ₂ >6.5kPa (yes/no) (%)	18/82
pH<7.35 (yes/no) (%)	34/66
ICU stay (days)	4±0.68
ESR on admission	45.34±5.55
CRP on admission (mg/L)	73.77±12.95
Erythrocytes on admission (x10 ¹² /L)	4.57±0.11
Haemoglobin on admission (g/L)	132.6±2.51
Haematocrit on admission (%)	40.68±0.89
Platelets on admission (10 ⁹ /L)	295±16.71
Leucocytes on admission (10 ⁹ /L)	12.1±0.84
Neutrophils (%)	80.11±1.71
Lymphocytes (%)	10±1.34
Eosinophils (%)	1.06±0.29
NLR	8.51±1.47
ESR on the 10 th day of hospital stay	25.98±4.07
CRP on the 10 th day (mg/L)	23.91±6.96
Erythrocytes on the 10 th day (x10 ¹² /L)	4.26±0.08
Haemoglobin on the 10 th day (g/L)	125.5±2.5
Haematocrit on the 10 th day (%)	39.07±1.04
Platelets on the 10 th day (x10 ⁹ /L)	237.58±18.05
Leukocytes on the 10 th day (x10 ⁹ /L)	9.22±0.46
Lymphocytes on the 10 th day (%)	21.58±1.54
Neutrophils on the 10 th day (%)	67.85±1.93
Eosinophils on the 10 th day (%)	1.46±0.23
NLR on the 10 th day of hospital stay	3.09±0.78

Data are shown as number of patients (percentage) or mean±SEM (standard error of mean), unless otherwise stated. Percentages are calculated for non-missing days; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CRP, C reactive protein; mMRC, modified medical research council dyspnoea scale; SBP, systolic blood pressure; ICU, intensive care unit; ESR, erythrocyte sedimentation rate; NLR, neutrophil to lymphocyte ratio

rate higher than 30 were identified as statistically significant negative predictors of the length of hospital stay ($p<0.05$). In a multivariate linear regression analysis model, by examining the independent predictors with acute exacerbation of COPD, platelets on the day of admission were the only statistically significant positive predictors of the length of hospital stay. At the same time, elevated body temperature and sputum volume were identified as statistically significant

negative predictors of the length of hospital stay ($p<0.05$) (Table 2).

DISCUSSION

Evaluation of the variation of the LOS for COPD exacerbation performed by Ruparel et al. identified that the mean LOS across Europe were higher than expected showing great variability in overall Europe, North America, Australia and Asia (8,9). The factors that are influencing the variability of LOS are patient-related, determined by the stage of the disease and exacerbation severity as well as treatment-related (10).

Predominantly related factors to a prolonged hospital stay in patients admitted with AECOPD are the place of admission and the need for more intensive care treatment (11). The study by Garcia-Sanz et al. (11) on 661 patients identified that prolonged stay due to AECOPD was primarily related to the unit patients are admitted to, the need for more intensive care treatment and the use of noninvasive mechanical ventilation. However, patients evaluated in our study were treated in ICU for a median of 4±0.68 days and continued treatment in the hospital ward with available medicamentous treatment due to satisfactory clinical improvement. The prospective study by Crisafulli et al. evaluated clinical variables predicting the risk of a hospital stay for longer than seven days in patients with severe AECOPD. They identified that the presence of an mMRC ≥ 2 and acute respiratory acidosis at admission independently increased the risk of a prolonged LOS for AECOPD (12). Most patients in our study were assigned with mMRC 3 on admission, which partially explains prolonged LOS with a median of 22.02±1.06 days. The study of Wang et al. exploring the independent predictors of prolonged LOS in AECOPD patients and identified three groups of patients with LOS <7 days, 7-10 days, and ≥ 11 days, respectively (13), and found that rates of hypertension and chronic cor pulmonale (CCP), neutrophil-lymphocyte ratio (NLR), and erythrocyte sedimentation rate (ESR) were independent predictors of prolonged LOS in AECOPD patients. The study of Gomez-Rosero et al. aimed to prove mean platelet volume (MPV), eosinophil count and neutrophil/lymphocyte ratio (NLR) as in-hospital prognostic factors, but identified only NLR as greater than 5 as a strong predictor of mortality or ICU admissions and a

Table 2. Independent clinical and laboratory predictors of length of hospital stay in patients with acute exacerbation chronic obstructive pulmonary disease (AECOPD)

Variable	Univariate linear regression analysis		Multivariate linear regression analysis	
	Regression coefficient (95% CI)	p	Regression coefficient (95% CI)	p
Gender	-3.00 (-10.48 – 4.48)	0.374		
Smoking status	3.75 (-4.90 – 12.40)	0.339		
Number of AECOPD	1.18 (-3.16 – 5.51)	0.541		
Upper respiratory tract infections	-3.80 (-19.21 – 11.61)	0.578		
Elevated body temperature	-7.20 [(-13.08 – (-1.32)]	0.023	-2.73 [(-4.68 – (-0.78)]	0.007
mMRC	2.85 (-4.63 – 10.33)	0.397		
Sputum	-4.36 [(-8.69 – (0.02)]	0.049	-0.77 (-2.63-1.09)	0.408
Sputum volume	-12.17 [(-20.95 – (-3.38)]	0.023	-5.92 [(-10.26 – (-1.17)]	0.009
Chest pain	12.37 (1.92 – 22.82)	0.027	2.55 (-1.89 – 6.99)	0.253
Spirometry on admission	-1.27 (-7.33 – 4.80)	0.637		
Respiratory rate >30/min	-19.51 [(-31.76 – (-7.26)]	0.007	-2.01 (-5.94 – 1.91)	0.307
ESR on admission	0.02 (-0.11 – 0.14)	0.761		
CRP on admission	0.15 (-0.11- 0.40)	0.220		
Erythrocytes (x10 ¹² /L)	-4.45 (-19.61-10.70)	0.509		
Haemoglobin (g/L)	-0.34 (-1.62- 0.93)	0.545		
Haematocrit (%)	2.56 (-3.45 -8.58)	0.347		
Platelets (x10 ⁹ /L)	0.07 (0.02-0.12)	0.013	0.03 (0.01-0.04)	0.005
Leucocytes (x10 ⁹ /L)	-1.96 (-6.04- 2.12)	0.293		
Neutrophils %	-0.35 (-0.99 – 0.31)	0.249		
Eosinophils %	-0.97 (-5.82 – 3.88)	0.651		
Basophils %	10.82 (-1.64 – 23.27)	0.079		
Monocytes %	0.50 (-3.18 – 4.18)	0.756		
On the 10th day				
ESR	-0.21 (-0.76 – 0.35)	0.405		
CRP (mg/L)	-0.04 (-0.27 – 0.19)	0.722		
Erythrocytes (x10 ¹² /L)	-21.38 (-48.67 – 5.91)	0.106		
Haemoglobin (g/L)	-0.18 (-1.68 – 1.32)	0.785		
haematocrit (%)	0.49 (-1.86 – 2.84)	0.637		
Platelets (x10 ⁹ /L)	-0.04 (-0.11 – 0.02)	0.161		
Leukocytes (x10 ⁹ /L)	1.95 (-0.28 – 4.19)	0.078		
Lymphocytes (%)	-0.73 (-2.11 – 0.66)	0.254		
Eosinophils (%)	4.01 (1.45 – 6.57)	0.008	0.95 (-0.17 – 2.07)	0.095
Basophils (%)	-9.95 (-44.80 – 24.90)	0.521		

ESR, erythrocyte sedimentation rate; CRP, C reactive protein; mMRC, modified medical research council dyspnoea scale

longer hospital stay in patients hospitalized with AECOPD (14). However, the results of our study identified platelets on the day of admission as the only statistically significant positive predictors of the LOS. In addition, an increase in mean values of nonspecific inflammatory markers such as leucocytes, CRP, and NLR were noted on admission in our study, with a significant decrease after ten days of hospital stay, which correlates with previous results.

According to available studies, COPD is linked with comorbidities such as congestive heart failure (CHF), fluid and electrolyte disorders, and renal failure (15). Results of Inabnit et al. identified that CHF was associated with a 28% greater length of stay ($p < 0.0001$), electrolyte disorders were associated with a 2-fold greater length of stay ($p < 0.0001$) while renal failure was associated with a 50% greater length of stay ($p < 0.0001$) (15). However, comorbidities on the day of ad-

mission were not evaluated in our study due to the lack or inconsistency of data. A larger sample, along with the analysis of impact of comorbidities on outcome, would provide more significant conclusions for clinical practice. In AECOPD patients, an improvement in clinical outcome is the result of successful therapy (16). Data on sputum culture suggest that bacterial infections often cause AECOPD, and sputum purulence and the presence of bacteria are strongly correlated (17). Antibiotics are the usual treatment in AECOPD; however, some patients treated with antibiotics show incomplete resolution, persistence of symptoms/signs, leading to an in-hospital treatment failure. That imposes a question of antibiotic efficacy in resolving identified bacterial infections regarding the adequacy of its use leading to the likelihood of future relapse (18).

Among numerous clinical factors related to early readmission, lung function decline rate

and dyspnoea severity score are among the most common (19). Moreover, numerous studies performed with a period of one-year observation on AECOPD patients, identified airflow obstruction severity, measured by FEV1, to be an important predictor factor for AECOPD readmission during the stable phase (20). In general, FEV1 values below 50% of the predicted values are associated with a higher risk of COPD readmission (21). The results of our study identified more than half of patients assigned with group 3 on admission according to spirometry findings with significant improvement after one day follow-up, which also correlated with previous data.

Taking into consideration research findings, our study determined certain laboratory and clinical

parameters influencing the prolonged hospital stay in patients with AECOPD.

In conclusion, future research should determine if better management of comorbidities can favourably impact the COPD disease burden. COPD patients frequently experience exacerbations. Increasing exacerbation frequency is associated with increased COPD-related costs, regardless of the cause. Future targets should be adjusted to identify COPD patients at risk of frequent exacerbations and appropriate disease management.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

1. GOLD-Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2022 report. <https://goldcopd.org/2022-gold-reports-2/> (22 June, 2022).
2. Halpin DMG, Criner GJ, Papi A, Singh D, Anzueto A, Martinez FJ, Agusti AA, Vogelmeier CF. Global Initiative for the diagnosis, management, and prevention of chronic obstructive lung disease. The 2020 GOLD Science Committee Report on COVID-19 and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2021;203: 24-36.
3. Donaldson GC, Law M, Kowlessar B, Singh R, Brill SE, Allinson JP, Wedzicha JA. Impact of prolonged exacerbation recovery in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015; 192:943-50.
4. Singanayagam A, Schembri S, Chalmers JD. Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2013; 10:81-9.
5. Donaldson GC, Müllerova H, Locantore N, Hurst JR, Calverley PM, Vestbo J, Anzueto A, Wedzicha JA. Factors associated with change in exacerbation frequency in COPD. *Respir Res* 2013; 14:79.
6. van Bragt JJMH, Vijverberg SJH, Weersink EJM, Richards LB, Neerincx AH, Sterk PJ, Bel EHD, Maitland-van der Zee AH. Blood biomarkers in chronic airways diseases and their role in diagnosis and management. *Expert Rev Respir Med* 2018; 12:361-74.
7. Natori H, Kawayama T, Suetomo M, Kinoshita T, Matsuoka M, Matsunaga K, Okamoto M, Hoshino T. Evaluation of the modified Medical Research Council Dyspnea scale for predicting hospitalization and exacerbation in Japanese patients with chronic obstructive pulmonary disease. *Intern Med* 2016; 55:15-24.
8. George PM, Stone RA, Buckingham RJ, Pursey NA, Lowe D, Roberts CM. Changes in NHS organization of care and management of hospital admissions with COPD exacerbations between the national COPD audits of 2003 and 2008. *QJM* 2011; 104:859-66.
9. Busby J, Purdy S, Hollingworth W. A systematic review of the magnitude and cause of geographic variation in unplanned hospital admission rates and length of stay for ambulatory care sensitive conditions. *BMC Health Serv Res* 2015; 15:324.
10. Ruparel M, López-Campos JL, Castro-Acosta A, Hartl S, Pozo-Rodriguez F, Roberts CM. Understanding variation in length of hospital stay for COPD exacerbation: European COPD audit. *ERJ Open Res* 2016; 2:00034-2015.
11. García-Sanz MT, González-Barcala FJ, Cánive-Gómez JC, García-Couceiro N, Alonso-Acuña S, Carreira JM. Prolonged stay predictors in patients admitted with chronic obstructive pulmonary disease acute exacerbation. *Lung India* 2018; 35:316-20.
12. Crisafulli E, Ielpo A, Barbata E, Ceccato A, Huerta A, Gabarrús A, Soler N, Chetta A, Torres A. Clinical variables predicting the risk of a hospital stay for longer than 7 days in patients with severe acute exacerbations of chronic obstructive pulmonary disease: a prospective study. *Respir Res* 2018; 19:261.
13. Wang H, Yang T, Yu X, Chen Z, Ran Y, Wang J, Dai G, Deng H, Li X, Zhu T. Risk factors for length of hospital stay in acute exacerbation chronic obstructive pulmonary disease: a multicenter cross-sectional study. *Int J Gen Med* 2022; 15:3447-58.
14. Gómez-Rosero JA, Cáceres-Galvis C, Ascuntar J, Atencia C, Vallejo CE, Jaimes F. Biomarkers as a prognostic factor in COPD exacerbation: a cohort study. *COPD* 2021; 18:325-32.
15. Inabnit LS, Blanchette C, Ruban C. Comorbidities and length of stay in chronic obstructive pulmonary disease patients. *COPD* 2018; 15:355-60.

16. Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 169:1298–303.
17. Miravittles M, Kruesmann F, Haverstock D, Perroncel R, Choudhri SH, Arvis P. Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis. *Eur Respir J* 2012; 39:1354–60.
18. Soler N, Esperatti M, Ewig S, Huerta A, Agustí C, Torres A. Sputum purulence-guided antibiotic use in hospitalised patients with exacerbations of COPD. *Eur Respir J* 2012; 40:1344–53.
19. Steer J, Norman EM, Afolabi OA, Gibson GJ, Bourke SC. Dyspnea severity and pneumonia as predictors of in-hospital mortality and early readmission in acute exacerbations of COPD. *Thorax* 2012; 67:117–21.
20. Wong AW, Gan WQ, Burns J, Sin DD, van Eeden SF. Acute exacerbation of chronic obstructive pulmonary disease: influence of social factors in determining length of hospital stay and readmission rates. *Can Respir J* 2008; 15:361–4.
21. Mantero M, Rogliani P, Di Pasquale M, Polverino E, Crisafulli E, Guerrero M, Gramegna A, Cazzola M, Blasi F. Acute exacerbations of COPD: risk factors for failure and relapse. *Int J Chron Obstruct Pulmon Dis* 2017; 12:2687–93.

Correlation between clinical outcomes and patients' satisfaction using tarsoconjunctival - Hughes flap for the reconstruction of eyelid defects

Nina Jovanović^{1,2}, Patricia Reisz-Majić^{3,4}, Sunita Mehic-Fazlić⁵, Selma Terzić⁶, Jasmina Alajbegović-Halimić⁷, Admir Dizdarević¹

¹Ophthalmology Department, Cantonal Hospital Zenica, ²School of Medicine, University of Zenica; Zenica, Bosnia and Herzegovina, ³Eye Clinic, Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Croatia, ⁴University Hospital Centre Osijek, Croatia, ⁵Otorhinolaryngology Department, Canton Hospital Zenica, Zenica, ⁶Sarajevo Canton Emergency Medical Service, ⁷Private Ophthalmology Practice, "Dr. Halimić"; Sarajevo, Bosnia and Herzegovina

ABSTRACT

Aim To examine and quantify patients' satisfaction and correlate with the objective clinical presentation after the treatment and to present a comprehensive literature review on tarsoconjunctival/Hughes flap technique.

Methods A review of more than 159 peer-review articles and a combined retrospective-prospective two-centres case series of 17 patients who underwent a two-stage modified Hughes flap procedure (2019-2021) to repair a lower eyelid defect caused by epithelial cancer was conducted. All patients were followed up for a minimum of six months. Patient macroscopic evaluation of redness, lid position, retraction, trichiasis, conjunctival overgrowth, tissue inflammation/infection and hypertrophic scarring were obtained, and findings were graded on a scale of 1 to 5 or binary YES/NO scale. Patients' satisfaction using a Likert-type scale and correlation with the clinical presentation were analysed.

Results Pearson correlation coefficient between patients' satisfaction and clinical presentation was 0.534. Out of 510 (the highest summed score for patients' satisfaction), the total score was 479 (93.9%); out of 187 (the highest summed score for clinical presentation), the total score was 162 (86.6%). Although both scores were high, a lower correlation coefficient and the higher satisfaction score can be explained by more realistic expectations in oncological patients compared to cosmetic ones.

Conclusion Hughes flaps provide multiple benefits in the reconstruction of selected patients with large defects, especially when poor wound healing is expected, or when local advancement flaps do not provide tension-free reconstruction. The rate of complications is low and manageable, whereas additional therapy is usually observational or symptomatic.

Key words: epithelial malignant skin tumour, Likert score, periorbital region

Corresponding author:

Nina Jovanović
Ophthalmology Department,
Canton Hospital Zenica, Zenica
Phone: +387 32 447 286;
Fax: +387 32 226 576;
Email: nina-jovanovic@uiowa.edu
ORID ID: <https://orcid.org/0000-0002-8003-0837>

Original submission:

26 August 2022;

Revised submission:

12 September 2022;

Accepted:

28 October 2022

doi: 10.17392/1531-22

Med Glas (Zenica) 2023; 20(1): 52-57

INTRODUCTION

Tarsoconjunctival (TC) or Hughes flap is used for the reconstruction of large lower eyelid defects which involve 50-70% of the eyelid. Other indications include cutaneous malignancy (1), lid retraction (2), trauma or orbital implant exposure (3), globe rupture (4), congenital and acquired defects. (5,6). The Hughes procedure was initially described by Dr Wendel Hughes in 1937 (7). He followed Gradengio's principle replacing "like with like" (8). The vascularized conjunctival flap overlaid the cornea after the lower eyelid repair with upper and lower lids closed, divided in a second-step procedure. Over the next decades, the procedure evolved and modifications were introduced by Hughes and others (9,10) in an attempt to minimize the number of complications by sparing the marginal upper lid tarsus and removing the levator muscle complex from the tarsoconjunctival flap and changing the location of the lid-splitting incision to minimize the adverse effect of this method (11).

There is controversial evidence in the literature advocating for or against Hughes flap reconstruction technique. One of the recurring controversies in the literature as well as in practice is the choice between Hughes flap combined with a free skin graft (12,13), free tarsoconjunctival (TC) graft combined with myocutaneous flap (14) or free tarsal graft with free skin graft (15) for eyelid defects reconstruction.

The aim of this study was to present objective clinical outcomes (complications and benefits), and correlate individual subjective satisfaction during and post-surgery and estimate overall success.

PATIENTS AND METHODS

Patients and study design

The retrospective-prospective two-centres study included all patients who underwent a lower eyelid defect repair using the Hughes flap due to primary or recurrent epithelial malignant skin tumour from January 2019 until January 2021 in the Eye Clinic University Clinical Centre Osijek, Croatia, and the Ophthalmology Department of the Cantonal Hospital Zenica, Bosnia and Herzegovina. Exclusion criteria included extensive defects that could not be repaired using a TC flap, malignant tumours other than epithelial origin

with metastasis, tumours extending in the orbit, and defective posterior lamella of the upper eyelid. All patients were followed up for a minimum of six months.

Photos were prospectively collected for the analysis before and after surgery (one, three and six months) for an independent reviewer evaluation. A patient macroscopic evaluation of lid colour and lid position were either graded on a numerical scale of 1 to 3 by both surgeons independently, attributing lowest number to the least favourable result, i.e. 1 equals poor result (decolorization, dark pigmentation or other deviations from surrounding skin colour), 2 equals good results (minimally visible changes to surrounding skin colour) and 3 equals excellent results (no visible change compared to surrounding skin); the presence of lid entropion, retraction, trichiasis, conjunctival overgrowth and hypertrophic scarring was noted using YES/NO categorical values by surgeons independently, and assigned value 0 for YES and 1 for NO for further analysis. For each patient, the total score of clinical presentation success was calculated where 11 was the maximum value.

The next was a patient satisfaction questionnaire after a 6-month follow-up via telephone interview or in-person visit using a common rating scale, Likert-type scale (16), generally used for survey research. Patient satisfaction with the surgery end-results via telephone interview using a grading scale of 5 to 1 that best describes patients' satisfaction with the surgery was used. The following grading system of statements was obtained: complete agreement, agreement, indecision/neutrality, disagreement, and complete disagreement, graded from 5 to 1, respectively (Table 2).

Additionally, a literature search was performed twice. First time using "tarsoconjunctival flap AND lower eyelid" and second time using "tarsoconjunctival flap AND/OR Hughes flap" with Boolean Operator "AND/OR". The first search generated 159 peer-reviewed and 292 full text and the second 37 peer-reviewed and 71 full text articles. Only peer-reviewed studies that included lower eyelid defects repaired using classical or modified tarsoconjunctival flap were reviewed and discussed.

The Ethical Committees of the Eye Clinic University Clinical Centre Osijek and the Cantonal Hospital Zenica approved the study (R2-3775/2022

and 00-03-35-38-12/22, respectively). An informed consent was obtained as a part of the informed consent for the surgical procedure.

Methods

All surgical procedures were done by two oculo-plastic surgeons (the first and the second author of the study).

Phase one of surgical technique. The initial surgical excision of the lower lid margin was performed, and the defect was measured by approximating the minimal amount of tissue needed. The ipsilateral upper lid was everted by using a lid retractor (V. Mueller™&Co, Becton, Dickinson and Company, U.S.) and the measurement was performed, marking the incision site, and separating tarsus from the overlying muscles preferably by blunt dissection. The tarsoconjunctival flap was then mobilized, transposed and secured to the lower eyelid blepharotomy incision site. Any bleeding of the upper defect was meticulously managed with cautery as this can lead to bleeding or hematoma. The inferior cut edge of the flap and the conjunctiva were sutured with a running 7-0 vicryl suture (17).

When using a full-thickness skin graft for the reconstruction of the anterior lamella, 6-0 or 7-0 absorbing sutures were commonly used, while if a myocutaneous flap was used to replace the anterior lamella, a running 7-0 vicryl suture to fixate the upper edge of the anterior lamellar flap to the upper edge of the Hughes flap was used (17).

Phase two of the surgical technique. Division

of the conjunctival pedicle, as the second stage, is done once the graft developed a blood supply (18-20). The procedure was performed in the ambulatory settings ensuring asepsis and analgesia, where the conjunctival flap was cut along the upper edge of the lower eyelid taking care to excise all the excess conjunctiva.

Statistical analysis

All variables were categorical and ordinal. For macroscopic evaluation descriptive statistics were performed. Findings were described using ordinal scale: poor, good, excellent; graded on a scale of 1 to 3 for score calculation; or assigned binary value YES vs. NO.

For patients' satisfaction analysis (Likert-type scale) a descriptive statistical analysis and median values were obtained, and the Pearson correlation coefficient was calculated.

RESULTS

The study generated results from 17 patients. The mean age was 72.41 (median: 77, range 58-88).

All 17 patients had no entropion, two had lower lid retraction, none had trichiasis and three had conjunctival overgrowth and hypertrophic scarring. Out of 17 patients, 10 had excellent lid position and seven had good; while seven had excellent and ten had good lid colour (Table 1).

Four patients had the score 11, six had the score 10, four had the score 9, one had 8, and two had 7. The sum of scores for all patients was 162, which was 86.6% of the total ideal score of 187.

Table 1. Post-surgical clinical characteristics of 17 patients

Patient ordinal number	Age (years)	Lid position [†]	Lid colour [†] (poor/good/excellent)	Entropion [†]	Lid retraction [†]	Trichiasis	Conjunctival overgrowth [†]	Hypertrophic scarring [†]
1	58	Excellent	Good	NO	NO	NO	NO	NO
2	82	Excellent	Good	NO	NO	NO	YES	NO
3	61	Excellent	Excellent	NO	NO	NO	NO	NO
4	80	Excellent	Excellent	NO	NO	NO	NO	NO
5	47	Excellent	Good	NO	NO	NO	NO	YES
6	84	Good	Good	NO	YES	NO	NO	YES
7	85	Good	Good	NO	NO	NO	NO	NO
8	49	Good	Excellent	NO	NO	NO	NO	NO
9	85	Good	Good	NO	YES	NO	NO	NO
10	74	Good	Good	NO	NO	NO	NO	NO
11	77	Good	Good	NO	NO	NO	YES	YES
12	88	Good	Excellent	NO	NO	NO	NO	NO
13	80	Excellent	Good	NO	NO	NO	NO	NO
14	72	Excellent	Good	NO	NO	NO	NO	NO
15	60	Excellent	Excellent	NO	NO	NO	NO	NO
16	85	Excellent	Excellent	NO	NO	NO	YES	NO
17	64	Excellent	Excellent	NO	NO	NO	NO	NO

[†](poor/good/excellent); [†]YES/NO;

Table 2. Likert score of the individual satisfaction of the post-surgical results

Patient ordinal number	Satisfaction with			Not bothered by symptoms of dry eye	Not having inflammation/redness of the operated eye compared to the non-operated	The most difficult thing for you was between two acts of surgery due to a closed eye	Total score
	Functional result of the operation (opening/closing the eyes)	Position of the eyelids	Aesthetic result of the operation				
1	5	5	5	5	5	5	30
2	4	4	3	5	4	4	24
3	5	4	4	5	5	5	28
4	5	5	5	5	5	5	30
5	5	5	4	5	4	4	27
6	5	4	4	4	5	4	26
7	5	5	5	4	5	5	29
8	5	5	5	4	5	5	29
9	5	5	5	3	4	5	27
10	5	5	4	5	4	5	28
11	5	4	4	5	5	5	28
12	5	5	5	4	4	5	28
13	5	5	5	4	4	5	28
14	5	5	5	4	5	5	29
15	5	5	5	4	4	5	28
16	5	5	5	5	5	5	30
17	5	5	5	5	5	5	30
Total score	84/85	81/85	78/85	76/85	78/85	82/85	479

For patients' satisfaction with the end results the sum of scores for patients ranged between 24 and 30, where the former was the lowest and the latter the highest. Out of 17 patients, three had the score 30. The median score was 28. The sum of scores for all patients was 479, which was 93.9% of the total ideal score of 510 (Table 2).

The Pearson correlation coefficient between patients' satisfaction and the clinical results was 0.534 (53.4%).

DISCUSSION

Viability, vascularization and thus the separation time of the Hughes flap pedicle has been questioned in the literature with controversial results (20-23). Research showed that the flap pedicle does not seem to affect the perfusion of the flap, but the rich vascularization of the eyelid and tear film (21). In that matter, the free skin graft revascularizes within 3 to 8 weeks, despite the previous study results of avascular flap (22). However, several studies indicated that flap vascularization is established between 3 and 4 weeks after without complications (23-25). This shows a gradual decrease in time of pedicle separation and greater comfort for patients using this method. Converging with this, Leibovitch concluded that the separation may be done after 7 days without compromising flap viability (26). Our study results showed good results in terms of flap survival after 3 weeks of lid closure. According to the

literature, most surgeons perform the procedure after 3-4 weeks (27). Benefits of early separation include faster recovery, easier monitoring and minimized duration of eye occlusion. However, it has been associated with lower eyelid retraction, especially if the period was less than 2 weeks (18), flap necrosis, corneal abrasion, foreign body sensation, mucous discharge and dry eye (19). Our study did not show any adverse effects following the separation.

According to Hawes, Hughes flaps are more likely to result in eyelid margin erythema compared to other techniques (1). In the Ekin and Ugurlu study, cosmetic outcomes of the surgery are usually defined as satisfactory if the reconstructed lid did not exhibit lagophthalmos, contour irregularity, notching, unmatched colour or noticeable scarring (28). In our study three patients had conjunctival overgrowth that could be managed by additional thermocauterisation; however, lid colour was good or excellent in all patients and there was no need for additional treatment, which is in agreement with results in Hawes's study where several postsurgical complications occurred but none requiring revision (1).

Leibovitch et al. (29) described complications related to FTSG such as hematomas, graft infections, partial or complete graft rejection, hypertrophy or contracture of the graft while Marcet, McNab and colleagues (30,31) found inadequate manipulation of the lobe for the posterior lame-

lla, such as excessive clamping, may contribute to graft rejection. In our study two (out of 17) patients had lower lid retraction, none had trichiasis and three had conjunctival overgrowth and hypertrophic scarring. Ten out of 17 patients had good lid colour versus excellent in 7 patients, but without required additional treatment.

Tear film instability with reduced tear breakup time test and epiphora was described by Zaky and al. (32) and explained by the size of the defect. Similarly, Klein-Theyer et al. (33) concluded that despite the favourable aesthetic and functional results there is a statistically significant difference in tear film quality, meibomian gland loss, subjective symptoms of discomfort, lid margin abnormalities affecting the ocular surface health, explained by the shift in Meibom glands direction (34). Our patients' series did not examine tear film, however, during interviews, one patient reported more severe dry eye symptoms, while 7 out of 17 reported being mildly bothered by dry eye symptoms.

Skin and conjunctival erythema occur due to vertical contraction of the eyelid, ectropion, lagophthalmos and conjunctival outgrowth, and are dependent on the anterior lamella repair. Since the anterior lamella choice is related to the posterior lamella selection, it is not clear if the posterior lamella type induces erythema (1). In the conclusion, Hawes indicated the size of the primary defect as the main factor in choosing between two surgical procedures, recommending Hughes TC flap for major defects (> 75% of the lower eyelid) or difficult healing within 4 weeks between two acts of surgery (1).

Comorbidities and contraindications for Hughes FC flap due to the need to close the eye for several weeks (e.g. acute angle-closure glaucoma, poor vision contralaterally, development of amblyopia) should be carefully and individually discussed (18).

In case of skin graft hypertrophy, triamcinolone or fluorouracil injections can be applied with simultaneous massage with anti-scar gels. At a later stage, CO₂ laser treatment can be performed. Three patients in our study experienced skin hypertrophy after the surgery but all refused additional treatment for scarring minimization.

All patients were administered steroid ointment with massage during postoperative recovery.

According to Zaky et al. nearly half of their case series had to use artificial tears to minimize symptoms from tear film instability and break-up time test decrease (32). For the loss of meibomian glands and tear film instability, therapy is symptomatic in the form of eye surface care. In case of an irregular eyelid margin or hyperaemia caused by an overgrown eyelid margin joint, additional excision with or without thermocauterisation can be performed. In case of lagophthalmos, eyelid ectropion or retraction, surgery is required, most often FTSG with or without additional horizontal shortening or suspension of the lateral edge of the lower eyelid, depending on the laxity of the eyelid. Today, this complication is rare and is more common in the shortened period between two acts of surgery. Less often, additional surgery is needed. However, Perry and Allen suggest using other surgical methods like lateral stabilization with a periosteal strip and myocutaneous advancement flap to avoid often seen complication with Hughes flap (35).

The main limitation of our study is the small sample size. However, the TC flap is a well known and frequently used procedure, thus we aimed to show a broad presentation of benefits and downsides of this procedure and compare it to different techniques. Additionally, we presented literature evidence of avoiding possible complications and managing adverse effects.

In conclusion, Hughes flaps provide multiple benefits in the reconstruction of large defects occupying more than 70% of lower eyelid loss, especially when poor wound healing is expected or when local advancement flaps do not provide tension-free reconstruction but with contraindication for specific patient groups. The rate of complications and side effects is low and manageable, whereas additional therapy is usually observational or symptomatic.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

- Hawes MJ, Grove AS, Jr., Hink EM. Comparison of free tarsoconjunctival grafts and Hughes tarsoconjunctival grafts for lower eyelid reconstruction. *Ophthalmic Plast Reconstr Surg* 2011; 27:219-23.
- Juniat V, Ryan T, O'Rourke M, Ng S, O'Donnell B, McNab AA, Selva D. Hughes flap in the management of lower lid retraction. *Orbit* 2021; 23:1-6.
- Chungkwon YOO M-SP, Tae-Soo LEE. Treatment of recalcitrant orbital implant exposure using upper tarsoconjunctival flap. *J Korean Ophthalmol Soc* 2001; 1787-92.
- Hughes L, Saxby E, Wright M. Tarsoconjunctival 'Hughes' flap for repair of globe perforation: A modified technique in the management of severe scleral necrosis. *Eur J Ophthalmol* 2021; 32:NP60-NP63.
- Chen Y, Al-Sadah Z, Kikkawa DO, Lee BW. A Modified Hughes Flap for correction of refractory cicatricial lower lid retraction with concomitant ectropion. *Ophthalmic Plast Reconstr Surg* 2020; 36:503-7.
- Cho RI. Correction of recalcitrant cicatricial lower lid retraction and entropion with transverse tarsotomy and tarsoconjunctival flap. *Ophthalmic Plast Reconstr Surg* 2019; 35:91-4.
- WL H. A new method for rebuilding a lower lid. *Arch Ophthalmol* 1937; 17:1008-17.
- Yano T, Karakawa R, Shibata T, Fuse Y, Suzuki A, Kuramoto Y, Suesada N, Miyashita H, Yoshimatsu H. Ideal esthetic and functional full-thickness lower eyelid "like with like" reconstruction using a combined Hughes flap and swing skin flap technique. *J Plast Reconstr Aesthet Surg* 2021; 74:3015-21.
- Hughes WL. Total lower lid reconstruction: technical details. *Trans Am Ophthalmol Soc* 1976; 74:321-9.
- Rohrich RJ, Zbar RI. The evolution of the Hughes tarsoconjunctival flap for the lower eyelid reconstruction. *Plast Reconstr Surg* 1999; 104:518-22.
- Cies WA, Bartlett RE. Modification of the Mustardé and Hughes methods of reconstructing the lower lid. *Ann Ophthalmol* 1975; 7:1497-502.
- Hughes WL. Reconstructive surgery of the eyelids. *Adv Ophthalmic Plast Reconstr Surg* 1986; 5:25-87.
- Hishmi AM, Koch KR, Matthaai M, Bölke E, Cursiefen C, Heindl LM. Modified Hughes procedure for reconstruction of large full-thickness lower eyelid defects following tumor resection. *Eur J Med Res* 2016; 21:7.
- Pham CM, Heinze KD, Mendes-Rufino-Uehara M, Setabutr P. Single-stage repair of large full thickness lower eyelid defects using free tarsoconjunctival graft and transposition flap: experience and outcomes. *Orbit* 2022; 41:178-83.
- Bortz JG, Al-Shweiki S. Free Tarsal Graft and Free Skin Graft for Lower Eyelid Reconstruction. *Ophthalmic Plast Reconstr Surg*. 2020; 36:605-9.
- Dukes K. Likert Scale. In: Armitage P and Colton T, ed. *Encyclopedia of Biostatistics*. Chichester: Wiley, 2005: 2786-7.
- Eye Rounds.org The University of Iowa. Hughes Flap (tarsal-conjunctival flap). <https://webeye.ophth.uiowa.edu/eyeforum/video/plastics/1/Hughes-Flap.htm> (26 October 2022).
- Mandour SS, Kakizaki H, Farahat HG, Hegazi KA, El Saadany AKI, Iwaki M. Use of modified Hughes flap versus auricular cartilage graft for replacement of posterior lamella in lower eyelid reconstruction. *J Clin Experiment Ophthalmol* 2011; 0:1-4.
- McKelvie J, Ferguson R, Ng SGJ. Eyelid reconstruction using the "Hughes" tarsoconjunctival advancement flap: Long-term outcomes in 122 consecutive cases over a 13-year period. *Orbit* 2017; 36:228-33.
- Tenland K, Memarzadeh K, Berggren J, Nguyen CD, Dahlstrand U, Hult J, Engelsberg K, Lindstedt S, Sheikh R, Malmström M. Perfusion monitoring shows minimal blood flow from the flap pedicle to the tarsoconjunctival flap. *Ophthalmic Plast Reconstr Surg* 2019; 35:346-9.
- Memarzadeh K, Gustafsson L, Blohmé J, Malmström M. Evaluation of the microvascular blood flow, oxygenation, and survival of tarsoconjunctival flaps following the modified Hughes Procedure. *Ophthalmic Plast Reconstr Surg* 2016; 32:468-72.
- Berggren J, Tenland K, Ansson CD, Dahlstrand U, Sheikh R, Hult J, Engelsberg K, Lindstedt S, Malmström M. Revascularization of free skin grafts overlying modified Hughes tarsoconjunctival flaps monitored using laser-based techniques. *Ophthalmic Plast Reconstr Surg* 2019; 35:378-82.
- Bartley GB, Messenger MM. The dehiscence Hughes flap: outcomes and implications. *Trans Am Ophthalmol Soc* 2002; 100:61-5.
- Seyhan NZT, Keskin M, Savaci N. Lower eyelid reconstruction with tarsoconjunctival flap in a xeroderma pigmentosum patient. *Eur J Plast Surg* 2012; 35:185-7.
- Ibrahim A, Chalhoub RS. 5-fu for problematic scarring: a review of the literature. *Ann Burns Fire Disasters* 2018; 31:133-7.
- Leibovitch I, Selva D. Modified Hughes flap: division at 7 days. *Ophthalmology* 2004; 111:2164-7.
- Aggarwal S, Shah CT, Kirzhner M. Modified second stage Hughes tarsoconjunctival reconstruction for lower eyelid defects. *Orbit* 2018; 37:335-40.
- Ekin MA, Ugurlu SK. Impact of the type of anterior lamellar reconstruction on the success of modified Hughes procedure. *Arq Bras Oftalmol* 2020; 83:11-8.
- Leibovitch I, Huilgol SC, Hsuan JD, Selva D. Incidence of host site complications in periorcular full thickness skin grafts. *Br J Ophthalmol* 2005; 89:219.
- Marcet MM, Lau IHW, Chow SSW. Avoiding the Hughes flap in lower eyelid reconstruction. *Curr Opin Ophthalmol* 2017; 28:493-8.
- McNab AA, Martin P, Bengner R, O'Donnell B, Kourt G. A prospective randomized study comparing division of the pedicle of modified hughes flaps at two or four weeks. *Ophthalmic Plast Reconstr Surg* 2001; 17:317-9.
- Zaky AG, Elmazar HM, Abd Elaziz MS. Longevity results of modified Hughes procedure in reconstructing large lower eyelid defects. *Clin Ophthalmol* 2016; 10:1825-8.
- Klein-Theyer A, Horwath-Winter J, Dieter FR, Haller-Schober EM, Riedl R, Boldin I. Evaluation of ocular surface and tear film function following modified Hughes tarsoconjunctival flap procedure. *Acta Ophthalmol* 2014; 92:286-90.
- Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol* 2000; 118:615-21.
- Perry C, Allen R. Repair of 50-75% full-thickness lower eyelid defects: Lateral stabilization as a guiding principle. *Indian J Ophthalmol* 2016; 64:563-7.

Association of HLA-B27 antigen with clinical and laboratory parameters in patients with juvenile idiopathic arthritis

Adisa Čengić¹, Velma Selmanović¹, Sniježana Hasanbegović¹, Nedim Begić¹, Emina Karčić², Elma Fejzić³

¹Paediatric Clinic, Clinical Centre University of Sarajevo, ²Department of Paediatrics, Cantonal Hospital Zenica, ³Institute for Transfusion Medicine of the Federation of Bosnia and Herzegovina, Sarajevo; Bosnia and Herzegovina

ABSTRACT

Aim To analyse the association of human leukocyte antigen B27 with clinical and laboratory parameters in patients with juvenile idiopathic arthritis (JIA) at the disease onset.

Methods A retrospective review of medical records of 25 HLA-B27 positive and 25 HLA-B27 negative JIA patients was performed. The diagnosis of JIA was based on the 1997-2001 International League Against Rheumatism (ILAR) criteria. Collected data: age, sex, HLA-B27 antigen presence, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid-factor (RF), antinuclear antibody (ANA), fever, rash, uveitis, enthesitis, inflamed joints and subtype of JIA.

Results HLA-B27 positive study group had more boys ($p=0.01$), higher erythrocyte sedimentation rate ($p=0.038$), higher presence of fever ($p=0.025$) and enthesitis ($p=0.024$). Any significant difference in age of the disease onset, CRP, ANA, RF, rash, uveitis, inflamed joint and dactylitis was not noticed. The most common subtype of JIA in the HLA-B27 positive patients was ERA (60%).

Conclusion This study showed that the presence of HLA-B27 antigen plays a significant role in determining the presenting clinical and laboratory characteristics in JIA patients.

Key words: arthritis, children, human leukocyte antigen

Corresponding author:

Nedim Begić
Paediatric Clinic,
Clinical Centre University of Sarajevo
Bolnička 25, 71 000 Sarajevo,
Bosnia and Herzegovina
Phone: +387 33 566 428;
Fax: +387 33 566 400;
E-mail: nedim_begic91@hotmail.com
Adisa Čengić ORCID ID: <https://orcid.org/0000-0001-5964-2305>

Original submission:

14 November 2022;

Revised submission:

19 December 2022;

Accepted:

23 December 2022

doi: 10.17392/1556-22

Med Glas (Zenica) 2023; 20(1): 58-62

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common paediatric rheumatological disorder. If untreated, it could result in significant disability and even fatal outcome (1). It is defined as the presence of arthritis of unknown aetiology that begins before the age of 16 years and persists for at least 6 weeks (2). According to the International League of Associations for Rheumatology (ILAR- 2001), JIA is classified into 6 subtypes: oligoarticular (persistent or extended), polyarticular (RF-negative or RF-positive), systemic (sJIA), psoriatic arthritis, enthesitis-related arthritis (ERA) and undifferentiated arthritis (3). The main characteristic of JIA is joint inflammation with tissue destruction (4). The etiopathogenesis of the disease is still not fully understood. There is strong evidence that genetics and environmental factors (infection, stress, hormones and trauma) could result in an autoimmune reaction targeting synovial tissue (1,5). The major genetic association of different categories of JIA was found within the Human Leukocyte Antigen (HLA). It is located on the sixth chromosome, including a large group of genes involved in immune regulation (6). There is a high prevalence of the HLA-B27 allele in patients with JIA ERA (arthritis with enthesitis), similar to spondyloarthropathy (7). HLA-B27 is a class I HLA molecule that is responsible for antigen processing and presentation.

It has been proposed that HLA-B27 drives the pathogenesis of JIA-ERA by three possible mechanisms: presentation of arthritogenic peptide that causes lymphocyte activation, dimerization on the surface of antigen-presenting cells causing CD4 T lymphocyte activation, or induction of endoplasmic reticulum stress, which results in secretion of interleukin-23 and interleukin -17 (8). Occurrence of HLA-B27 antigen in children is also associated with other JIA categories, such as oligoarthritis and polyarthritis, especially among girls (9). In Bosnia and Herzegovina there are no studies that analyse effects of HLA- B27 antigen positivity in JIA patient.

The aim of this study was to analyse the association of human leukocyte antigen B27 with the clinical and laboratory parameters in patients with juvenile idiopathic arthritis (JIA) at the disease onset.

PATIENTS AND METHODS

Patients and study design

A retrospective, non-randomized clinical study was conducted at the Department of Allergology, Rheumatology and Clinical Immunology, Paediatric Clinic, Clinical Centre University of Sarajevo. The study included 50 patients who were diagnosed and treated in our Department: 25 consecutive JIA HLA-B27 negative patients and 25 consecutive JIA HLA B-27 positive patients. The period of data collection for HLA-B27 negative group was between January 2022 and July 2022, and for HLA- B27 positive group between January 2019 and July 2022. JIA diagnosis was made according to the ILAR criteria (International League Against Rheumatism) (1).

According to the presence or absence of HLA-B27, the patients were divided into two groups.

Methods

The patient data were collected from medical histories. All JIA patients underwent rheumatological clinical examination including the determination of the number and type of inflamed joint and presence of enthesitis. Arthritis was defined if at least two of the following criteria were present: inflammatory pain, limited mobility, and/or swelling. Enthesitis was specified as tenderness over the insertion site of tendon or ligaments on palpation and/or demonstrated by magnetic resonance imaging (MRI). Active sacroiliitis was defined by the presence of bone marrow oedema and contrast enhancement at the sacroiliac joint (SIJ) on MRI. Small joints included the midcarpal, carpometacarpal, metacarpophalangeal, and interphalangeal joints at the upper extremities and the talonavicular, calcaneocuboid, naviculocuneiform, tarsometatarsal, metatarsophalangeal, and interphalangeal joints of the lower extremities. Samples for HLA-B27, C- reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), rheumatoid factor (RF) typing were collected from peripheral blood. RF was considered to be positive if values were more than 15 IU/ml. HLA-B27 typing was performed using PCR- SSP kit Oleorup (UVP, Cambridge, United Kingdom) and PCR-SSO Immucor Lifecodes (Luminex Corporation, Austin, Texas,

United States of America). The presence of uveitis was diagnosed by an ophthalmologist.

Statistical analysis

The comparison of non-parametric data was performed using Mann-Whitney test as the distribution of the variables indices in the sample was non-Gaussian (according to the Shapiro-Wilks criteria). Pearson's χ^2 test was used to determine the connection between qualitative characteristics. In all statistical tests $p < 0.05$ was considered statistically significant.

RESULTS

The study included 50 children, 25 HLA-B27 positive and 25 HLA-B27 negative JIA patients. In the HLA-B27 positive group, boys prevailed, 16 (64%), over the girls, nine (36%) ($p = 0.01$). In the HLA-B27 negative group there were 19 (76%) girls and six (24%) boys ($p = 0.01$). HLA-B27 positive patients were older at the disease onset with median age of 13 years (IQ 8-14) than HLA B27 negative, median age was 7.60 years (IQ 3.6-13) ($p = 0.05$). The two groups were largely similar in clinical presentation except for fever ($p = 0.025$), which was found more often in patients with positive HLA-B27 (Table 1).

Table 1. Characteristics of juvenile idiopathic arthritis (JIA) patients with positive and negative HLA-B27

Variable	HLA-B27 +	HLA-B27 -	p
Mean age (min-max.) (years)	11.0±4.99 (1-17)	8.35 (5.02)	0.05
Median age (years) (IQ interquartile range)	13 (8-14.9)	7.60 (3.6-13)	0.05
Males (No, %)	16 (64.0%)	6 (24.0%)	0.01
Extra articular manifestations (No, %)			
Fever	5 (20.0)	0	0.025
Rash	5 (20.0)	4 (16.0)	0.500
Uveitis	3 (12.0)	1 (4.0)	0.300

In HLA-B27 positive patients, ANA was found positive in five (20%), rheumatoid factor in two (8%) cases but without significant difference. The analysis of erythrocyte sedimentation rate showed median value of 28 mm/h (IQ 12-37) in HLA-B 27 positive children, and median value of 16 mm/h (IQ 6-25) within HLA- B27 negative group ($p = 0.038$). No statistically significant difference of CRP and RF between the two groups was found (Table 2).

It was shown that enthesitis was typical for JIA with HLA-B27 association ($p = 0.024$). The data

Table 2. Laboratory characteristics of juvenile idiopathic arthritis (JIA) patients with positive and negative HLA-B27

Parameter	HLA-B27+	HLA-B27-	p
CRP median (IQ range)	6.2 (1.8-23.8)	5.1 (4-16.8)	0.823
Median ESR mm (IQ range)	28 (12-37)	16 (6-25)	0.038
ANA positivity (No, %)	5 (20.0)	10 (40.0)	0.108
RF positivity (No, %)	2 (8.0)	1 (4.0)	0.500

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody; RF, rheumatoid factor;

analysis showed no differences in the type of inflamed joint, presence of dactylitis, uveitis and rash in relation to the positivity of HLA-B27. Spine involvement was observed in three patients within the HLA-B27 positive group, and in two within the HLA-B27 negative group. Hip arthritis was more often diagnosed in children with HLA- B27 positivity but without statistically significant difference between the two groups (Table 3). HLA-B27 antigen was most frequently found in patients with enthesitis-related arthritis, and the HLA-B27-positive ratio was also high in polyarticular JIA, in 15 (60%) and seven (28%) cases, respectively (Table 4).

Table 3. Characteristics of arthritis of juvenile idiopathic arthritis (JIA) patients with positive and negative HLA-B27

Inflamed joint	No (%) of patients		p
	HLA-B27+	HLA-B27-	
Knee	18 (72.0)	18 (72.0)	0.623
Talocrural joint	11 (44.0)	16 (64.0)	0.387
Radiocarpal joint	7 (28.0)	6 (24.0)	0.500
Hip	9 (36.0)	4 (16.0)	0.098
Sacroiliac joint	5 (20.0)	1 (4.0)	0.095
Spine	3 (12.0)	2 (8.0)	0.500
Temporomandibular joint	0 (0.0)	1 (4.0)	0.500
Enthesitis	7 (28.0)	1 (4.0)	0.024
Small joints hand/feet	10 (40.0)	9 (36.0)	0.500
Dactylitis	3 (12.0)	1 (4.0)	0.269

Table 4. Subtype of juvenile idiopathic arthritis (JIA) with positive and negative HLA-B27

Subtype of JIA	No (%) of patients	
	HLA- B27+	HLA-B27-
Poliarticular form	7 (28.0)	13 (52.0)
ERA	15 (60.0)	4 (16.0)
Oligoarticular form	1 (4.0)	7 (28.0)
Psoriatic	1 (4.0)	1 (4.0)
Undifferentiated	1 (4.0)	0 (0.0)

ERA, enthesitis related arthritis;

DISCUSSION

This is the first study in Bosnia and Herzegovina analysing the correlation between HLA -B27 antigen and clinical and laboratory characteristics of paediatric patients suffering from JIA. Genetic studies are needed in order to comprehend the aetiology, pathogenesis of JIA and therapy response. Our study found a positive correlation of

male gender and HLA-B27 positivity, which was previously shown by several authors in different genetic backgrounds (9,10,11). According to the published data of Thomson et al. 76% of children with arthritis and enthesitis (ERA) have positive HLA- B27 (7); our study showed 60 %. HLA-B27 antigen is a strong risk factor for the development of enthesitis-related arthritis (12). HLA -B27 prevalence in JIA patients varies from 27.1% in Poland (10) to 21% in Nordic countries (13). Our analysis confirmed a high rate of hip arthritis (36%) in HLA- B27 positive group and a low rate of dactylitis and spine involvement. Additionally, we found that JIA patients with HLA- B27 positivity had higher ESR than the negative group, but we could not find significantly different values of CRP. At the disease onset, fever occurred more often in HLA- B27 positive group as well as the enthesitis. A study of Guo et al. did not find significant difference in fever between the two groups, although fever was described as a prime symptom in 35.6 % patients (14). Marino et al. did not find a positive correlation between HLA- B 27 positivity in JIA patients and occurrence of uveitis (15), similarly to our study. A large prospective study, which used data from Research in Arthritis in Canadian Children Emphasizing Outcomes inception cohort (ReACCh) and included 247 children, concluded that ERA patients outnumbered RF polyarticular JIA and that the rate of uveitis was 10% (16).

HLA-B27 positive individuals appear to be predisposed to excessive bone formation regardless of spondyloarthritis disease status (17). HLA-B27 is of great importance in paediatric and adult rheumatology and is subject of many ongoing studies (10). HLA-B27 positivity has been associated with worse radiographic damage, more typical marginal syndesmophytes, and more frequent syndesmophyte symmetry in spondyloarthritis (SpA) patients, where JIA-ERA can be included (18). HLA-B27 individuals appear pre-

disposed to excessive bone formation regardless of spondyloarthritis disease status (19). Liu CH et al. studied mesenchymal stem cells (MSCs) of HLA-B27 positive SpA patients and concluded that HLA-B27 directly activates the tissue non-specific alkaline phosphatase (TNAP) pathway in syndesmophyte pathogenesis, enhance bone mineralization and ectopic bone formation at inflamed entheses (20).

JIA is a very heterogenous disease and in everyday practice there are not many clinical and laboratory markers that can serve as prognostic factors (1). HLA- B27 is known to be related to spondyloarthropathy in adults (21), but in children with JIA, HLA- B27 has a role only in disease classification. Data from Peltoniemi at al. cohort, which was a multicentric Finnish study on 167 JIA patients, showed that, after 8 years of follow-up, 41% of HLA-B27 positive patients were not in remission compared to 33% HLA-B27 negative children; furthermore, the Finnish study showed that HLA-B27 positive patients were older than HLA-B27 negative at the time of JIA diagnosis, which is in concordance with our results (22).

The main limitation of this study is the small sample size.

In conclusion, our study confirmed that HLA-B27 antigen plays an important role in determination of clinical and laboratory characteristic of JIA patients. Overall, the results obtained were only partially in accordance with the studies from other countries, which can be due to the different genetic background of the studied population. It is required to study a larger sample size and analyse the therapy response of JIA patients regarding the HLA-B27 presence.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

1. Cassidy JT, Pett RE. Chronic arthritis in childhood. In: Cassidy JT, Petty RE, Laxer RM, eds. Textbook of Pediatric Rheumatology. Philadelphia: Elsevier, 2005; 206-300.
2. Martini A, Ravelli A, Avcin T, Beresford MW, Burgos-Vargas R, Cuttica R, Ilowite NT, Khubchandani R, Laxer RM, Lovell DJ, Petty RE, Wallace CA, Wulffraat NM, Pistorio A, Ruperto N. Pediatric Rheumatology International Trials Organization (PRINTO). Toward New Classification Criteria for Juvenile Idiopathic Arthritis: First Steps, Pediatric Rheumatology International Trials Organization International Consensus. J Rheumatol 2019; 46:190-197.

3. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet* 2007; 369:767–78.
4. Twilt M, Pradsgaard D, Spannow AH, Horlyck A, Heuck C, Herlin T. Joint cartilage thickness and automated determination of bone age and bone health in juvenile idiopathic arthritis. *Pediatr Rheumatol Online J* 2017; 15:63.
5. Horton DB, Shenoi S. Review of environmental factors and juvenile idiopathic arthritis. *Open Access Rheumatol* 2019; 11:253–67.
6. Hinks A, Cobb J, Marion MC, Prahalad S, Sudman M, Bowes J, Martin P, Comeau ME, Sajuthi S, Andrews R, Brown M, Chen WM, Concannon P, Deloukas P, Edkins S, Eyre S, Gaffney PM, Guthery SL, Guthridge JM, Hunt SE, Thompson S. Dense genotyping of immune loci in juvenile idiopathic arthritis identifies 14 new susceptibility loci. *Nat Genet* 2013; 45:664–69.
7. Thomson W, Barrett JH, Donn R, Pepper L, Kennedy LJ, Ollier WE, Silman AJ, Woo P, Southwood T. Juvenile idiopathic arthritis classified by the ILAR criteria: HLA associations in UK patients. *Rheumatology* 2002; 41:1183–9.
8. Chen B, Li J, He C, Li D, Tong W, Zou Y, Xu W. Role of HLA-B 27 in the pathogenesis of ankylosing spondylitis. *Mol Med Rep* 2017; 15:1943–51.
9. Stanevicha V, Eglite J, Zavadska D, Sochnevs A, Lazareva A, Guseinova D, Shantere R, Gardovska D. HLA B27 allele types in homogeneous groups of juvenile idiopathic arthritis patients in Latvia. *Pediatr Rheumatol Online J* 2010; 8:26.
10. Žuber Z, Turowska-Heydel D, Sobczyk M, Chudek J. Prevalence of HLA-B27 antigen in patients with juvenile idiopathic arthritis. *Reumatologia* 2015; 53:125–30.
11. Goirand M, Breton S, Chevallier F, Duong NP, Uettwiller F, Melki I, Mouy R, Wouters C, Bader-Meunier B, Job-Deslandre C, Quartier P. Clinical features of children with enthesitis-related juvenile idiopathic arthritis / juvenile spondyloarthritis followed in a French tertiary care pediatric rheumatology centre. *Pediatr Rheumatol Online J* 2018; 16–21.
12. Srivastava R, Phatak S, Yadav A, Bajpai P, Aggarwal A. HLA B27 typing in 511 children with juvenile idiopathic arthritis from India. *Rheumatol Int* 2016; 36:1407–11.
13. Berntson L, Nordal E, Aalto K. HLA-B27 predicts a more chronic disease course in an 8-year follow up cohort of patients with juvenile idiopathic arthritis. *J Rheumatol* 2013; 40:725–31.
14. Guo R, Cao L, Kong X, Liu X, Xue H, Shen L, Li X. Fever as an initial manifestation of enthesitis-related arthritis subtype of juvenile idiopathic arthritis: retrospective study. *PLoS One* 2015; 10:1–6.
15. Marino A, Weiss PF, Brandon TG, Lerman MA. Juvenile Spondyloarthritis: focus on uveitis. *Pediatr Rheumatol Online J* 2020; 18:70.
16. Chhabra A, Robinson C, Houghton K, Cabral DA, Morishita K, Tucker LB, Petty RE, Larché M, Batt-hish M, Guzman J. Long-term outcomes and disease course of children with juvenile idiopathic arthritis in the ReACCh-Out cohort: a two-centre experience. *Rheumatology* 2020; 59:3727–30.
17. Tay SH, Yeo JG, Leong JY, Albani S, Arkachaisri T. Juvenile Spondyloarthritis: What more do we know about HLA-B27, enthesitis, and new bone formation? *Front Med* 2021; 8:666772.
18. Coates LC, Baraliakos X, Blanco FJ, Blanco-Morales EA, Braun J, Chandran V, Fernandez-Sueiro JL, FitzGerald O, Gallagher P, Gladman DD, Gubar E, Korotaeva T, Loginova E, Lubrano E, Mulero J, Pinto-Tasende J, Queiro R, Sanz J, Szentpetery A, Helliwell PS. The phenotype of axial spondyloarthritis: is it dependent on HLA-B27 status? *Arthritis Care Res* 2021; 73:856–60.
19. Aschermann S, Englbrecht M, Bergua A, Spriewald BM, Said-Nahal R, Breban M, Schett G, Rech J. Presence of HLA-B27 is associated with changes of serum levels of mediators of the Wnt and hedgehog pathway. *Joint Bone Spine* 2016; 83:43–6.
20. Liu CH, Raj S, Chen CH, Hung KH, Chou CT, Chen IH, Chien JT, Lin IY, Yang SY, Angata T, Tsai WC, Wei JC, Tzeng IS, Hung SC, Lin KI. HLA-B27-mediated activation of TNAP phosphatase promotes pathogenic syndesmophyte formation in ankylosing spondylitis. *J Clin Invest* 2019; 129:5357–73.
21. Fisher C, Ciurtin C, Leandro M, Sen D, Wedderburn LR. Similarities and Differences Between Juvenile and Adult Spondyloarthropathies. *Front Med* 2021; 31:16.
22. Peltoniemi S, Nordal EB, Lahdenne P, Aalto K. 8-year follow-up study: differences between HLA-B27 positive and negative children with juvenile idiopathic arthritis in Finland. *Arthritis Rheumatol* 2015; 67:10.

Outcomes of acute kidney injury in critically ill children who need renal replacement therapy

Danka Pokrajac, Admir Hadžimuratović, Ismeta Kalkan, Emina Hadžimuratović, Verica Mišanović, Duško Anić, Aida Mustajbegović-Pripoljac

Paediatric Clinic, Clinical Centre University of Sarajevo, Sarajevo, Bosnia and Herzegovina

ABSTRACT

Aim To determine an outcome of acute kidney injury (AKI) in critically ill children (CIC) who needed renal replacement therapy (RRT) and were admitted to the Paediatric and Neonatal Intensive Care Unit (PICU and NICU) at the Paediatric Clinic, University Clinical Centre Sarajevo (UCCS).

Methods The research included 81 children with AKI. The Kidney Disease: Improving Global Outcomes (KDIGO) criteria to define AKI was used. Other laboratory findings and imaging tests were made depending on children's primary disease that led to the AKI.

Results Among 81 children with AKI, 38 were girls and 43 boys. A total of 39 (48.1%) patients died; the death was due to the nature of the primary disease and multiple organ failure syndromes. Out of the total of 81 patients the highest mortality rate was found in children in the first year of life, 22 (56.4%), while 17 (43.6%) patients died after the first year of life.

Conclusion Without an accurate diagnosis at the right time, due to the lack of adequate biomarkers for AKI screening, the heterogeneity of AKI, comorbidities often lead to unfavourable outcomes of the disease, among CIC, especially in infants with low birth weight and extreme immaturity. Some causes of AKI are preventable and can be reduced by a better organization of primary and secondary health care.

Key words: dialysis, morbidity, mortality

Corresponding author:

Danka Pokrajac
Paediatric Clinic,
University Clinical Centre Sarajevo
Patriotske lige 81, 71000 Sarajevo,
Bosnia and Herzegovina
Phone: +387 33 566 445;
Fax: +387 33 566 525;
E-mail: dankapokrajac@hotmail.com
ORCID ID: <https://orcid.org/0000-0002-5998-5620>

Original submission:

19 November 2022;

Revised submission:

12 December 2022;

Accepted:

17 December 2022

doi: 10.17392/1562-22

Med Glas (Zenica) 2023; 20(1): 63-70

INTRODUCTION

Acute kidney injury (AKI) is the result of various causes and is associated with significant morbidity and mortality (1). AKI is a very common complication in hospitalized patients (2). Unfortunately, an estimate of renal function based on serum creatinine, urea, and diuresis is poorly sensitive and specific for recording early changes in renal function especially, in paediatric AKI (3). Until now standardized definitions for paediatric AKI have included the Paediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease (pRIFLE), AKI Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO), which are most commonly used (3,4). From time to time, researchers have discovered several proteins that could be used as potential early biomarkers of AKI. They have not yet been fully used in clinical settings due to various reasons (5). Since there is no standard definition of AKI or reliable biomarkers, it is not possible to detect AKI on time, which is the main reason for a delay with adequate therapy and consequently a high mortality rate (6).

In general, AKI occurs in 2% to 5% of hospitalized adults and in the neonatal period in the Neonatal Intensive Care Unit (NICU) varies from 8% to 60% (7-9). Also, AKI is common in Paediatric Intensive Care Units (PICUs) with the prevalence of 10% to 35% (10).

Some forms of AKI can be managed conservatively, but severe patients require some dialysis techniques or renal replacement therapy (RRT) (11,12). RRT was indicated for specific situations, like electrolyte imbalances, anuria, refractory acidosis, fluid overload, uremic organ involvement (pericarditis, encephalopathy, neuropathy, myopathy), progressive severe dysnatremia, malignant hyperthermia and removal of endogenous toxins (e.g. ammonia)/exogenous toxins (i.e., poisons), and it was not dependent on the class of AKI (12). The optimal timing of RRT initiation remains controversial until now (13).

We decided to examine the outcome of AKI in critically ill children who needed RRT in Bosnia and Herzegovina (B&H) because of its relatively high prevalence and association with a poor outcome. Our internal annual data from the Paediatric Clinic show that every year acute kidney injury affects up to 12.0% of all hospitalized and up to 60.0%

intensive care unit patients. In our Clinic, only in B&H, all dialysis techniques in children have been performed since 2006 by paediatric nephrologists, which we consider to be great success, because only paediatric nephrologists can understand the etiology, pathology, pathophysiology, diagnosis and treatment of AKI in children. A few years ago, the use of dialysis techniques was started in the University Clinical Hospital in Mostar (B&H) by paediatric nephrologists. There is a lot of research on this topic in the world, especially in high-income countries, where most articles on this issue come from, but they are quite uneven and as such are difficult to compare (2,4,7). Also, follow-up studies evaluating the relationship between children's AKI and long-term outcome are generally rare. The awareness that geographical, ethnic and other specific factors of each country have an influence on the etiology of AKI is important for the treatment of these patients. In addition, B&H has a poor disease prevention program, primarily immunization programs, which was the reason why some infectious diseases were the cause of severe forms of AKI and even deaths. Unfortunately, in the developing countries, in rural regions, the etiological factors remain as dehydration, sepsis, and haemolytic uremic syndrome (11). Also, in these countries, there is a problem of a lack of technical and economic support in performing different RRT modalities and other sophisticated diagnostic and therapeutic procedures necessary for the treatment of critically ill children in intensive care units (12). These have been among the important reasons for high mortality rate in these patients for decades.

Recent studies on the paediatric epidemiology of AKI, more clearly defining newer biomarkers and newer criteria for risk stratification of children admitted to intensive care units, are very promising. There is also new research on machines made specifically for smaller children with smaller extracorporeal volumes (13). It should always be remembered that the best is the individual approach to each patient.

The aim of the study was to determine the outcome of acute kidney injury in critically ill children (CIC) who needed renal replacement therapy and were admitted to the Paediatric and Neonatal Intensive Care Unit at the Paediatric Clinic, University Clinical Centre Sarajevo (UCCS).

Patients and methods

Patients and study design

This retrospective descriptive study based on data from patients' medical records included all 81 children who required some of the dialysis techniques due to definition of stage 2 and 3 AKI at the Paediatric Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU) at the Paediatric Clinic, University Clinical Centre Sarajevo (UCCS) between 1 January 2006 and 1 October 2021. The KDIGO criteria to define AKI were used (14). Severe acute kidney injury was defined as stage 2 or 3 AKI at the plasma creatinine level ≥ 2 times the baseline level or urine output <0.5 mL per kilogram of body weight per hour for ≥ 12 hours (3).

Methods

The estimated glomerular filtration rate was calculated with the use of the original Schwartz formula (15). All AKI patients had detailed history, physical examination and laboratory data: serum levels of urea, creatinine, serum electrolyte, acid-base balance, uric acid, cholesterol, triglycerides, proteinogram, C - reactive protein, complete blood count, urinalysis with microscopy, urine culture, urinary electrolytes, creatinine and urea nitrogen. In some cases creatine phosphokinase was determined (if rhabdomyolysis was suspected), eosinophils count in urine sample (if the patient was receiving a medication with the potential to cause interstitial nephritis), stool sample for enteropathogenic *Escherichia coli* (if the haemolytic uremic syndrome was suspected). Anti-nuclear antibody, anti-double-stranded deoxyribonucleic acid, anti-streptolysin O titre, complement component C3 and C4 level, anti-nuclear cytoplasmic antibody, anti-glomerular basement membrane antibody (if the patient had history, signs and symptoms consistent with glomerulonephritis), 24-hour urine for calcium, oxalate, citrate, creatinine, uric acid (in patients with confirmed nephrolithiasis), electrocardiogram, chest X-ray and ultrasonography of abdomen. Other special investigations, echocardiography, electroencephalography, abdominal computed tomography scan (if trauma or abdominal mass was suspected), spiral computed tomography scan (if nephrolithiasis was suspected), and kidney biopsy, performed when it was necessary.

The research was conducted at different Clinics of the UCCS. Peritoneal dialysis with the stay-safe system, and different types of haemodialysis on the device Multifiltrate Acute Therapy are available at the Clinic. Haemodialysis with peritoneal dialysis was combined where it was necessary.

Statistical analysis

Categorical data are presented as counts and percentages and were analysed with the χ^2 test and Fisher's exact test, as appropriate. The $p < 0.05$ was taken as statistically significant.

RESULTS

The age of patients who were on dialysis for AKI was from 12 days to 17 years and 2 months; the mean age of AKI presentation was 6.28 years. Gender was represented with 43 (53.1%) males and 38 (46.9%) females ($p = 0.815$). AKI was presented in 42 (51.9%) infants and in 39 (48.1%) children after the first year of age ($p = 0.9383$).

The prerenal causes of AKI were noticed in 57 (70.4%) patients, renal in 23 (28.4%), and postrenal in one child (1.2%), with predominance of prerenal causes of AKI ($p = 0.0096$).

The causes of AKI were different depending on the age of the children (Table 1).

Table 1. Etiological factors of acute kidney injury (AKI) among children older than one year of age

Etiology	No (%) of children
Haemolytic-uremic syndrome (HUS)	10 (25.6)
Systemic diseases with macrophage activation syndrome (MAS)	3 (7.7)
Glomerulonephritis	3 (7.7)
Tumours	3 (7.7)
Meningococcal disease	3 (7.7)
Leucosis	2 (5.2)
Diseases represented as just one case of AKI*	15 (38.4)
Total	39 (100.0)

*drug-induced AKI with propofol, non-steroidal anti-inflammatory drug, acute liver injury induced by paracetamol, hepatitis unknown cause, after surgery of hydatid cyst of lung and liver, tubulointerstitial nephritis, sepsis in child with severe anomalies of urinary system with myelomeningocele and hydrocephalus, case of sepsis after unusual, unexplained and accidental perforation of ventriculus, case of sepsis after surgery of volvulus in child with West syndrome, Hantavirus pulmonary syndrome (HPS), Salmonellosis and dehydration, septic shock and acute respiratory distress syndrome (ARDS), varicella and disseminated intravascular coagulation (DIC), mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome and neonatal hyperammonemic encephalopathy.

In children over the first year of life in 10 cases the cause was haemolytic-uremic syndrome (HUS) associated with diarrhoea. Three cases

each were the cause of AKI: systemic disease in combination with macrophage activation syndrome, glomerulonephritis (two of them had AKI due to nephrotoxicity of the calcineurin inhibitor in case of focal and segmental glomerulosclerosis, and in one case it was a severe form of Henoch–Schönlein – nephritis -HSPN), tumour (*ovarian cancer, retinoblastoma and lymphoma*), which quickly led to leukaemia (ALL) and one with acute myeloid leukaemia (AML) associated with sepsis quickly ended in death.

Among children older than one year of age interesting and rare diseases that were represented as a single case of AKI were found in 15 (38.46%) out of the total of 39 children (Table 1).

A total of 39 (48.1%) patients died, and the death was caused by the nature of their primary disease and multisystem failure syndrome (Tables 2, 3). The highest number of deaths was noticed in children in the first year of life, 22 (56.4%), compared to 17 (43.6%) after the first year of life ($p=0.7298$).

Table 2. Primary etiological causes of death in infants with acute kidney injury (AKI)

Cause of death	No (%) of children
Congenital heart diseases	7 (31.9)
Perinatal asphyxia + respiratory distress syndrome	6 (27.3)
Sepsis in Premature Babies	4 (18.2)
Multiple congenital anomalies	3 (13.6)
Neonatal hyperammonemic encephalopathy	1 (4.5)
Coagulopathy and hepatic dysfunction (cause was unknown)	1 (4.5)
Total	22 (100.0)

Table 3. Etiological causes of death after the first year of life with acute kidney injury (AKI)

Causes of death	No (%) of children
Tumours	3 (17.6)
Meningococcal disease	2 (11.7)
Congenital heart disease	2 (11.7)
Diseases represented as a single case of AKI*	10 (59.0)
Total	17 (100.0)

*systemic diseases with macrophage activation syndrome, glomerulonephritis in Henoch–Schönlein purpura, leucosis, acute liver injury induced by paracetamol, sepsis in a child with severe anomalies of urinary system with myelomeningocele and hydrocephalus, case of sepsis after unusual, unexplained and accidental perforated of ventriculus, case of sepsis after surgery of volvulus in a child with West syndrome, varicella and DIC, MELAS syndrome and neonatal hyperammonemia encephalopathy.

The primary etiological causes of death from AKI were different depending on the age of the children (Table 2, 3). In infants causes of death included congenital heart disease, perinatal asphyxia with respiratory distress syndrome,

sepsis in premature babies, multiple congenital anomalies, neonatal hyperammonemia encephalopathy, coagulopathy and hepatic dysfunction (a cause was unknown). Etiological causes of death after the first year of life were: tumours (*ovarian cancer, retinoblastoma and lymphoma*), meningococcal disease, congenital heart disease. It should be mentioned that we noted among children older than one year of age interesting and rare diseases that were represented as a single case of death in children with AKI (Table 3).

Out of the total of 81 patients with AKI, 39 (48.1%) fully recovered, two (2.5%) children had chronic kidney disease (CKD), one (1.3%) child had a transplantation due to the end-stage renal disease, and 39 (48.1%) patients died during the acute phase (Table 4).

Table 4. Overall outcome in acute kidney injury (AKI) in children

Outcomes	No (%) of children
Complete recovery	39 (48.1)
Partial recovery (chronic renal disease)	2 (2.5)
Renal replacement therapy (RRT)	1 (1.3)
Death	39 (48.1)
Total	81 (100.0)

DISCUSSION

In the Paediatric Clinic of the UCCS in 1998, the Paediatric and Neonatal Intensive Care Unit were established for intensive treatment of infants and older children. This contributed to admitting the most difficult patients almost from all B&H. In addition to patients with severe internal diseases, a large percentage of surgical patients (38.27%), especially those following complex heart anomalies surgery (54.84%) and severe infectious diseases and malignancy are treated at the PICU and NICU. In most developed countries in the intensive care units (ICUs) for children, the proportion of surgical patients is around 50% (16).

Scientific and technological advances during the second half of the 20th century and in two decades in the 21st century enabled the development of dialysis techniques and their good application in children (17). At the Paediatric Clinic of the UCCS, dialysis began just before the war in 1992 in B&H; after a 5-year break during the war, peritoneal dialysis continued, and haemodialysis has been performed since 2009 (18).

Each modality of RRT has advantages and disadvantages. Peritoneal dialysis can be used in

small children such as premature babies, because it seems to be a feasible procedure without major complications. Haemodialysis removes fluid and toxins rapidly, but it is dangerous for small children and hemodynamically unstable patients (19). Mortality in patients requiring renal replacement is high, up to 66% (20,21).

As in our study, in most studies the AKI prevalence in boys is higher in relation to girls. The males prevalence of 56.4% in the USA (22), 53% in Norway (23), 50.8% in Belgium (24), 57.9% in Germany (25) and 68.6% in Nigeria (26) was noticed. The mean age of children with AKI presentation in our study was 6.28 years similarly to Norway (6.0 years) and Belgium (6.1 years), while in Nigeria it was 4.8 years (23-26).

For many years the diagnosis and management of AKI was based on the inadequate concept of classification to three main categories: prerenal, intrinsic (renal) and postrenal. If these pre- and/or post-renal conditions persist, they will eventually evolve to into renal cellular damage and hence intrinsic renal disease (7).

A large proportion of prerenal causes of AKI occurs in underdeveloped countries with poorly developed prevention (26-28). In our study, a large percentage of prerenal causes of AKI was the result of multifactorial causes in the state of multiorgan failure due to severe primary diseases, especially in newborns and infants. Many patients with AKI have a mixed etiology where sepsis, severe infections, various post-operative conditions of congenital anomalies, especially heart defects in newborns, malignancy, chronic kidney, heart, liver or gastrointestinal disease, use of inotropes, aminoglycosides and other multiple nephrotoxic drugs and ischemia, in a single patient, complicating primary disease recognition and treatment (29). Our results from this field of paediatric nephrology observed changes in the pathology of comorbidity of AKI in critically ill children, which is of great importance for further investigations and management of these patients. Studies have found that the causes of AKI have changed dramatically in the last few decades. It has been noted that earlier causes of AKI in hospitalized children, such as haemolytic uremic syndrome, glomerulonephritis, and primary renal diseases, have been replaced by sepsis, critically basic serious illness status, congenital heart disease (7, 30-32), postsurgical, po-

stransplantation, and oncological illness. This was also the case in our study, especially in children younger than one year of age.

In various studies, the prevalence of newborns with AKI in the intensive care unit is high, even up to 60% (33). The reason for this high span of AKI in newborns resulted from non-uniformity of the examined parameters in the studies that investigate this issue. It must not be forgotten that in newborns, the mechanism of autoregulation of blood flow through the kidney is still immature, and consequently any agent can damage this precise mechanism and lead to AKI (34).

The AKI frequently occurs in children under the age of one year (35). In our study of newborns and infants with AKI, death was caused by a combination of cardiac insufficiency caused by complex heart defects, which were operable or inoperable in the first place, which were complicated by other usual unfavourable factors in the ICU. It should also be kept in mind that AKI patients who need RRT and are on mechanical ventilation, with mixed etiology require a significantly longer stay in the ICU and after that standard hospital therapy and care, which represents a great burden for the health system (4,9,13,31).

Newborns with severe asphyxia, a low score of the Apgar test, open ductus arteriosus, and whose mothers used antibiotics and non-steroidal anti-inflammatory drugs during pregnancy and very-low-birthweight (<1500g), could reach AKI up to 40% and to 60% in extremely low birthweight (<1000g) compared to those with moderate asphyxia and normal birth weight (9,36). These patients are extremely susceptible to sepsis. The pathophysiology of sepsis in AKI patients is very complex and involves inflammation, oxidative stress microvascular dysfunction and amplification of injury via secretion of cytokines by tubular cells, as well as the application of many diagnostic and therapeutic procedures (37). AKI is a clinically relevant immunocompromised state (38).

The pathophysiology of hypoxia/ischemia-induced AKI is not well understood. The kidney is a vascular organ so it is highly susceptible to injury related to ischaemia, resulting in vasoconstriction, endothelial injury, and activation of inflammatory processes (31).

Each acute kidney injury in the period of active nephrogenesis before 34 weeks of the gestation leads to decreased number of nephrons and subsequent glomerulomegaly (30).

These facts are the reason for the high mortality rate in newborns and infants.

Several studies have demonstrated that genetic risk factors are involved in AKI in some newborns and children (39). Polymorphism of the angiotensin-converting enzyme gene, tumour necrosis factor alpha, interleukin 1b, 6, 8 and 10 genes were investigated to determine if polymorphisms of these genes would lead to a more intense inflammatory response and predispose newborns to AKI (40,41).

Bosnia and Herzegovina is a country with a small population. For this reason, the results of our study are limited in the involved number of critically ill children with AKI who required renal replacement therapy. According to etiological factors of AKI obtained from this research, B&H is between developed and developing countries. We have found interesting and rare individual cases that led to AKI and even fatal outcomes (38,46). These patients, who had primary serious life-limiting diseases, were immunocompromised, and some of them had drug-induced AKI. It is understandable that despite all procedures, which are applied in intensive care unit and RRT in this group of patients, mortality was very high, even 66.67% (10).

The prevalence of AKI and mortality rate in pre-term infants and newborns has increased despite numerous improvements in ICU and the use of renal replacement therapy worldwide. The reason for this are aggressive therapeutic procedures, especially surgical, increased use of RRT, mechanical ventilation, longer stays in the ICU, hypoalbuminemia, and transportation services to seriously ill children (42). Published mortality rates for such patients in the USA, Belgium, Nigeria, Argentina and Brazil range from 11% to 46% (7, 24, 26, 43, 44). In our study a high percentage of mortality is quite expected considering the treatment of the most severe cases in intensive care units. Children who have AKI as a component of multisystem failure have a much higher mortality rate, which was the case especially in children under one year of age.

In our research of all surviving children, only one patient had developed end-stage renal disease and after one period of haemodialysis, kidney transplantation was performed. In two patients there was chronic kidney disease, hypertension and permanent tubular dysfunction, which requires careful monitoring and therapeutic and dietary measures. In a Belgian study 15% of children died, while 16.1% developed CKD (24). Previously it was thought that such patients were at a low risk for late complications (45), but several recent studies have demonstrated that CKD can evolve from AKI (20, 23). For this reason such children need long-term follow-up of their renal function.

In our opinion, describing the epidemiological and etiological aspects of this serious condition in Bosnia and Herzegovina makes an important contribution to evaluating the national relevance and burden on the healthcare system since it is the most expensive medical service.

In conclusion, the heterogeneity of AKI case-mix, comorbid factors, and the complex nature of the pathophysiology of AKI, without accurate diagnosis at the right time, due to the lack of reliable biomarkers for AKI screening, do not allow for early detection of AKI, leading to delays in the induction of treatment until the renal injury is well advanced. Timely recognition of patients at risk or with possible acute kidney injury is essential for early intervention to minimize further damage and improve outcomes, especially in infants, in case of low birth weight and extreme immaturity. Some causes of AKI are preventable, and it should be possible to reduce mortality and morbidity by better organization of primary and secondary healthcare. In addition, an optimal paediatric dialysis program should provide all dialysis modalities for all children and well-trained healthcare personnel. We are fortunate that at the Paediatric Clinic, University Clinical Centre Sarajevo, we can provide all modalities of dialysis techniques to critically ill children with AKI in intensive care units.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

- Bhojani S, Stojanovic J, Melhem N, Maxwell H, Houtman P, Hall A, Singh C, Hayes W, Lennon R, Sinha MD, Milford DV. The incidence of paediatric acute kidney injury identified using an AKI e-alert algorithm in six English hospitals. *Front Pediatr* 2020; 8:29.
- Parikh RV, Tan TC, Salyer AS, Auron A, Kim PS, Ku E, Go AS. Community-based epidemiology of hospitalized acute kidney injury. *Pediatrics* 2020; 146(3):e20192821.
- Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, Goldstein SL. AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions. *Clin J Am Soc Nephrol* 2015;10:554–61.
- Sethi SK, Bunchman T, Chakraborty R, Raina R. Pediatric acute kidney injury: new advances in the last decade. *Kidney Res Clin Pract* 2021; 40:40–51.
- Beker BM, Corleto MG, Fieiras C, Musso CG. Novel acute kidney injury biomarkers: their characteristics, utility and concerns. *Int Urol Nephrol* 2018; 50:705–13.
- Yoon SY, Kim JS, Jeong KH, Kim SK. Acute kidney injury: biomarker-guided diagnosis and management. *Medicina* 2022; 58:340.
- Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL. Epidemiology of acute kidney injury in critically ill children and young adults. *N Engl J Med* 2017; 376:11–20.
- Chowdhary V, Vajpeyayula R, Jain M, Maqsood S, Raina R, Kumar D, Mhanna MJ. Comparison of different definitions of acute kidney injury in extremely low birth weight infants. *Clin Exp Nephrol* 2018; 22:117–25.
- Jetton JG, Boohaker LJ, Sethi SK, Wazir S, Rohatgi S, Soranno DE, Chishti AS, Woroniecki R, Mammen C, Swanson JR, Sridhar S, Wong CS, Kupferman JC, Griffin RL, Askenazi DJ. Incidence and outcomes of neonatal acute kidney injury (AWAKEN): a multicentre, multinational, observational cohort study. *Lancet Child Adolesc Health* 2017; 1:184–94.
- Kavaz A, Ozçakar ZB, Kendirli T, Oztürk BB, Ekim M, Yalçinkaya F. Acute kidney injury in a paediatric intensive care unit: comparison of the pRIFLE and AKIN criteria. *Acta Paediatr* 2012; 101:e126–e9.
- Annigeri RA, Ostermann M, Tolwani A, Vazquez-Rangel A, Ponce D, Bagga A, Ravindra C, Mhta LR. Renal support for acute kidney injury in the developing world. *Kidney Int Rep* 2017; 2:559–78.
- Kluwer W. Dialysis therapies in acute kidney injury for children. *Indian J Nephrol* 2020; 30:579–86.
- Valdenebro M, Martín-Rodríguez L, Tarragón B, Sánchez-Briales P, Portolés J. Renal replacement therapy in critically ill patients with acute kidney injury: 2020 nephrologist's perspective. *Nefrologia* 2021; 41:102–14.
- Levi TM, de Souza SP, de Magalhães JG, de Carvalho MS, Cunha AL, de Oliveira Dantas JG, Cruz MG, Guimarães YLM, Cruz CMS. Comparison of the RIFLE, AKIN and KDIGO criteria to predict mortality in critically ill patients. *Rev Bras Ter Intensiva* 2013; 25:290–6.
- Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976; 58:259–63.
- Restrepo JM, Mondragon MV, Forero-Delgadillo JM, Lasso RE, Zemanate E, Bravo Y, Castillo GE, Tetay S, Cabal N, Calvache JA. Acute renal failure in children. Multicenter prospective cohort study in medium-complexity intensive care units from the Colombian southeast. *PLoS One* 2020; 15:e0235976.
- Tang YS, Tsai YC, Chen TW, Li SY. Artificial kidney engineering: the development of dialysis membranes for blood purification. *Membranes* 2022; 12:177.
- Miličić-Pokrajac D. Pedijatrijski RRT pacijenti u Bosni i Hercegovini (Pediatric RRT patients in Bosnia and Herzegovina). In: Resić H, Mešić E. Nadomještanje bubrežne funkcije u Bosni i Hercegovini 2001–2014. (Replacement kidney function in Bosnia and Herzegovina 2001–2014) [in Bosnian]. Sarajevo: Štamparija Fojnica, 2015: 79–87.
- Raina R, Lam S, Raheja H, Krishnappa V, Hothi D, Davenport A, Chand D, Kapur G, Schaefer F, Sethi SK, McCulloch M, Bagga A, Bunchman T, Warady BA. Pediatric intradialytic hypotension: recommendations from the Pediatric Continuous Renal Replacement Therapy (PCRRRT) Workgroup. *Pediatr Nephrol* 2019; 34:925–41.
- Cho MH. Pediatric acute kidney injury: focusing on diagnosis and management. *Child Kidney Dis* 2020; 24:19–26.
- Naik S, Sharma J, Yengkom R, Kalrao V, Mulay A. Acute kidney injury in critically ill children: risk factors and outcomes- Indian J Crit Care Med 2014; 18:129–33.
- Sutherland SM, Ji J, Sheikh FH, Widen E, Tian L, Alexander SR, Ling XB. AKI in hospitalized children: epidemiology and clinical associations in a national cohort. *Clin J Am Soc Nephrol* 2013; 8:1661–9.
- Jenssen GR, Hovland E, Bangstad HJ, Nygård K, Vold L, Bjerre A. The incidence and aetiology of acute kidney injury in children in Norway between 1999 and 2008. *Acta Paediatr* 2014; 103:1192–7.
- Keenswijk W, Vanmassenhove J, Raes A, Dhont E, Vande Walle J. Epidemiology and outcome of acute kidney injury in children, a single center study. *Acta Clinica Belgica* 2017; 72:405–12.
- Marzuillo P, Baldascino M, Guarino S, Perrotta S, Miraglia Del Giudice E, Nunziata F. Acute kidney injury in children hospitalized for acute gastroenteritis: prevalence and risk factors. *Pediatr Nephrol* 2021; 36:1627–35.
- Esezobor CI, Ladapo TA, Osinaike B, Lesi FE. Paediatric acute kidney injury in a tertiary hospital in Nigeria: prevalence, causes and mortality rate. *PLoS One* 2012; 7:e51229.
- Vachvanichsanong P, Dissaneewate P, Lim A, McNeil E. Childhood acute renal failure: 22-year experience in a university hospital in southern Thailand. *Pediatrics* 2006; 118:e786–91.
- Bhattacharya M, Dhingra D, Mantan M, Upare S, Sethi GR. Acute renal failure in children in a tertiary care center. *Saudi J Kidney Dis Transpl* 2013; 24: 413–7.

29. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. *Clin Biochem Rev* 2016; 37:85-98.
30. Stritzke A, Sumesh Thomas S, Amin H, Fusch C, Lodha A. Renal consequences of preterm birth. *Mol and Cell Pediatr* 2017; 4:2.
31. Gaut JP, Liapis H. Acute kidney injury pathology and pathophysiology: a retrospective review. *Clin Kidney J* 2021; 14:526–36.
32. Ricci Z, Raggi V, Marinari E, Vallesi L, Di Chiara L, Rizzo C, Gist KM. Acute kidney injury in pediatric cardiac intensive care children: not all admissions are equal: a retrospective study. *Cardiothorac Vasc Anesth* 2022; 36:699-706.
33. Ibiebele I, Algert CS, Bowen JR, Christine, Roberts CL. Pediatric admissions that include intensive care: a population-based study. *BMC Health Serv Res* 2018 ;18:264.
34. Post EH, Vincent JL. Renal autoregulation and blood pressure management in circulatory shock. *Crit Care* 2018; 22: 81.
35. Coleman C, Tambay Perez A, Selewski DT, Steflik HJ. Neonatal acute kidney injury. *Front Pediatr* 2022; 10:842544.
36. Lee CC, Chan OW, Lai MY, Hsu KH, Wu TW, Lim WH, Wang YC. Incidence and outcomes of acute kidney injury in extremely-low-birth-weight infants. *PLoS One* 2017;12:e0187764.
37. Manrique-Caballero CL, Del Rio-Pertuz G, Gomez H. Sepsis-associated acute kidney injury. *Crit Care Clin* 2021; 37:279–301.
38. Formeck CL, Joyce EL, Fuhrman DY, Kellum JA. Association of acute kidney injury with subsequent sepsis in critically ill children. *Pediatr Crit Care Med* 2021; 22:e58-e66.
39. Vilander LM, Kaunisto MA, Pettilä V. Genetic predisposition to acute kidney injury – a systematic review. *BMC Nephrol* 2015; 16:197.
40. Vasarhelyi B, Toth-Heyn P, Treszl A, Tulassay T. Genetic polymorphism and risk for acute renal failure in preterm infants. *Pediatr Nephrol* 2005; 20:132–5.
41. Kadi FA, Yuniati T, Sribudiani Y, Rachmadi D. The association of rs187238, rs19465518 and rs1946519 IL-8 polymorphisms with acute kidney injury in preterm infants. *BioMedicine* 2021; 11:43-50.
42. Leghrouz B, Kaddourah A. Impact of acute kidney injury on critically ill children and neonates. *Front Pediatr* 2021; 26:9:635631.
43. Martin SM, M.D. Balestracci A, Aprea V, Bolasell C, Wainsztein R, Debaisi G, Rosón G. Acute kidney injury in critically ill children: incidence and risk factors for mortality. *Arch Argent Pediatr* 2013; 111:412-7.
44. Riyuzoa MC, Silveira LV, Macedoa CS, Fioretto JR. Predictive factors of mortality in pediatric patients with acute renal injury associated with sepsis. *J Pediatr (Rio J)* 2017; 93:28.
45. Rifkin DE, Coca SG, Kalantar-Zadeh K. Does AKI truly lead to CKD? *JASN* 2012; 23:979-84.

The relationship between C-reactive protein, anthropometric parameters and lipids in menopausal transition

Dženana Softić, Lejla Mešalić

Department of Gynaecology and Obstetrics, University Clinical Centre Tuzla, ²School of Medicine, University of Tuzla; Tuzla, Bosnia and Herzegovina

ABSTRACT

Aim To investigate the relationship between C-reactive protein, anthropometric parameters, and lipids in women in the menopausal transition.

Methods This cross-sectional study included 150 women divided into three groups: premenopausal (n=50), perimenopausal (n=50), and postmenopausal (n=50). All women were interviewed, body mass index (BMI) and waist-hip ratio (WHR) values were calculated, and a blood sample was taken for laboratory analysis. The values of the lipids were determined including triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol, while low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) cholesterol values were obtained through formulas. The concentration of CRP was determined by immunoturbidimetry on the Architect ci8200 device.

Results The BMI of postmenopausal women was significantly higher than that of premenopausal ($p=0.025$) and perimenopausal women ($p=0.010$). The ratio of the waist-hip circumference of postmenopausal women was significantly higher than the ratio of the waist-hip circumference of premenopausal women ($p<0.001$), as well as that of perimenopausal women ($p<0.001$). A significant difference in CRP concentration was found only between the postmenopausal and premenopausal groups ($p=0.009$). CRP significantly positively correlated with BMI in all three groups. A significant positive correlation was found between CRP and WHR in the perimenopause and in the postmenopause group. No significant correlation was found between CRP and lipid parameters in any group.

Conclusion An increase in body weight or obesity in the postmenopausal period, increase in CRP concentration, and positive correlation between these parameters suggest that entering menopause could mean a potential increase in the risk of developing cardiovascular and metabolic diseases.

Key words: body mass index, inflammation, lipids, menopause, waist-hip ratio

Corresponding author:

Dženana Softić

University Clinical Centre Tuzla

Trnovac bb, 75 000 Tuzla,

Bosnia and Herzegovina

Phone: +387 62 311 663;

E-mail: dzeny_512@hotmail.com

ORCID ID: [https://orcid.org/0000-0001-](https://orcid.org/0000-0001-8326-456X)

8326-456X

Original submission:

02 December 2022;

Revised submission:

08 December 2022;

Accepted:

14 December 2022

doi: 10.17392/1565-22

INTRODUCTION

Menopause is a permanent cessation of menstruation due to the reduction of egg cells. The result is a sudden drop in endogenous estradiol. During the transition to menopause, women undergo phenotypic, metabolic, and biochemical changes that increase the risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Whether these changes are independent of aging itself is a matter of debate (1). Women gain weight during the transition to menopause. Although this may be influenced by age rather than menopause per se, the transition to menopause is independently associated with an increase in adipose tissue, particularly in the abdominal region (2). In perimenopausal women, there is a decrease in lean body mass and a significant decrease in energy consumption, mainly due to fat oxidation, which favours an increase in total body and visceral fat without significant changes in energy intake (3). Visceral adiposity increases the production of pro-inflammatory cytokines, increases circulating free fatty acids, and promotes the formation of reactive oxygen species, contributing to the development of insulin resistance and, consequently, CVD (4).

Adipose tissue dysfunction in obesity results in a shift from an anti-inflammatory to a pro-inflammatory profile (5). Obesity-related inflammation begins in the adipose tissue and liver with increased macrophage infiltration and expression of pro-inflammatory cytokines. The obesity-induced inflammatory response also results in increased circulating cytokines such as interleukin (IL)-6 and tumour necrosis factor- α (TNF α) and increased acute phase proteins, C-reactive protein, and serum amyloid A and causes systemic inflammation (6). Therefore, overloaded, dysfunctional adipose tissue is associated with the activation of immune cells and inflammatory mediators, both locally in the adipose tissue and systemically, resulting in a low degree of chronic inflammatory state (6,7).

Menopause, age and increased distribution of abdominal fat tissue are three independent and important factors that disrupt the lipoprotein profile from the beginning of the menopausal transition (8). Cardiovascular risk associated with menopause is primarily attributed to a change in the lipid profile towards atherogenesis, which is

characterized by an increase in the concentration of total cholesterol (TC), low-density lipoprotein (LDL-C) and triglycerides, and a decrease in the concentration of high-density lipoprotein (HDL-C) (9,10). Some studies suggest a reversal in the protective association of HDL-C and cardiovascular disease during the menopausal transition, pointing to a decrease in estrogen during menopausal transition (MT) and an increase in C-reactive protein (CRP) as the leading causes (11). With the onset of menopause, the direction of the association between HDL cholesterol and the cardiovascular risk appears to change from protective to detrimental. Previous studies have shown increased values of total cholesterol, triglycerides, LDL, apo B and decreased values of HDL and apo A in postmenopause (10-13).

Similar studies have not been conducted in our region yet.

The aim of this study was to investigate the relationship between C-reactive protein, anthropometric parameters, and lipids in menopausal transition, as well as the relationship between components of the metabolic syndrome and the risk of developing cardiovascular diseases in menopausal transition.

PATIENTS AND METHODS

Patients and study design

This cross-sectional study included 150 women divided into three groups: premenopausal (n=50), perimenopausal (n=50), and postmenopausal (n=50). The first group was aged between 45-50 years, the second between 50-55 years, and the third over 55 years. The study was conducted in the period between April and July 2022. The women were processed at the Clinic for Gynaecology and Obstetrics and the Polyclinic for Laboratory Diagnostics of the University Hospital Tuzla, previously stratified according to the inclusion and exclusion criteria of the study. The inclusion criteria were as follows: do not take hormone replacement therapy or anticonvulsants, do not take medications that could affect the lipid profile, do not suffer from hyperthyroidism, hypogonadism, liver disease, and myxedema.

The Ethical Committee of University Clinical Centre Tuzla approved the study. All women signed an informed consent.

Methods

All women were interviewed, body mass index (BMI) and waist-hip ratio (WHR) values were calculated, and a blood sample was taken for laboratory analysis. A special question-form was created and it was conducted the interview with the examinees. Body mass, height, waist, and hip circumference were measured, and BMI and WHR were determined. The BMI was calculated according to the formula: $BMI = \text{body weight} / \text{body height}^2$ (kg/m²). Obesity was considered as BMI >30 kg/m². The WHR was calculated as the ratio of waist circumference and hip circumference. Blood for laboratory analysis was taken by venipuncture from the cubital vein in the early morning hours on an empty stomach. From the blood sample, the lipid profile values were determined by a standard method, including triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol, while the low-density lipoprotein (LDL) - and very-low-density lipoprotein (VLDL) cholesterol were obtained through formulas. The concentration of C-reactive protein was determined by immunoturbidimetry on the Architect ci8200 device (Abbott Laboratories, Hercegovina lijek Mostar, Bosnia and Herzegovina).

Statistical analysis

Results are expressed as mean ($\bar{X}$) and standard error of the arithmetic mean (SEM), and as median and interquartile range (25-75 percentile). To test the significance of the difference in the deviation from the normal distribution, the Kolmogorov-Smirnov or Shapiro-Wilk test was used. Independent numerical variables were analysed by ANOVA test and t-test for those that met the conditions for application, i.e. by appropriate non-parametric tests (Kruskal-Wallis test and Mann-Whitney U test) for variables with an irregular distribution. The χ^2 test was used to analyse categorical variables. The correlations between the variables were assessed by Spearman's test. A $p < 0.05$ was taken as statistically significant.

RESULTS

The median age of premenopausal women was 47.0 (45.0-48.9), perimenopausal 52.0 (49.0-55.0), and postmenopausal 59.0 (57.0-61.0) years old ($p < 0.001$). Menarche in the premeno-

Table 1. Values of anthropometric parameters, C-reactive protein and lipid profile parameters in women in the menopausal transition

Parameter	Premenopausal group (n=50)	Perimenopausal group (n=50)	Postmenopausal group (n=50)	p
BMI (kg/m ²)	25.59 (23.94-28.74)	25.37 (23.65-28.10)	27.72 (25.47-31.22)*†	<0.05
WHR	0.80±0.05	0.80±0.05	0.85±0.08*†	<0.001
Total cholesterol (mmol/L)	5.35 (4.93-6.41)	6.08 (5.44-6.82)*	6.01 (5.34-6.92)*	<0.05
Triglycerides (mmol/L)	1.47 (0.96-1.89)	1.54 (1.06-2.16)	1.53 (1.13-2.45)	0.247
LDL-cholesterol (mmol/L)	3.74±0.93	4.19±0.94*	4.13±0.95*	<0.05
HDL-cholesterol (mmol/L)	1.47±0.30	1.50±0.33	1.44±0.35	0.598
VLDL-cholesterol (mmol/L)	0.66 (0.43-0.85)	0.70 (0.48-0.98)	0.69 (0.51-1.11)	0.243
C-reactive protein (mg/dL)	1.0 (0.0-1.8)	1.0 (0.37-2.20)	1.0 (0.60-4.10)*	<0.05

Results are expressed as mean ($\bar{X}$) and standard error of the arithmetic mean (SEM), and as median and interquartile range (25-75 percentile).

* $p < 0.05$ comparison to the premenopausal group; † $p < 0.05$ comparison to the perimenopausal group

BMI, body mass index; WHR, waist-hip ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein;

pausal group was at 13.0 (13.0-14.0) years, perimenopausal 14.0 (13.0-14.25) years, and postmenopausal at 14.0 (13.0-15) years ($p = 0.371$).

Body mass index in premenopausal women was 25.59 (23.94-28.74) kg/m², in perimenopausal 25.37 (23.65-28.10) kg/m², while 27.72 (25.47-31.22) kg/m² in postmenopausal women. The body mass index of postmenopausal women was significantly higher than that of premenopausal ($p = 0.025$) and that of perimenopausal ($p = 0.010$). The waist-hip ratio in premenopausal women was 0.80±0.05, in perimenopausal women 0.80±0.05, and in postmenopausal 0.85±0.08. The ratio of the waist-hip circumference of postmenopausal women was significantly higher than the ratio of the waist-hip circumference of premenopausal women ($p < 0.001$), as well as that of perimenopausal women ($p < 0.001$). Concentrations of total cholesterol in the perimenopausal and postmenopausal groups were significantly higher than in the premenopausal group ($p = 0.020$). In contrast, the total cholesterol concentrations between women in perimenopause and postmenopause did not differ significantly ($p = 0.865$). The concentrations of LDL-cholesterol in the perimenopausal ($p = 0.019$) and the postmenopausal ($p = 0.041$) group were significantly higher than

in the premenopausal group, 4.19 ± 0.94 mmol/L, 4.13 ± 0.95 mmol/L, and 3.74 ± 0.93 mmol/L, respectively. The concentration of HDL-cholesterol, triglycerides, and VLDL-cholesterol between the groups was not significant. A significant difference in CRP concentration was found only between the postmenopausal and premenopausal groups, 1.0 (0.60 – 4.10) mg/dL and 1.0 (0.0 – 1.8) mg/dL, respectively ($p=0.009$). The median concentration of total cholesterol in the postmenopausal group was higher than in the other.

C-reactive protein significantly positively correlated with BMI in the premenopausal group ($Rho=0.510$; $p<0.01$), in the perimenopausal group ($Rho=0.304$; $p<0.05$), and in the postmenopausal group ($Rho=0.418$; $p<0.01$). A significant positive correlation was found between CRP and WHR in the perimenopause group ($Rho=0.304$; $p<0.05$) and in the postmenopause group ($Rho=0.293$; $p<0.01$). No significant correlation was found between CRP and lipid profile parameters in any studied groups (Table 2).

Table 2. Correlation of C-reactive protein, anthropometric parameters and lipid profile in the studied groups

Parameter	C-reactive protein correlation (Rho)		
	Premenopausal group (n=50)	Perimenopausal group (n=50)	Postmenopausal group (n=50)
BMI (kg/m ²)	0.510*	0.304†	0.418*
WHR	0.189	0.313†	0.293†
C-reactive protein (mg/dL)	0.114	-0.015	0.179
Total cholesterol (mmol/L)	0.161	0.054	0.174
Triglycerides (mmol/L)	-0.030	0.027	-0.157
LDL-cholesterol (mmol/L)	0.043	0.136	0.125
HDL-cholesterol (mmol/L)	0.017	-0.010	0.175

* $p<0.001$; † $p<0.005$;

BMI, body mass index; WHR, waist-hip ratio; LDL, low-density lipoprotein; HDL, high-density lipoprotein

DISCUSSION

The results of our research showed that the BMI of postmenopausal women was significantly higher than BMI of premenopausal, as well as that of perimenopausal women. Also the ratio of the waist-hip circumference of postmenopausal women was significantly higher than in the other two groups. A significant difference in the CRP concentration was found only between the postmenopausal and premenopausal groups. The

concentrations of total cholesterol in the perimenopausal and postmenopausal groups were significantly higher than the concentrations of total cholesterol in the premenopausal group. In contrast, the total cholesterol concentrations between the subjects in perimenopause and postmenopause did not differ significantly. The concentrations of LDL-cholesterol in the perimenopausal group and the postmenopausal group were significantly higher than the concentration of LDL-cholesterol in the premenopausal group, and the concentrations of HDL-cholesterol, triglycerides, and VLDL-cholesterol between the examined groups did not differ significantly.

It was shown that the average BMI of postmenopausal women was higher than that of premenopausal women, even if they had better eating habits. An important result in Bhurosa et al. (14) study showed that the mean anthropometric values of waist circumference, WHR and BMI were significantly higher in postmenopausal women. In a study by Giannini et al. (15) the prevalence of obesity was higher in postmenopausal women than in premenopausal women. It results from a multifactorial process that includes reduced energy consumption due to physical inactivity, sometimes accompanied by depression, muscle atrophy, and lower basal metabolism. Some authors believe menopause is not associated with weight gain but leads to an increase in total body fat and a redistribution of body fat from the periphery to the trunk, resulting in visceral adiposity (16). In a study conducted by Hummadi et al. (17) it is commonly assumed that the volume of fat mass increases with age and results in a higher BMI recorded during aging. Higher levels of LDL-C, TC, and TG were detected in postmenopausal women than in the groups of premenopausal women. At the same time, HDL did not differ significantly between premenopausal and postmenopausal women, as shown in a meta-analysis conducted by Li et al. (18). A significant increase in TC, TG, and LDL-c with a significant decrease in the level of HDL-C was found in postmenopausal compared to premenopausal women in a study by Hamza et al. (19). Higher CRP values in postmenopause and significantly higher levels of CRP in perimenopause compared to premenopause were found in a study conducted by Ebong et al. (20). The authors conclude

that higher TNF- α characterizes postmenopausal status and that CRP may be associated with increased cardiovascular risk in postmenopausal women due to its association with higher intra-abdominal fat (21). Opposite results were presented by Sharma et al. (22), who proved that women with early menopause had higher CRP values than women in late menopause. Our research showed that C-reactive protein significantly positively correlated with BMI in all three experimental groups. A significant positive correlation was found between CRP and WHR in the perimenopause group and in the postmenopause group.

In a sample of 61 obese postmenopausal women, plasma CRP levels were found to be positively associated with dual X-ray absorptiometry-measured total body fat. Plasma CRP level was significantly reduced by weight loss. The authors concluded that obesity was a significant predictor of plasma CRP in postmenopausal women on a cross-sectional basis (23). In the study by Chi-

tra et al. (24), a positive correlation was found between BMI and increased level of hs-CRP suggesting that underlying pathology of obesity was involved, as fat cells secrete several substances that have adverse effects on the body (such as increased inflammation, hardening of the arteries and blood clotting).

In conclusion, considering that our results showed a tendency to increase body weight or obesity in the postmenopausal period and an increase in CRP concentration, as well as positive correlation between these parameters, we believe that entering menopause can potentially increase the chances of developing cardiovascular and metabolic diseases.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

REFERENCES

1. Slopian R, Wender-Ozegowska E, Rogowicz-Frontczak A, Meczekalski B, Zozulinska-Ziolkiewicz D, Jaremek JD, Cano A, Chedraui P, Goulis DG, Lopes P, Mishra G, Mueck A, Rees M, Senturk LM, Simoncini T, Stevenson JC, Stute P, Tuomikoski P, Paschou SA, Anagnostis P, Lambrinoudaki I. Menopause and diabetes: EMAS clinical guide. *Maturitas* 2018; 117:6-10.
2. Juppi HK, Sipilä S, Fachada V, Hyvärinen M, Cronin N, Aukee P, Karppinen JE, Selänne H, Kujala UM, Kovanen V, Karvinen S, Laakkonen EK. Total and regional body adiposity increases during menopause-evidence from a follow-up study. *Aging Cell* 2022; 21:e13621.
3. Ho SC, Wu S, Chan SG, Sham A. Menopausal transition and changes of body composition: a prospective study in Chinese perimenopausal women. *Int J Obes (Lond)* 2010; 34:1265-74.
4. Han CY. Roles of reactive oxygen species on insulin resistance in adipose tissue. *Diabetes Metab J* 2016; 40:272-9.
5. Trim W, Turner JE, Thompson D. Parallels in immunometabolic adipose tissue dysfunction with ageing and obesity. *Front Immunol* 2018; 9:169.
6. Möller K, Ostermann AI, Rund K, Thoms S, Blume C, Stahl F, Hahn A, Schebb NH, Schuchardt JP. Influence of weight reduction on blood levels of C-reactive protein, tumor necrosis factor- α , interleukin-6, and oxylipins in obese subjects. *Prostaglandins Leukot Essent Fatty Acids* 2016; 106:39-49.
7. Mair KM, Gaw R, MacLean MR. Obesity, estrogens and adipose tissue dysfunction - implications for pulmonary arterial hypertension. *Pulm Circ* 2020;10:2045894020952019.
8. Berg G, Mesch V, Boero L, Sayegh F, Prada M, Royer M, Muzzio ML, Schreier L, Siseles N, Benencia H. Lipid and lipoprotein profile in menopausal transition. Effects of hormones, age and fat distribution. *Horm Metab Res* 2004; 36:215-20.
9. Ambikairajah A, Walsh E, Cherbuin N. Lipid profile differences during menopause: a review with meta-analysis. *Menopause* 2019; 26:1327-33.
10. Anagnostis P, Bitzer J, Cano A, Ceausu I, Chedraui P, Durmusoglu F, Erkkola R, Goulis DG, Hirschberg AL, Kiesel L, Lopes P, Pines A, van Trotsenburg M, Lambrinoudaki I, Rees M. Menopause symptom management in women with dyslipidemias: An EMAS clinical guide. *Maturitas* 2020; 135:82-88.
11. El Khoudary SR, Wang L, Brooks MM, Thurston RC, Derby CA, Matthews KA. Increase HDL-C level over the menopausal transition is associated with greater atherosclerotic progression. *J Clin Lipidol* 2016; 10:962-69.
12. Ko SH, Kim HS. Menopause-associated lipid metabolic disorders and foods beneficial for postmenopausal women. *Nutrients* 2020; 12:202.
13. Choi Y, Chang Y, Kim BK, Kang D, Kwon MJ, Kim CW, Jeong C, Ahn Y, Park HY, Ryu S, Cho J. Menopausal stages and serum lipid and lipoprotein abnormalities in middle-aged women. *Maturitas* 2015; 80:399-405.
14. Bhurosy T, Jeewon R. Food habits, socioeconomic status and body mass index among premenopausal and post-menopausal women in Mauritius. *J Hum Nutr Diet* 2013; 1:114-22.
15. Giannini A, Caretto M, Genazzani AR, Simoncini T. Menopause, hormone replacement therapy (HRT) and obesity. *Curre Res Diabetes & Obes J* 2018; 7: 555704.

16. Ahmed HS. Metabolic and hormonal changes associated with menopause. *Mustansiriya Med J* 2017; 16:77-82.
17. Hummadi MH, Ahmed HS, Hussien Z, Ali Z. Assessment of serum Interleukin-6 and Leptin levels in postmenopausal Iraqi women. *Int J Pharm Res* 2020; 12:1.
18. Li H, Sun R, Chen Q, Guo Q, Wang J, Lu L, Zhang Y. Association between HDL-C levels and menopause: a meta-analysis. *Hormones (Athens)* 2021; 20:49-59.
19. Hamza A, Abbas M, Elfaki, Ibrahim M, Abdalhabib EK, Karar T. Assessment of plasma lipid profile among Sudanese menopausal women in Khartoum State-Sudan. *Biomed Pharmacol J* 2019; 12:2037-41.
20. Ebong IA, Schreiner P, Lewis CE, Appiah D, Ghelani A, Wellons M. The association between high-sensitivity C-reactive protein and hypertension in women of the Cardia study. *Menopause* 2016; 23:662-8.
21. Sites CK, Toth MJ, Cushman M, L'Hommedieu GD, Tchernof A, Tracy RP, Poehlman ET. Menopause-related differences in inflammation markers and their relationship to body fat distribution and insulin-stimulated glucose disposal. *Fertil Steril* 2002; 77:128-35.
22. Sharma N, Sharma RK, Tewari S, Chauhan M, Bhatia A. Association of periodontal inflammation, systemic inflammation, and duration of menopausal years in postmenopausal women. *Quintessence Int* 2018; 49:123-31.
23. Tchernof A, Nolan A, Sites CK, Ades PA, Poehlman ET. Weight loss reduces C-reactive protein levels in obese postmenopausal women. *Circulation*. 2002; 105:564-9.
24. Chitra J, Deshpande S. An observational study to predict the risk of stroke in post-menopausal women using Hs-CRP and Qstroke. *Indian J Physiother Occup Ther* 2019; 13:139-43.

CT advantages of potential use of polymer plastic clips in neurocranium

Samir Delibegović¹, Mirela Delibegović², Muhamed Katica³, Muamer Obhodžaš³, Muhamed Oduž⁴

¹School of Medicine, University of Tuzla, Tuzla, ²Clinic for Radiology, University Clinical Centre Tuzla, ³Veterinary Faculty, Department of Clinical Sciences of Veterinary Medicine, University of Sarajevo, Sarajevo, ⁴Veterinary Station "Mak-vet d.o.o. Breza", Breza; Bosnia and Herzegovina

ABSTRACT

Aim Clips in neurosurgery are made of titanium alloys, which reduce artifacts on computed tomography (CT). The radiological advantage of plastic clips on the CT image was demonstrated when they were placed in an inter-hemispherical position at an angle of 90°. The aim of this study was to investigate the behaviour of the clip placed at different angles.

Methods Sixty heads of domestic pigs were divided into two groups, in group 1 a titanium clip was placed to the interhemispheric position at an angle of 90°, 45°, 0°, ten heads for each angle. In group 2 a plastic clip was placed in the same way. CT scan of the brain was performed for each angle. The size of the density and possible artifact were measured on CT.

Results The size of the titanium clip ranged from 17.05 mm at an angle of 0° in the axial plane to 91.47 mm at an angle of 0° in the sagittal plane. The average size of the plastic clip ranged from 6.4 mm at an angle of 0° in the axial plane to 23.22 mm in an angle of 90° in the sagittal plane. Artifacts were observed only in the titanium clip.

Conclusion Plastic clips have shown radiological advantages over titanium clips in the CT image. The average density size of the plastic clip in all planes and all angles was smaller than the titanium clip.

Key words: aneurysm clipping, artifacts, computed tomography

Corresponding author:

Samir Delibegović
Clinic for Surgery,
University Clinical Centre Tuzla
Trnovac bb, 75000 Tuzla,
Bosnia and Herzegovina
Phone: +387 35 303 500;
Fax: +387 35 250 474;
E-mail: sam.delibey@gmail.com
ORCID ID: <https://orcid.org/0000-0003-0525-3288>

Original submission:

10 October 2022;

Revised submission:

22 November 2022;

Accepted:

26 December 2022

doi: 10.17392/1547-22

INTRODUCTION

Neurosurgical treatment of intracranial aneurysms with permanent closure using “spring clips” placed above the neck of the aneurysm was introduced more than forty years ago, and has become the standard procedure (1). But researchers have observed significant artifacts around the clips, which can cover contrast about them. Although the fourth generation of clips in neurosurgery is made of titanium and its alloys, in order to reduce artifacts on computed tomography (CT) and magnetic resonance (MR) scan (2), they continue to interfere with image interpretation.

However, artifacts usually depend on physical properties of the material from which the clips are made. The physical properties of plastic materials, their lower atomic number and density (3), make them attractive for use in CT. Plastic clips are a diamagnetic material (4) and cause fewer artifacts than titanium clips, which are standard in neurosurgery.

The radiological advantage of plastic clips was shown in CT imaging when placed in the frontobasal, interhemispheric position at a 90° angle, in an animal model (5), however, the advantages and possible artifacts at different angles and different planes are unknown.

Bearing in mind that polymer plastic clips are increasingly used in endoscopic surgery, our study intends to examine the CT characteristics of plastic clips at different angles, after application to the pig neurocranium, and compare it with standard titanium clips.

MATERIALS AND METHODS

Materials and study design

This prospective clinical study was performed at the Department of Surgery, Veterinary Faculty, University of Sarajevo, and in the Clinic for Radiology and Nuclear Medicine, University Clinical Centre Tuzla during 2020.

The experimental part of the study, craniotomy and placing of clips, was performed at the Veterinary Faculty, University of Sarajevo, Department of Surgery, and CT and MRI were performed in the University Clinical Centre (UKC) Tuzla, Clinic for Radiology and Nuclear Medicine. The Ethical Committee of the UKC Tuzla approved this research (No:02-09/2-63-13).

Treatment of animals was in accordance with the principles of the Declaration of Helsinki.

Methods

Sixty heads of domestic pigs (*Sus scrofa domestica*) with white hair, “Danish Landras”, were taken in this study. Inclusion criteria were healthy adults, with no head or brain damage during the sacrifice. Excluding criteria were immature young animals, as well as diseased ones and specimens where head and brain damage occurred during sacrifice. The animals were divided into two groups; group I in which a permanent titanium clip was placed in the neurocranium - at an angle of 90°, 45° and 0°, 10 heads for each angle, and group II in which a plastic polymer clip was placed in the neurocranium - at an angle of 90°, 45° and 0°, 10 heads for each angle.

Operative procedure. A craniotomy was performed on the head of a domestic pig. After an arcuate incision from the right to the left orbital arch, the subcutaneous tissue and muscles of the frontal region were dissected and denuded from the bone. The temporalis muscle was removed, and in this region the trepanation was opened with a drill and then connected with a Gili saw, thus performing a craniotomy. The intact dura was incised with a scalpel, and the accesses to the brain was obtained.

In the first group of animals, the permanent Yasargil FT 746 T clip (external size 15.2 mm, length of clip leg 8.1 mm, weight 0.2 g) was placed in the frontobasal, interhemispheric position, at an angle of 90°, 45° and 0°.

In the second group of animals, the polymer Hemo-lok clip ML (external size 9.3 mm, weight 0.05 g) was placed in the same position at an angle of 90°, 45° and 0°.

CT scan. After the operative procedure, a brain CT scan was performed using a 64-slice CT (Siemens Somatom Sensation, Erlangen, Germany) (mAs 380, 120 KW, slice 5.0 mm, delay 4 sec., scan time 12.18 sec., 59.43 mGrey). Scans were performed in the axial, sagittal, and coronal planes, a brain window W:80, L:40.

Parameters of monitoring. The density expressed in Hounsfield units (HUI) was monitored on axial CT sections through the placement site of the titanium and plastic clips and its size expressed

ssed in mm was measured. If artifacts are observed, the measure of their size is expressed in mm.

We analysed CT images taken after the titanium and plastic clip placement at 90°, 45°, and 0°, in the soft tissue window and the brain window, in the axial, sagittal, and coronal cross-sections.

The artefacts seen in the CT brain window in axial, sagittal, and coronal cross-sections were then analysed.

Statistical analysis

Results are expressed as mean values with standard deviation. The statistical significance of the differences was tested by the Kolmogorov-Smirnov test. The difference at the level of $p < 0.05$ was considered statistically significant. Statistical analysis was performed in the Statistica 10.0 program for the Windows application.

RESULTS

The densities of the plastic and titanium clips were measured on each CT scan. If we look at the average size of the plastic and titanium clips at different angles on the CT scan (Table 1), we can observe that it ranged from 6.4 mm at an angle of 0° in the axial plane to 23.22 mm at an angle of 90° in the sagittal plane. The size of the titanium clip ranged from at least 17.05 mm at an angle of 0° in the axial plane to 91.47 mm in the sagittal plane at an angle of 0°.

Table 1. Average size of plastic and titanium clip at an angle of 0°, 45° and 90° on CT scans in the soft tissue window (MT) and brain window (MP)

Clips	Angle=0°		Angle =45°		Angle =90°	
	Plastic clip	Titanium clip	Plastic clip	Titanium clip	Plastic clip	Titanium clip
MT_CT_sag	16.853	72.541	12.709	67.649	14.688	63.939
MT_CT_ax	6.414	17.048	7.537	20.243	12.052	51.101
MT_CT_kor	12.131	35.948	9.956	39.780	5.016	20.062
MP_CT_sag	22.868	91.469	22.812	85.380	23.222	73.080
MP_CT_ax	10.727	28.936	13.647	35.390	17.930	85.162
MP_CT_kor	21.371	46.799	16.733	51.626	11.999	31.124

To test the difference between the sizes of the titanium and plastic clips at an angle of 90°, 45° and 0°, i.e. at which angle was the largest and the smallest, respectively, in the sagittal, axial, coronal plane (including all angles and all planes), we used Kolmogorov - Smirnov test.

There was a statistically significant difference in the distributions of the MP_CT variable between the plastic and titanium clips ($p < 0.001$). The

same is true of all the other variables tested for which a difference was found (Figure 1, 2).

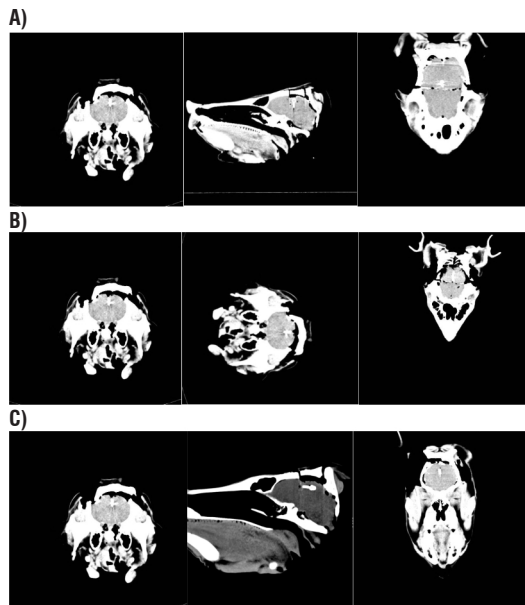


Figure 1. CT of a titanium clip, the brain window, sagittal (left), coronal (middle), and axial cross-sections (right) at A) 90°, B) 45° and C) 0° (Delibegović M, 2020)

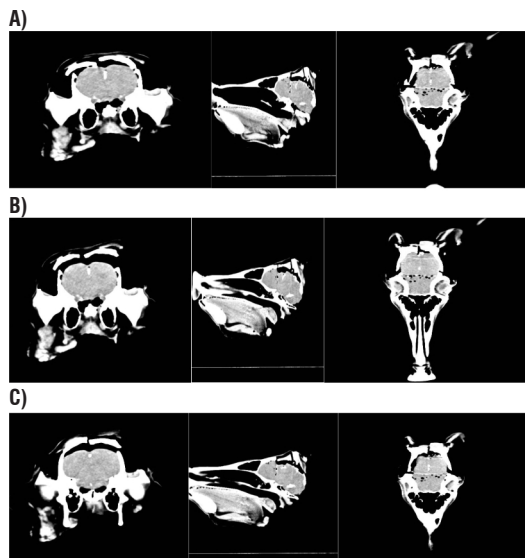


Figure 2. CT of a plastic clip, the brain window, sagittal (left), coronal (middle), and axial cross-sections (right) at A) 90°, B) 45° and C) 0° (Delibegović M, 2020)

It was observed that the size of the artifacts was the smallest at the angle of 45° in all three sections (Table 2, Figure 3).

Table 2. Size of artifact at angles 0°, 45° and 90° in all three cross-sections

Angle	Axial cross-sections	Sagittal cross-sections	Coronal cross-sections
0°	15.5±3.6 x 1.8±0.4	7.5±3.8 x 0.8±0.5	7.5±3.8 x 0.8±0.5
45°	8.8±0.6 x 1.6±0.6	6.3±3.7 x 1.1±0.5	6.3±3.7 x 1.1±0.5
90°	10.8±4.7 x 1.4±0.4	13.6±0.6 x 1.5±0.5	13.6±0.6 x 1.5±0.5

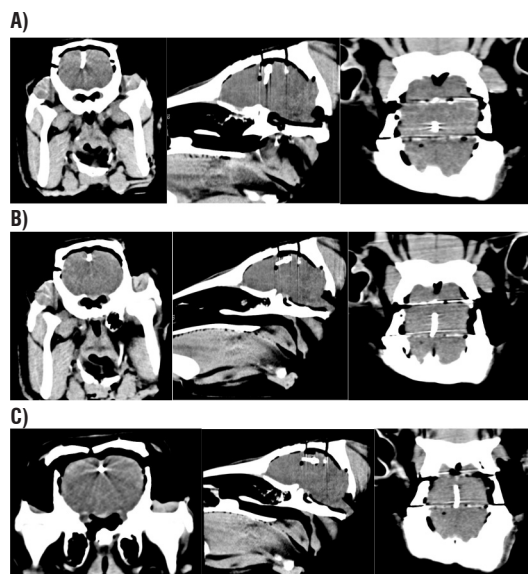


Figure 3. Artifacts seen in the CT of a titanium clip, the brain window, sagittal (left), coronal (middle), and axial cross-sections (right) at A) 90°, B) 45° and C) 0° (Delibegović M, 2020)

DISCUSSION

The CT and MR compatibility of neurosurgical clips is an essential requirement. Metallurgical and physical tests of clips have proven MR compatibility of clips made of non-ferromagnetic materials. However, these investigations have revealed significant artifacts around the clips, which may cover the contrast in their vicinity (6-9).

Artifacts are structures in the image that do not correspond to the spatial distribution of tissues in the plane of the image. To avoid diagnostic misinterpretation, it is recommended to learn how to detect artifacts. However, artifacts usually depend on the physical properties of the material from which the clips are made (10). The latest generation of clips in neurosurgery is made of titanium and its alloys, which reduces artifacts on CT and MR scans (1).

Metal implants in patients' bodies cause strong, striped artifacts that will overshadow or make crucial information less clear and reduce image quality. The academic community believes that the explanation for this phenomenon is beam homogenization (11,12).

In addition to the attempts to reduce artifacts by changing the composition of the materials used to make the clips, imaging techniques have been developed to reduce artifacts (13).

The causes of metal artifacts are quite complicated. Depending on the shape and density of metal

objects, the appearance of artifacts can be significant (14). Metal objects can cause beam homogenization, partial volume, aliasing, under-range in electronic data acquisition, or dynamic range overflow in the reconstruction process (15).

When the cause of metal artifacts is dominated by air beam homogenization, artifacts can be corrected algorithmically, and various algorithms are presented (16-21). So far, no effective and affordable scheme for the correction of metal artifacts has been found. Often, the correction of metal artifacts is complicated by the movement of the patient, which creates additional projection inconsistency and worsens striped artifacts. An additional area next to the metal object was also destroyed (22). For many clinical applications, the interface between the implant and adjacent bone and soft tissue is of great interest to the clinician (23).

The use of Hem-o-lock clips, which are non-resorptive, polymeric structures, for ligation of blood vessels, ureters, bile ducts, and appendix bases, has been documented in more than 1,000 surgical procedures (24-26). However, there are no reports of their use in neurosurgery, although plastic clips have some potential benefits.

The physical properties of plastic materials, their lower atomic number and density (2), make them attractive for the use in CT. The radiological advantage of plastic clips has been shown when placed in the frontobasal, interhemispheric position at an angle of 90°, in an animal model (5). However, it is not known what the advantages and possible artifacts are at different angles and in different planes.

Our study showed that the average shadow size of the plastic clip in CT soft tissues (MT) and brain window (MP) in the sagittal, axial and coronal planes, and at an angle of 0°, 45° and 90° was smaller compared to the titanium clip.

The orientation of the clips significantly affects the size of the artifact. Artifacts are worst with a clip in an aneurysm at an angle of 45° and 90°, on 3D CT and DS angiography (27). The smallest artifacts can be expected when the longer axis of the clip is perpendicular to the longer axis of the wrinkle scanner and therefore in the plane of the cut (28).

Titanium clips, well documented, reduce artifacts observed relative to ferromagnetic clips. However, some shortcomings remain due to metallic characteristics such as a large part of the spring,

and production difficulties (29).

Clip artifacts can also affect the quality of three-dimensional CT angiography, which is used as a diagnostic method in postoperative evaluation after aneurysm clipping. The expression and distribution of these artifacts depend on the clip-stand angle and the plane of the image reconstruction (30). Most neurosurgeons would agree that it is ideal for patients with aneurysms, ruptured and non-ruptured, to undergo imaging follow-up after placement of a permanent clip. This approach is justified by the importance of determining whether a parent vessel has stenosis or if there is a residual neck aneurysm. The need for an immediate postoperative angiogram and another one after three years was emphasized (31). However, the present artifacts interfere with the interpretation of the image.

REFERENCES

- Huelser M, Sippl C, Linsler S, Knosp E, Wadiura L, Oertel J. A New clip generation for microsurgical treatment of intracranial aneurysms—the first case series. *World Neurosurgery* 2019; 130: e160-5.
- Zopfs D, Lennartz S, Pennig L, Glauner A, Abdullayev N, Bremm J, et al. Virtual monoenergetic images and post-processing algorithms effectively reduce CT artifacts from intracranial aneurysm treatment. *Sci Rep* 2020; 10:6629.
- Shrivastava A. *Introduction to Plastics Engineering*. 1st ed. Amsterdam: Elsevier Inc. 2018.
- Delibegovic S, Batalovic M, Delibegovic M, Bjakovic M. The effect of the shape of a clip on the magnetic field during magnetic resonance imaging examinations. *Med Glas (Zenica)* 2022; 19:41-5.
- Delibegovic S. Radiologic advantages of potential use of polymer clips in neurosurgery. *World Neurosurg* 2014; 3-4:549-51.
- Okuchi S, Fushimi Y, Yoshida K, Nakajima S, Sakata A, Hinoda T, Otani S, Sagawa H, Zhou K, Yamao Y, Okawa M, Nakamoto Y. 5. Comparison of TGSE-BLADE DWI, RESOLVE DWI, and SS-EPI DWI in healthy volunteers and patients after cerebral aneurysm clipping. *Sci Rep* 2022; 12:17689.
- Kim JH, Ahn SJ, Park M, Kim YB, Joo B, Lee W, Suh SH. Follow-up imaging of clipped intracranial aneurysms with 3-T MRI: comparison between 3D time-of-flight MR angiography and pointwise encoding time reduction with radial acquisition subtraction-based MR angiography. *J Neurosurg* 2021; 1-6.
- Higo Y, Komagata S, Katsuki M, Kawamura S, Koh A. 1.5 Tesla Non-ultrashort but Short Echo Time Magnetic Resonance Angiography Describes the Arteries Near a Clipped Cerebral Aneurysm. *Cureus* 2021;13:e16611.
- Shinohara Y, Ohmura T, Sasaki F, Inomata T, Itoh T, Kinoshita T. Appropriate iMAR presets for metal artifact reduction from surgical clips and titanium burr hole covers on postoperative non-contrast brain CT. *Eur J Radiol* 2021; 141:109811.
- Kim H, Yoo SK, Kim DW, Lee H, Hong CS, Han MC, Kim JS. Metal artifacts reduction in kv CT images throughout two-step sequential deep convolutional neural networks by combining multi/modal imaging (MARTIAN). *Sci Rep* 2022; 12:20823.
- Romero Bhathal J, Chassagne F, Marsh L, Levitt MR, Geindreau C, Aliseda A. Modeling flow in cerebral aneurysm after coils embolization treatment: a realistic patient-specific porous model approach. *Cardiovasc Eng Technol* 2022. Online ahead of print.
- Min CK, Kim KA. Reducing metal artifacts between implants in cone-beam CT by adjusting angular position of the subject. *Oral Radiol* 2021; 37:385-394.
- Kim B, Shim H, Baek J. A streak artifact reduction algorithm in sparse-view CT using a self-supervised neural representation. *Med Phys* 2022. Online ahead of print.
- Cao Z, Gao X, Chang Y, Liu G, Pei Y. A novel approach for eliminating metal artefacts based on MVCBCT and CycleGAN. *Front Oncol* 2022; 12:1024160.
- Morton N, O'Brien R, Keall P, Reynolds T. System requirements to improve adaptive 4-dimensional computed tomography (4D CT) imaging. *Biomed Phys Eng Express* 2022; 8.
- Zhu Q, Wang Y, Zhu M, Tao X, Bian Z, Ma J. An adaptive CT metal artifact reduction and algorithm that combines projection interpolation and physical correction. *Nan Fang Yi Ke Da Xue Xue Bao* 2022; 42:832-9.
- Zhou L, Liu H, Zou YX, Zhang G, Su B, Lu L, Chen YC, Yin X, Jiang HB. Clinical validation of an AI-based motion correction reconstruction algorithm in cerebral CT. *Eur Radiol* 2022; 32: 8550-9.
- Dwyer A, Korlaet M, Callary SA, Robertson T, Smitham P, Solomon LB. Impact of computed tomography metal artifact reduction protocol on periprosthetic tissue characterization after total hip arthroplasty: A cadaveric study. *J Orthop Res* 2022. Online ahead of print.

In conclusion, plastic clips have shown radiological advantages over standard titanium clips in the computed tomography images. The average density size of the plastic clips in all planes and all angles were smaller than the titanium clips, and they do not cause artefacts. Neuroradiologists and neurosurgeons should be aware of the CT advantage of plastic clips. Before their use in human medicine, further studies of the aneurysmal model are needed.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

19. Eisenhut F, Schmidt MA, Kalik A, Struffert T, Feulner J, Schlaffer SM, Manhart M, Doerfler A, Lang S. clinical evaluation of an innovative metal-artifact-reduction algorithm in fd-ct angiography in cerebral aneurysms treated by endovascular coiling or surgical clipping. *Diagnostics (Basel)* 2022; 12:1140.
20. Fu Z, Johnson K, Altbach MI, Bilgin A. Cancellation of streak artifacts in radial abdominal imaging using interference null space projection. *Magn Reson Med* 2022; 88:1355-69.
21. Anhaus JA, Schmidt S, Killermann P, Mahnken A, Hofmann C. Iterative metal artifact reduction on a clinical photon counting system-technical possibilities and reconstruction selection for optimal results dependent on the metal scenario. *Phys Med Biol* 2022; 67.
22. Puvanasunthararajah S, Camps SM, Wille ML, Fontanarosa D. Combined clustered scan-based metal artifacts reduction algorithm (CCS-MAR) for ultrasound-guided cardiac radioablation. *Phys Eng Sci Med* 2022; 45:1273-87.
23. Kunz AS, Patzer TS, Grunz JP, Luetkens KS, Hartung V, Hendel R, Fieber T, Genest F, Ergün S, Bley TA, Huflage H. Metal artifact reduction in ultra/high-resolution cone/beam CT imaging with a twin robotic X-ray system. *Sci Rep* 2022; 12:15549.
24. Delibegovic S, Matovic E. Hem-o-lok plastic clips in securing of the base of the appendix during laparoscopic appendectomy. *Surg Endosc* 2009; 23:2851-4.
25. Takago S, Nishida S, Nishida Y. The usefulness of nonabsorbable polymer clips for the closure of supra-aortic vessel's stump. *Gen Thorac Cardiovasc Surg* 2022; 70:825-7.
26. Koc G, Ekin GR, Ergani B, Ilbey YO. A comparison of renal vascular control techniques during laparoscopic nephrectomy. *J Minim Access Surg* 2021; 17:192-6.
27. Sagara Y, Kiyosue H, Hori Y, Sainoo M, Nagatomi H, Mori H. Limitations of three-dimensional reconstructed computerized tomography angiography after clip placement for intracranial aneurysm. *J Neurosurg* 2005; 103:656-61.
28. Mamourin AC, Pluta DJ, Eskey CJ, Merlis AI. Optimizing computed tomography to reduce artifacts from titanium aneurysm clips: an in vitro study. *J Neurosurg* 2007; 107: 1238-43.
29. Kim JH, Ahn SJ, Park M, Kim YB, Joo B, Lee W, Suh SH. Follow-up imaging of clipped intracranial aneurysms with 3-T MRI: comparison between 3D time-of-flight MR angiography and pointwise encoding time reduction with radial acquisition subtraction-based MR angiography. *J Neurosurg* 2021; 29:1-6.
30. Pechlivanis I, König M, Engelhardt M, Scholz M, Heuser L, Hardeß A, Schmieder K. Evaluation of clip artefacts in three-dimensional computed tomography. *Cent Eur Neurosurg* 2009; 70:9-14.
31. Schwandt E, Kockro R, Kramer A, Glaser M, Ringel F. Presurgical selection of the ideal aneurysm clip by the use of a three-dimensional planning system. *Neurosurg Rev* 2022; 45:2887-94.

Risk of anterior cruciate ligament injury in population with elevated body mass index

Hasan N. Alsayed¹, Mohammed Abdulrahman Alkhateeb², Asma Abdulaziz Aldossary³, Khalid Mohsen Houbani⁴, Yousef Mohammed Aljamaan¹, Yousef A. Alrashidi⁵

¹Department of Orthopaedic Surgery, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, ²Department of Plastic Surgery, Dammam Medical Complex, Dammam ³Department of Dermatology, Dammam Medical Complex, Dammam, ⁴Department of Family Medicine, Johns Hopkins Aramco Healthcare, Dhahran, ⁵Department of Orthopaedics, College of Medicine, Taibah University, Al Madinah Al Munawara; Saudi Arabia ¹Department of Orthopaedic Surgery, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, ²Department of Plastic Surgery, Dammam Medical Complex, Dammam ³Department of Dermatology, Dammam Medical Complex, Dammam, ⁴Department of Family Medicine, Johns Hopkins Aramco Healthcare, Dhahran, ⁵Department of Orthopaedics, College of Medicine, Taibah University, Al Madinah Al Munawara; Saudi Arabia

ABSTRACT

Aim Anterior cruciate ligament (ACL) injury is among the most common orthopaedic injuries. The elevated body mass index (BMI) can contribute to non-contact ACL injury. This study aims to assess the risk of ACL injury among elevated BMI population people (BMI ≥ 25 Kg/m²).

Methods This is a cross sectional study that was conducted in a tertiary care centre in the Kingdom of Saudi Arabia. A total of 302 patients, who had an ACL reconstruction surgery in a ten-year-period (January 2008 to December 2018) were included.

Results Sport related injury is significantly higher among the overweight and obese groups ($p=0.002$). Moreover, the combined ACL tear was higher among the overweight and obese groups ($p=0.001$). In univariate regression analysis for the selected baseline characteristics, it was found that individuals with higher BMI have chance to develop combined (ACL) injury 2 times higher when compared to those with isolated ACL injury ($p=0.003$). Also, the ACL type, mode of injury, types of injury and type of sports were statistically significant in univariate regression analysis. However, only the mode of injury was statistically significant after controlling the confounding factors. Other selected variables like type of sport, type of injury and ACL type were not significant.

Conclusion Elevated BMI was associated with a higher risk of developing combined ACL tear as well as reinjured individuals.

Key words: anterior cruciate ligament reconstruction, BMI, knee injury, obesity, sport injury

Corresponding author:

Mohammed Abdulrahman Alkhateeb
Department of Plastic Surgery,
Dammam Medical Complex
5343 King Khalid, Dammam,
Saudi Arabia
Phone: +966138155777;
E-mail: alkhateeb.m2a@gmail.com
Hasan N. Alsayed ORCID ID: 0000-0002-
9108-630X

Original submission:

25 July 2022;

Revised submission:

19 October 2022;

Accepted:

08 November 2022

doi: 10.17392/1517-22

INTRODUCTION

Anterior cruciate ligament (ACL) tear is among the most common orthopaedic injuries (1,2). The annual ACL injury rate in the United States is reported to be between 100000 – 200000 (3). Many factors have been associated with ACL injury including modifiable and non-modifiable risk factors. In fact, understanding the modifiable risk factors is crucial in employing preventative measures (4,5). One of the modifiable risk factors is an elevated body mass index (BMI), which can contribute to the development of non-contact ACL injury and associated with articular injuries in the presence of ACL tear (6). Reportedly, elevated BMI in both genders is associated with increasing the rate of knee injuries (7,8). Noyes et al. found that 75% of ACL injuries were due to non-contact mechanism (9).

Limited studies assessed the association between BMI and the risk of ACL injury (10). World Health Organization (WHO) considers obesity as a worldwide health issue which is associated with many chronic disorders. WHO classified the BMI between 25 - 30 kg/m² as an overweight and more than 30 kg/m² as obesity (11). In the Kingdom of Saudi Arabia (KSA), the prevalence of overweight population is 30.7% in males and 28.4% in females. Moreover, the prevalence of obesity is more in females, accounting for 23.6% compared with 14.2% in the male population (12). Although obesity is an emerging health issue in the KSA and ACL injury is one of the most common injuries faced by orthopaedic surgeons, there is only one national study, up to authors' knowledge, which assessed the association between these variables (1,12).

The aim of this study is to evaluate the risk of ACL injury in a population with an elevated BMI (BMI $\geq$ 25 Kg/m²) in a tertiary care centre in Al-Khobar city, KSA.

PATIENTS AND METHODS

For this cross-sectional study, which was conducted in a tertiary care centre in Al Khobar, KSA, data were collected in a ten-year period (January 2008 to December 2018). The study included all patients who underwent ACL reconstruction using either semitendinosus (semi-T) or bone-tendon bone (BTB) autograft/allograft. Patients' demographics and other variables related to the injury and surgery were obtained via an electronic file system. Three

hundred and two patients were included, and 13 patients were excluded due to missing data, so the total cohort was 289. An institutional review board approval was granted for the study.

Methods

The rate of isolated anterior cruciate ligament tear, multi-ligamentous tears and associated meniscal injuries were compared between normal BMI and elevated BMI groups in conjunction with baseline variables. Multi-ligamentous tears were defined as an ACL tear plus one or more of the following: medial collateral ligament, the lateral collateral ligament and posterior cruciate ligament tears. The collected data included the date of admission, duration of injury and date of surgery, along with height (m) and weight (kg) represented by the BMI.

The sample was categorized into three main categories, based on WHO classification of BMI, the normal BMI group (17.9-24.9), overweight (25-29.9) and obese group. The obese group included the three main classes: Class I for BMI between (30- 34.9), Class II BMI between (35- 39.9) and Class III for BMI of 40 and above. Mechanisms of injury involving the type of sport, either contact sports (e.g., football and basketball), non-contact sports (e.g., jogging and jumping) or non-sport injuries (e.g., falls) were considered. The presence or absence of surgical revision was documented.

Statistical analysis

The data were described using numbers and percentages for all categorical variables. The relationship between the BMI level and baseline characteristics of patients was conducted using the χ^2 test. The $p < 0.05$ was accepted as the significant level for all statistical tests. Univariate and multivariate regression analysis had been conducted as well to predict the likelihood effect of the BMI $\geq$ 25 kg/m² against the significant variables drawn from the cross tabulation where the unadjusted and adjusted odds ratio (OR) as well as 95% confidence interval (CI) were also being reported.

RESULTS

The age range of 289 patients was 12-55 years old (mean 28.3 ± 7.5). Nearly all patients were males, 284 (98.3%). Injuries were mostly due to sport activities, 201 (69.6%), while 88 (30.4%) were due to

non-sport. The mean BMI was 27.6 (SD 4.8). Based on BMI classification, 86 (29.8%) patients had normal BMI, 116 (40.1%) were overweight and the 87 (30.1%) were obese. Three out of four patients had the ACL injury for the first time. Most patients had an isolated ACL injury, 110 (38.1%). Combined ACL with medial meniscus injury accounted for 97 (33.6%) patients. The ACL with lateral meniscus injury accounted for 26 (9%), and ACL with both menisci were 32 (11 %). The relationship between the level of BMI and baseline characteristics of patients showed that the mode of injury ($p=0.018$) isolated ACL injury ($p=0.003$), and ACL injury type ($p=0.007$) significantly influence the level of BMI (Table 1).

Table 1. Relationship between the level of body mass index (BMI) and clinical characteristics of 289 patients with anterior cruciate ligament (ACL) injury

Variable	N (%) of patients			p
	Total (n=289)	Elevated BMI (≥ 25 kg/m ²) (n=203)	Normal BMI (<25 kg/m ²) (n=86)	
Age group				
≤30 years	193 (66.7)	128 (63.1)	65 (75.6)	0.039
>30 years	96 (33.2)	75 (36.9)	21 (24.4)	
Gender				
Male	284 (98.3)	198 (97.5)	86 (100)	0.142
Female	5 (01.7)	05 (02.5)	0	
Type of sports				
Football	190 (65.7)	121 (59.6)	69 (80.2)	0.001
Non-football	99 (34.2)	82 (40.4)	17 (19.8)	
Leg injured				
Left	129 (44.6)	92 (45.3)	37 (43.0)	0.595
Right	158 (54.7)	109 (53.7)	49 (57.0)	
Both	2 (0.70)	02 (01.0)	0	
Isolated				
Isolated	113 (39.1)	68 (33.5)	45 (52.3)	0.003
Combined	176 (60.9)	135 (66.5)	41 (47.7)	
Type of injury				
Sport	201 (69.6)	130 (64.0)	71 (82.6)	0.002
Non-sport	88 (30.4)	73 (36.0)	15 (17.4)	
Classification of injury				
Contact	97 (33.6)	65 (32.0)	32 (37.2)	0.393
Non-contact	192 (66.4)	138 (68.0)	54 (62.8)	
Mechanism of injury				
Fall	37 (12.8)	31 (15.3)	06 (07.0)	0.146
Twisting	163 (56.4)	110 (54.2)	53 (61.6)	
Trauma	89 (30.8)	62 (30.5)	27 (31.4)	
Type of graft				
Semi-T	269 (93)	189 (94.0)	80 (93.0)	0.747
BTB	20 (6.9)	14 (06.0)	06 (07.0)	
Source of graft				
Autograft	284 (98.2)	198 (98.5)	86 (100)	0.255
Allograft	05 (1.7)	05 (01.5)	0	
Mode of injury				
Reinjured	74 (25.6)	60 (29.6)	14 (16.3)	0.018
Non-reinjured	215 (74.4)	143 (70.4)	72 (83.7)	
ACL type				
Isolated ACL	110 (38.1)	67 (33.0)	43 (50.0)	0.007
Non-isolated ACL	179 (61.9)	136 (67.0)	43 (50.0)	

BMI, body mass index; Semi-T, semitendinosus; BTB, bone-tendon bone; ACL, anterior cruciate ligament

The results of univariate analysis predicted that those who had reinjured ACL were 2.16 times more likely in the elevated BMI group (UOR=2.16; 95% CI=1.13–4.12; $p=0.020$). After conducting multivariate for the latter, the risk decreased to 1.97 (AOR=1.97; 95% CI=1.00–3.85; $p=0.049$). For ACL type, the risk of injury in elevated BMI group in the non-isolated ACL group was 2.03 times higher than those with isolated ACL (UOR=2.03; 95% CI=1.21–3.39; $p=0.007$) (Table 2).

Table 2. Univariate and multivariate regression analysis to determine independent significant factors associated with body mass index (BMI ≥ 25 kg/m²) in 289 patients with anterior cruciate ligament injury

Variable	UOR (95% CI)	p	AOR (95% CI)	p
Age group				
≤30 years	Ref		Ref	
>30 years	1.81 (1.03–3.20)	0.040	1.61 (0.89–2.92)	0.115
Type of sports				
Football	0.36 (0.19–0.66)	0.001	1.92 (0.69–5.26)	0.206
Non-football	Ref		Ref	
Isolated				
Isolated	Ref		Ref	
Combined	2.18 (1.30–3.64)	0.003	1.66 (0.67–4.12)	0.271
Type of Injury				
Sport	2.66 (1.42–4.97)	0.002	0.74 (0.26–2.12)	0.575
Non-sport	Ref		Ref	
Mode of injury				
Reinjured	2.16 (1.13–4.12)	0.020	1.97 (1.00–3.85)	0.049
Non-reinjured	Ref		Ref	
ACL type				
Isolated ACL	Ref		Ref	
Non-isolated ACL	2.03 (1.21–3.39)	0.007	1.33 (0.54–3.32)	0.535

UOR, unadjusted Odds Ratio; AOR, adjusted Odds Ratio; CI, Confidence Interval, Ref, reference category

DISCUSSION

Our study focused on addressing the association between elevated BMI and ACL injury. Understanding the association between these variables in this study is crucial. Obesity is a major public health problem that causes burden on the patient and the society affecting a large number of countries worldwide (13). The overall world prevalence of obesity and overweight in the KSA was 35.6% and 36.9%, respectively, that makes 72.5% of the population falling in either overweight or obese category (11). Surprisingly, in our study obese and overweight patients were 30.1% and 40.1% of the study's population respectively, which accounted for 70.2 % of the total number.

Thein et al. reported that increased BMI in both genders is associated with an elevated prevalence of knee injuries, but it was more significant in females in terms of having more associated meniscal and ligamentous injuries (8). In our study,

most of the patients were male accounting for 98.3%; that makes it difficult to draw a statistical conclusion because the sample is not representative for the gender.

In our study, the patients with high BMI were more prone to develop non-isolated ACL injuries than isolated ACL compared to patients with normal BMI ($<25 \text{ kg/m}^2$). Also, there was a significant difference in the reinjury rate, which was significantly less in the group with normal BMI. This was the only significant finding after adjustment to confounders. The risk of ACL tears and particularly combined ACL tears were significantly higher across the high BMI group.

A recent systematic review showed that the non-contact injuries in the patients with normal BMI account for 49%, while in the elevated BMI, the non-contact injuries reach 40% indicating no significant difference between the two groups (6). Al Jassir et al. have found that the BMI was not counted as a risk factor of injury; their study did not include ACL cases with traumatic injuries, partial tear, revision ligament surgery, multi-ligamentous injury and patients with current or old hamstring injuries (14). In contrary, all first and reinjured patients with contact and non-contact injuries were included in our study. In a study by Ballal et al. on the functional outcome of primary ACL reconstruction with hamstring graft, there was no significant difference between the patients with normal and high BMI in terms of mean age, postoperative length of stay or injury mechanism (15).

Our research focused on the role of elevated BMI and its relationship to ACL injury. As BMI is one of the modifiable factors, understanding the relationship between these variables will give us a clue to improve the prevention strategies of ACL injuries. In Bojicic et al. study, sagittal magnetic resonance (MRI) images had been collected and specific radiological measurements had been quantified in addition to patients' demographic data suggesting that high BMI was associated with a risk of developing ACL injury in presen-

ce of increased value of lateral posterior tibial slope (16). Derraik et al. reported an association between patients with elevated BMI and the progressive decrease in physical functions, therefore, such a deficit can include patients who suffer from orthopaedic diseases such as ACL injuries (17). Identifying and understanding the risk factors and the mechanism of ACL injury are of great importance for the patients and clinicians as it helps to design neuromuscular training programs for athletes (18).

ACL injury can cause knee joint instability leading ultimately to cartilage damage and the development of knee osteoarthritis (19,20).

Our study showed that the patients with an elevated BMI had a higher risk for developing isolated as well as non-isolated ACL tear.

A limitation of our study is that BMI was only measured at the time of hospital admission and may not indicate the true BMI measure at the time of injury. The study did not differentiate between partial or complete ACL injuries. Also, the sampling design of this study was non-probability sampling based on the patients who visited the medical centre. Moreover, both partial and complete tears were considered and submitted together.

In conclusion, understanding the association between an elevated BMI and ACL injury is important in the implementation of appropriate preventive measures. Recent literature suggests having an elevated BMI is a modifiable risk factor for ACL injury. Many questions remain unanswered, including the type of body fat mass versus the lean and how much is the hazardous amount of weight gain, all these questions could be the target of future research.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

REFERENCES

1. Hagmeijer M, Hevesi M, Desai V, Sanders T, Camp C, Hewett T, Stuart M, Saris D, Krych A. Secondary meniscal tears in patients with anterior cruciate ligament injury: relationship among operative management, osteoarthritis, and arthroplasty at 18-year mean follow-up. *Am J Sports Med* 2019; 47:1583-90.
2. Barth K, Lawton C, Touhey D, Selley R, Li D, Balderama E, Nuber G, Hsu W. The negative impact of anterior cruciate ligament reconstruction in professional male footballers. *Knee* 2019; 26:142-148.

3. Gordon A. Anterior cruciate ligament injuries. In: Garrik JG, editor. *Orthopaedic Knowledge Update Sports Medicine 3*. Rosemont, IL: American Academy of Orthopaedic Surgeons, 2004; 169.
4. Dauty M, Crenn V, Louguet B, Grondin J, Menu P, Fouasson-Chailloux A. Anatomical and neuromuscular factors associated to non-contact anterior cruciate ligament injury. *J. Clin Med* 2022; 11:1402.
5. Uhorchak JM, Scoville CR, Williams GN, Arciero RA, St Pierre P, Taylor DC. Risk factors associated with noncontact injury of the anterior cruciate ligament: a prospective four-year evaluation of 859 West Point cadets. *Am J Sports Med* 2003; 31:831-42.
6. Pfeifer CE, Beattie PF, Sacko RS, Hand A. Risk factors associated with non-contact anterior cruciate ligament injury: a systematic review. *Int J Sports Phys Ther* 2018;13:575-87.
7. Ulusoy G, Kızılgöz V, Sivrioğlu A. Relationship between body mass index and articular injuries accompanying primary anterior cruciate ligament tear in male knees: a retrospective observational study. *J knee Surg* 2022; 33:1156-62.
8. Thein R, Hershkovich O, Gordon B, Burstein G, Tenenbaum S, Derazne E, Shamis A, Afek A, Kreiss Y. The prevalence of cruciate ligament and meniscus knee injury in young adults and associations with gender, body mass index, and height a large cross-sectional study. *J Knee Surg* 2017; 30:565-70.
9. Noyes FR, Mooar PA, Matthews DS, Butler DL. The symptomatic anterior cruciate-deficient knee. Part I: the long-term functional disability in athletically active individuals. *J Bone Joint Surg Am* 1983; 65:154-62.
10. Hermassi S, Hayes LD, Schwesig S. Can body fat percentage, body mass index, and specific field tests explain throwing ball velocity in team handball players? *App Sci* 2021;11:3492.
11. WHO Expert Committee on Physical Status : the Use and Interpretation of Anthropometry (1993 : Geneva, Switzerland) & World Health Organization. (1995) Physical status : the use of and interpretation of anthropometry , report of a WHO expert committee. World Health Organization. <https://apps.who.int/iris/handle/10665/37003> (23 October 2022)
12. Al-Othaimeen AI, Al-Nozha M, Osman AK. Obesity: an emerging problem in Saudi Arabia. *East Mediterr Health J* 2007; 13:441-8.
13. Agha M, Agha R. The rising prevalence of obesity: part A: impact on public health. *Int J Surg Oncol* 2017; 2:17
14. ALJassir F, Nasser A, Bin Khidhr R. The anthropometric measurements as predisposing factor for non-contact anterior cruciate ligament injury in middle-aged women. *Saudi Journal of Sports Medicine* 2018; 18:67-70.
15. Ballal MS, Khan Y, Hastie G, Hatcher A, Coogan S, McNicholas MJ. Functional outcome of primary hamstring anterior cruciate ligament reconstruction in patients with different body mass index classes. *Arthroscopy* 2013; 29:1314-21.
16. Bojicic KM, Beaulieu ML, Imaizumi Krieger DY, Ashton-Miller JA, Wojtys EM. Association between lateral posterior tibial slope, body mass index, and ACL injury risk. *Orthop J Sports Med* 2017; 5:2325967116688664.
17. Derraik JG, de Bock M, Hofman PL, Cutfield WS. Increasing BMI is associated with a progressive reduction in physical quality of life among overweight middle-aged men. *Sci Rep* 2014; 4:3677.
18. Shimokochi Y, Shultz SJ. Mechanisms of noncontact anterior cruciate ligament injury. *J Athl Train* 2008; 43:396-408.
19. Webster K, Hewett TE. Anterior cruciate ligament injury and knee osteoarthritis: an umbrella systematic review and meta-analysis. *Clin J Sport Med* 2022; 32:145-52.
20. Ripani U, Manzarbeitia-Arroba P, Guijarro-Leo S, Urrutia-Graña J, De Masi-De Luca A. Vitamin C may help to reduce the knee's arthritic Symptoms. Outcomes assessment of nutraceutical therapy. *Med Arch* 2019; 73:173-7.

Computer-assisted navigation for intramedullary nailing of intertrochanteric femur fractures: a preliminary result

Michele Coviello¹, Francesco Ippolito², Antonella Abate², Giacomo Zavattini¹, Domenico Zaccari¹, Andrea Leone¹, Giovanni Noia³, Vincenzo Caiaffa², Giuseppe Maccagnano³

¹Department of Basic Medical Science, Neuroscience and Sensory Organs, Azienda Ospedaliero Universitaria Consorziata Policlinico, Bari, ²Orthopaedic and Traumatology Unit, "Di Venere" Hospital, Via Ospedale di Venere, Bari, ³Orthopaedics Unit, Department of Clinical and Experimental Medicine, Faculty of Medicine and Surgery, University of Foggia, Policlinico Riuniti di Foggia, Foggia; Italy

ABSTRACT

Aim To demonstrate a reduction of risk factors ray-depending in proximal femur nailing of intertrochanteric femur fractures, comparing standard technique with computer-assisted navigation system.

Methods One hundred patients hospitalised between October 2021 and June 2022 with intertrochanteric femur fractures type 31-A1 and 31-A2 were prospectively enrolled and divided randomly into two groups. A study group was treated with computer-assisted navigation system ATLAS (Masmec Biomed, Modugno, Bari, Italy) (20 patients), while a control group received the standard nailing technique. The same intertrochanteric nail was implanted by a single senior surgeon, Endovis BA 2 (EBA2, Citieffe, Calderara di Reno, Bologna, Italy). The following data were recorded: the set-up time of operating room (STOR; minutes); surgical time (ST; minutes); radiation exposure time (ETIR; seconds) and dose area product (DAP; cGy·cm²).

Results Patients underwent femur nailing with computer-assisted navigation system reported more set-up time of operating room (24.87 ± 4.58 ; $p < 0.01$), less surgical time (26.15 ± 5.80 ; $p < 0.01$), less time of radiant exposure (4.84 ± 2.07 ; $p < 0.01$) and lower dose area product (16.26 ± 2.91 ; $p < 0.01$).

Conclusion The preliminary study demonstrated that computer-assisted navigation allowed a better surgical technique standardization, significantly reduced exposure to ionizing radiation, including a reduction in surgical time. The ATLAS system could also play a key role in residents improving learning curve.

Key words: computer-assisted surgery, fluoroscopy, internal fixation, intertrochanteric fracture, nailing

Corresponding author:

Michele Coviello
Department of Basic Medical Science,
Neuroscience and Sensory Organs,
Azienda Ospedaliero
Universitaria Consorziata Policlinico
Piazza Giulio Cesare, 11, 70124 Bari, Italy
Phone: +39 393 816 5088;
Fax: +39 080 501 5702;
E-mail: michelecoviello91@gmail.com
ORCID ID: <https://orcid.org/0000-0003-3585-1000>

Original submission:

19 October 2022;

Accepted:

17 November 2022

doi: 10.17392/1549-22

INTRODUCTION

Intertrochanteric fractures represent the most frequent elderly fractures that an orthopaedic surgeon may encounter in his daily practice (1), more than wrist and shoulder fractures (2). Elderly people (> 65 years old) are most affected by this fracture and the simultaneous presence of other comorbidities, such as osteoporosis, makes the management more complicated (3-5). Obesity also represents an important risk of fracture than normal-weight due to metabolic factors and increased risk of falls (6). Due to the biomechanical advantages and the soft tissue respect, intramedullary nailing has proven to be the most widely used device in the treatment of the disease (7, 8). Bone healing, early mobilization and full weight bearing restored as soon as possible are the main surgery goals (9, 10). Over the years, the need for less invasive, faster procedures and concerns about the effects of radiation exposure (11) have been the main drivers for the evolution of computer-assisted surgery, which is finding various fields of application (7).

Computer-assisted navigation systems have been successfully used in several orthopaedic surgical procedures, including spine and total hip/knee replacement (12-14). It has been also studied in some trauma surgical procedures, i.e. percutaneous screw implant for medial femoral neck fractures and acetabular fractures (15-17). Three-dimensional (3D) reconstruction surgical instruments tracking real time and novel devices within a surgical field are just some of the salient features of computer assisted surgery, which often simplify some surgical phases as in achieving a correct positioning of the guide wire through the femoral neck (18).

The aim of this study was to describe the preliminary results of a new navigated intramedullary system and to compare it with fluoroscopy guided traditional procedure as a proximal femur treatment, highlighting the differences between the two procedures in terms of preoperative setting and variations in ionizing radiation received.

PATIENT AND METHODS

Patient and study design

All patients hospitalized at the Orthopaedic and Traumatology Unit, "Di Venere" Hospital in Bari, due to intertrochanteric femur fractures during

the period from October 2021 to June 2022, were involved in this prospective observational study according to the recommended STROBE guidelines (19). Inclusion criteria were: diagnosis of an intertrochanteric femur fracture (AO Classification 31-A1 or 31-A2) (20) and low energy mechanism of injury (i.e. fall from standing, twist). Exclusion criteria were: less than 18 years, high energy mechanism of injury (e.g. motor vehicle accident, fall from height), open fracture, multiple injuries to the lower extremity, refused to give written consent, need for open reduction. The patients were divided into two groups using a predefined program (<http://www.randomization.com>). Prior to the surgery, the circulating nurse reviewed the random-numbers list. A study group was represented by patients who were treated with computer-assisted navigation of intramedullary nailing and a control group included patients treated with the standard nailing technique.

For each patient, the following data were recorded: age, gender, BMI (body mass index), side of surgery, time to surgery, fracture classification (20), American Society of Anesthesiologists Score (ASA) (21), the set-up time of operating room (STOR), surgical time (ST), radiation exposure time (ETIR) and dose area product (DAP).

Demographic data were recorded at patient admission, while studied outcomes were collected after surgery.

The study was approved by the local Ethics Committee of the Faculty of Medicine, University of Bari. An informed consent was obtained from all study participants before the data collection.

Methods

All procedures were done by single senior orthopaedic trauma surgeons with more than 10 years of intertrochanteric procedures experience. All procedures were performed under spinal anaesthesia. The patient was placed on a traction bed. The closed reduction was performed, under C-arm control, to restore the anatomical position of fragments. The control group received standard EBA2 nailing (Citieffe, Calderara di Reno, Bologna, Italy). The first step of the surgical procedure was a small proximal incision at the greater trochanter level. Using manufacturer's instruments, the trochanteric hole was made to insert the guide pin and successively the femur

nail. Two cephalic screws were inserted after measurements. The distal locking screw was applied if necessary. The final position of the fragments and the implant were controlled with uniplanar fluoroscopy in AP and lateral views. The same views were used for the first postoperative radiographs. A standardized operative technique was used following the manufacturer's instructions. All these steps require fluoroscopy.

The ATLAS system (Masmec Biomed, Modugno, Bari, Italy) is a computer-assisted navigation for intramedullary nailing using the same surgical steps of the EBA2 standard, but does not require fluoroscopy, except for the correct close initial reduction. Firstly, the navigation system scans two radiographic images acquired after reduction (i.e. anteroposterior and axial hip views). The ATLAS system is composed of a viewer (i.e. an infrared ray's emitter and receiver), sensors (spheres that reflects infrared rays), a processing and display unit (a computer that elaborates data acquired (Figure 1) and supports for specific sensors for each surgical instrument (Figure 2A), the patient (Figure 2B) and C-ARM (Figure 2C).

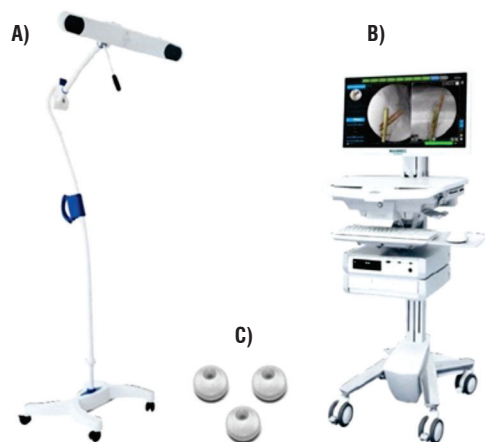


Figure 1. Computer-assisted navigation system. A) viewer; B) sensors; C) processing unit (Di Venere Hospital, 2022)

Due to infrared rays the system locates the patient and surgical instruments in space. The processing unit elaborates the fluoroscopic images acquired after the reduction to navigate the subsequent surgical steps without further fluoroscopic rays.

The Endovis BA 2 (EBA2) Citieffe nail is made of titanium alloy and is 180 mm long with a metaphyseal angle of 5° a proximal diameter of 13.5 mm and a distal diameter of 10 mm. It has two oblique screws with a self-drilling cervico-cephalic angle of 130° for proximal locking, thereby preventing

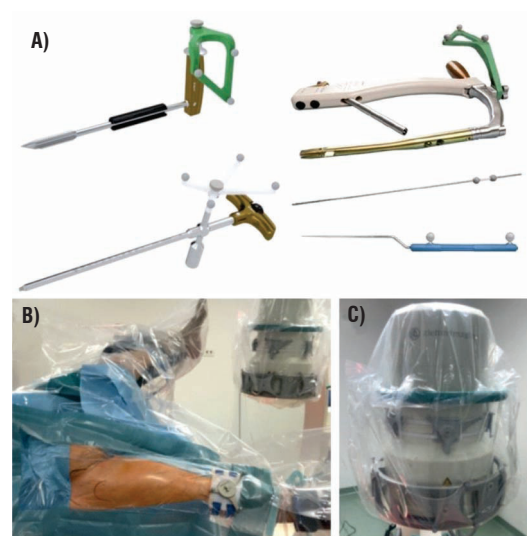


Figure 2. Computer-assisted navigation system. A) specific sensors implemented for each instrument; B) support for patient specific sensors; C) support for C-ARM specific sensors (Di Venere Hospital, February 2022)

the rotation of the femoral head and neck. The distal end of the nail consists of a 4-ray 30-mm “diapason”, which offers gradual reduction in stiffness and reduces stress shielding (22).

Preoperative and postoperative x-rays as an example of the procedure are illustrated in Figure 3.

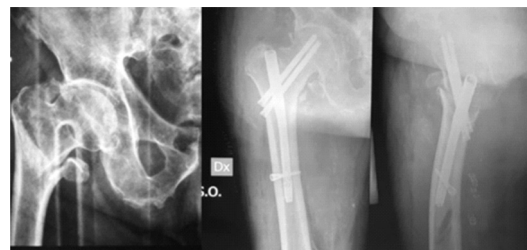


Figure 3. Preoperative and postoperative x-ray views of intertrochanteric femur nailing (Di Venere Hospital, 2022)

As a primary endpoint, the radiation exposure time was analysed to detect if computer-assisted navigation reduces the radiation risk for the patient and surgical team. The set-up time of operating room, surgical time and dose area product were assessed as a secondary endpoint.

Statistical analysis

Descriptive statistics were calculated for the overall sample and for follow-up. Categorical variables were presented as numbers or percentages. Continuous variables were presented as mean and standard deviation (SD). Due to the non-homogeneous distribution of the values using the Kolmogorov-Smirnov test ($p > 0.05$), non-parametric tests were considered. To compare avera-

ge values between the groups at the same times, the U Mann–Whitney test or Fischer’s test were used, when appropriate.

RESULTS

One hundred consecutive patients who underwent intertrochanteric femur fractures were enrolled in this study and allocated into two groups, 20 patients in the study group and 80 patients in the control group. The study group mean age was 84.42 ± 9.68 years with 13 (65%) females, and BMI of 22.38 ± 4.84 kg/m². The control group was made up of 80 patients, mean age 83.48 ± 9.23 years, 54 (67.5%) females, and BMI of 24.25 ± 5.87 kg/m² (Table 1). No statistical differences emerged between the groups according to preoperative features.

Table 1. Characteristics of the study population

Variable	Study group (20 patients)	Control group (80 patients)	P
Age (mean±SD) (years)	84.42±9.68	83.48±9.23	0.53
Gender (female) (No; %)	13 (65)	54 (67.5)	0.51
BMI (mean±SD) (Kg/m ²)	22.38±4.84	24.25±5.87	0.17
Side (left) (No; %)	9 (45)	41 (51.2)	0.80
Surgical time (minutes) (mean±SD)	38.67±4.12	40.19±3.26	0.12
Fracture classification (No; %)			0.60
31-A1	8 (40)	32 (40)	
31-A2	12 (60)	48 (60)	
ASA Classification	2.91±0.59	3.06±0.49	0.26

BMI, body mass index; ASA Classification, American Society of Anesthesiologists Classification

All the patients were treated within 48 hours after admission according to the Italian Society of Orthopaedics and Traumatology recommendation (23).

The study group had more set-up time of operating room (24.87 ± 4.58) ($p < 0.01$), less surgical time (26.15 ± 5.80) ($p < 0.01$), less time of radiant exposure (4.84 ± 2.07) ($p < 0.01$) and lower dose area product (16.26 ± 2.91) ($p < 0.01$) (Table 2).

Table 2. Differences in studied outcomes between the groups*

Outcome	Study group	Control group	p
STOR (minutes)	24.87±4.58	18.08±3.66	< 0.01
ST (minutes)	26.15±5.80	33.40±8.58	< 0.01
ETIR (seconds)	4.84±2.07	58.08±21.99	< 0.01
DAP (cGy·cm ²)	16.26±2.91	149.58±55.60	< 0.01

*mean±SD

STOR, the set-up time of operating room; ST, surgical time; ETIR, radiation exposure time; DAP, dose area product

None of the patients experienced any skin complications. None of the patients needed revision surgery due to infection or mechanical complication in the early period. No intraoperative complication was recorded.

DISCUSSION

Over the past several years, an increasing number of intertrochanteric femur fractures has been reported with intramedullary fixation representing the gold standard treatment (24). The internal fixation with intramedullary nailing allows early mobilization and early weight-bearing of the patient due to the respecting the biology of the fracture (25, 26). Indeed, David et al. conducted a study comparing three different fixation methods in trochanteric fractures, finding higher inflammatory markers in a patient treated with dynamic hip screw (DHS) plate osteosynthesis despite the treatment of the patient with an intramedullary nail (27). Furthermore, Vitamin C also may have a key role in reducing the patient’s inflammatory state (28). The fracture displacement, lack of fracture site direct visualization and unstable bare-handed operation can also make it difficult to select the trochanteric entry point (29,30). Repositioning the guide wire through repeated punctures can lead to the loss of fracture reduction (30), disruption of surrounding soft tissue structures and increased blood loss (31), although the use of intraoperative tranexamic acid may help in reducing bleeding (32). All these extra steps prolong the operation time, increase surgical complication rates and expose both surgeons and patient to more radiation (33). With the computer-assisted navigation system, internal fixation of the fracture can obtain the best surgical efficiency and accuracy, less surgical injury and reduction of radiation exposure (34). Although we demonstrated the set-up time of the operating room was higher in the study group due to the more complex preparation of surgical instrument, the guided system showed some advantages compared with conventional fluoroscopy-guided nails; the analysis conducted on the computer-assisted navigated procedure highlighted a statistically significant reduction of ETIR and DAP. These results were predictable because the only two fluoroscopy views were at the beginning of surgery. Hayda et al. reviewed a significant correlation between radiation exposure time, DAP and cancer or cataract risk in orthopaedic surgeons (35). This is in accordance with Matityhau et al. review identifying spinal surgery and intramedullary nailing as the procedure with the highest exposure to ionising radiation (36). We demonstrated the ATLAS nailing system significantly reduced the radiation exposure time

of about 12-fold, and the DAP of about 9-fold if compared with control group. Interestingly, our results showed the highest DAP value recorded during EBA2 standard nail surgery is 205 cGy·cm², whereas during the ATLAS implantation the maximum recorded DAP was 19 cGy·cm²; on the other hand, in the study group, set-up time was longer than standard procedures because of the installation of a sensor for each surgical instrument including C-Arm and the positioning of the viewer and display unit. Nevertheless, we assume that the set-up time may decrease over time as the surgeon and theatre operators gain experience, actually our last registered measurements were lower while the first were the highest.

We deliberately, included the first twenty records of each outcome in this preliminary study, avoiding biasing the results with a trial phase. The surgical time reduction within the study group reported by a single senior surgeon may be considered independent of operator's surgical skills. The mean EBA2 standard nail surgical time was higher than the ATLAS group in the present study. Similar results were found by Honl et al. which analysed how assisted navigation procedure was faster than the classic one (37). Furthermore, the navigated nailing system could have a key role in the residents' learning curve for intertrochanteric fractures intramedullary nailing (38). This system permits to avoid intra-operative technical mistakes and may provide real-time operative views and relative positioning of surgical instruments, thus better understanding the three-dimensional anatomy of the surgical procedure (39,40). Currently, we scheduled a study about the role of the ATLAS nailing system in orthopaedic residents' learning curves in order to fully understand the educational potential of this innovative surgical device.

This study has some limitations. The sample size was limited, and the groups were not homoge-

neous. Postoperative radiographic outcomes such as tip-apex distance or clinical scores at different follow ups were not evaluated.

On the other hand, we preliminarily presented a new computer-assisted navigation for intramedullary nailing never described before, which has proven effective and safe in the data observed. Furthermore, we reported the first twenty recorded measurements avoiding biasing due to a pilot phase, demonstrating the system reproducibility, and also we performed a rigorous method of patient selection with inclusion/exclusion criteria. Our results should be confirmed by a large sample size-controlled study.

Further studies will be necessary to assess the accuracy of the surgical procedure taking into account objective parameters such as tip-apex distance or tip-to-head-surface distance.

In conclusion, despite the small study group, the present preliminary study highlights a reduction in surgical time, exposure time to ionizing radiation and reduction of dose area product. The ATLAS system reduces the time lost in searching for the correct positioning of the device and improves implantation accuracy. In contrast, the assisted procedure requires more set-up time of operating room. The ATLAS system is a simple, intuitive and innovative surgical device that can revolutionise the management of intertrochanteric femoral fractures in the future. Furthermore, cost analysis is necessary to evaluate the feasibility of the computer-guided procedure and its impact on patient outcomes compared to the standard surgery.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

1. Carvajal-Pedrosa C, Gómez-Sánchez RC, Hernández-Cortés P. Comparison of outcomes of intertrochanteric fracture fixation using percutaneous compression plate between stable and unstable fractures in the elderly. *J Orthop Trauma* 2016; 30:e201-e6.
2. Maccagnano G, Solarino G, Pesce V, Vicenti G, Coviello M, Nappi VS, Giannico OV, Notarnicola A, Moretti B. Plate vs reverse shoulder arthroplasty for proximal humeral fractures: The psychological health influence the choice of device? *World J Orthop* 2022; 18:297-306.
3. Rinonapoli G, Ruggiero C, Meccariello L, Bisaccia M, Ceccarini P, Caraffa A. Osteoporosis in men: a review of an underestimated bone condition. *Int J Mol Sci* 2021; 22:2105.
4. Bisaccia MRG, Meccariello L, Ripani U, Pace V, Rollo G, Ibáñez-Vicente C, Bisaccia O, Gómez-Garrido D, Guijarro-Leo S, De Masi De Luca A, Caraffa A. Osteoporosis in male patients: epidemiology, clinical aspects and DEXA scan assessment. *Clin Cases Miner Bone Metab* 2019; 16:31-5.

5. Gupta RK, Gupta V, Gupta N. Outcomes of osteoporotic trochanteric fractures treated with cement-augmented dynamic hip screw. *Indian J Orthop* 2012; 46:640-5.
6. Rinonapoli G, Pace V, Ruggiero C, Ceccarini P, Bisaccia M, Meccariello L, Caraffa A. Obesity and bone: a complex relationship. *Int J Mol Sci* 2021; 22:13662.
7. Zhang Y, Zhang S, Wang S, Zhang H, Zhang W, Liu P, Ma J, Pervaiz N, Wang J. Long and short intramedullary nails for fixation of intertrochanteric femur fractures (OTA 31-A1, A2 and A3): A systematic review and meta-analysis. *Orthop Traumatol Surg Res* 2017; 103:685-90.
8. Lanzetti RM, Caraffa A, Lupariello D, Ceccarini P, Gambaracci G, Meccariello L, Manfreda F, Maiettini D, Vicente CI, Scialpi M, Bisaccia O, Rinonapoli G, Bisaccia M. Comparison between locked and unlocked intramedullary nails in intertrochanteric fractures. *Eur J Orthop Surg Traumatol* 2018; 28:649-58.
9. Kubiak EN, Beebe MJ, North K, Hitchcock R, Potter MQ. Early weight bearing after lower extremity fractures in adults. *J Am Acad Orthop Surg* 2013; 21:727-38.
10. Meccariello L, Bisaccia M, Ronga M, Falzarano G, Caraffa A, Rinonapoli G, Grubor P, Pace V, Rollo G. Locking retrograde nail, non-locking retrograde nail and plate fixation in the treatment of distal third femoral shaft fractures: radiographic, bone densitometry and clinical outcomes. *J Orthop Traumatol* 2021; 22:33.
11. Gowda SR, Mitchell CJ, Abouel-Enin S, Lewis C. Radiation risk amongst orthopaedic surgeons - Do we know the risk? *J Perioper Pract* 2019; 29:115-21.
12. Moretti L, Coviello M, Rosso F, Calafiore G, Monaco E, Berruto M, Solarino G. Current trends in knee arthroplasty: are Italian surgeons doing what is expected? *Medicina (Kaunas)*. 2022; 58.
13. Jones CW, Jerabek SA. Current role of computer navigation in total knee arthroplasty. *J Arthroplasty* 2018; 33:1989-93.
14. Zhang Q, Han XG, Xu YF, Fan MX, Zhao JW, Liu YJ, He D, Tian W. Robotic navigation during spine surgery. *Expert Rev Med Devices* 2020; 17:27-32.
15. Huntsman KT, Riggelman JR, Ahrendtsen LA, Ledonio CG. Navigated robot-guided pedicle screws placed successfully in single-position lateral lumbar interbody fusion. *Robot Surg* 2020; 14:643-7.
16. Figueroa F, Wakelin E, Twiggs J, Fritsch B. Comparison between navigated reported position and postoperative computed tomography to evaluate accuracy in a robotic navigation system in total knee arthroplasty. *Knee*. 2019; 26:869-75.
17. Ciolli G, Caviglia D, Vitiello C, Lucchesi S, Pinelli C, De Mauro D, Smakaj A, Rovere G, Meccariello L, Camarda L, Maccauro G, Liuzza F. Navigated percutaneous screw fixation of the pelvis with O-arm 2: two years' experience. *Med Glas (Zenica)* 2021; 18:309-15.
18. Crookshank MC, Edwards MR, Sellan M, Whyne CM, Schemitsch EH. Can fluoroscopy-based computer navigation improve entry point selection for intramedullary nailing of femur fractures? *Clin Orthop Relat Res* 2014; 472:2720-7.
19. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61:344-9.
20. Marsh JL, Slong TF, Agel J, Broderick JS, Creevey W, DeCoster TA, Prokuski L, Sirkin MS, Ziran B, Henley B, Audigé L. Fracture and Dislocation Classification Compendium - 2007. *J Orthop Trauma* 2007; 21:S1-S6.
21. Ryan SP, Politzer C, Green C, Wellman S, Bolognesi M, Seyler T. Albumin versus American Society of Anesthesiologists Score: which is more predictive of complications following total joint arthroplasty? *Orthopedics* 2018; 41:354-62.
22. Caiaffa V, Vicenti G, Mori C, Panella A, Conserva V, Corina G, Scialpi L, Abate A, Carrozzo M, Petrelli L, Picca G, Aloisi A, Rollo G, Filippini M, Freda V, Pansini A, Puce A, Solarino G, Moretti B. Is distal locking with short intramedullary nails necessary in stable pertrochanteric fractures? A prospective, multicentre, randomised study. *Injury* 2016; 47:S98-106.
23. Italian society of orthopaedics and traumatology. Proximal femur fractures in the elderly guidelines. <https://siot.it/wp-content/uploads/2022/01/LG-380-SIOT-Fratture-Femore-anziano-1.pdf> (11 November 2011)
24. Augat P, Bliven E, Hackl S. Biomechanics of femoral neck fractures and implications for fixation. *J Orthop Trauma* 2019; 33:S27-32.
25. Socci AR, Casemyr NE, Leslie MP, Baumgaertner MR. Implant options for the treatment of intertrochanteric fractures of the hip. *Bone & Joint* 2017; 99:128-33.
26. Ziranu A, Noia G, Cipolloni V, Coviello M, Maccaagnano G, Liuzza F, Maccauro G, Nasto LA, Pola E. Revision surgery using retrograde nail versus replating in nonunion distal femur fracture treated with plate. *Adv Orthop* 2022; 2022:1-8.
27. David GG, Michele B, Umberto R, Cioacă F, Andrea S, Alfonso C, Cristina IV, Maria ML, Antonio HJ, Giuseppe R, Luigi M. Metabolic shock in elderly pertrochanteric or intertrochanteric surgery. Comparison of three surgical methods. Is there a much safer? *Rom J Anaesth Intensive Care* 2020; 27:17-26.
28. Ripani U, Manzarbeitia-Arroba P, Guijarro-Leo S, Urrutia-Graña J, De Masi-De Luca A. Vitamin C may help to reduce the knee's arthritic symptoms. Outcomes assessment of nutraceutical therapy. *Med Arch* 2019; 73:173-7.
29. Duan S-j, Liu H-s, Wu W-c, Yang K, Zhang Z, Liu S-d. Robot-assisted percutaneous cannulated screw fixation of femoral neck fractures: preliminary clinical results. *Orthop Surg* 2019; 11:34-41.
30. Prasarn ML, Cattaneo MD, Achor T, Ahn J, Klinger CE, Helfet DL, Lorich DG. The effect of entry point on malalignment and iatrogenic fracture with the Synthes lateral entry femoral nail. *J Orthop Trauma* 2010; 24:224-9.
31. Lan H, Tan Z, Li Kn, Gao Jh, Liu Th. Intramedullary nail fixation assisted by orthopaedic robot navigation for intertrochanteric fractures in elderly patients. *Orthop Surg* 2019; 11:255-62.

32. Schiavone A, Bisaccia M, Inkov I, Rinonapoli G, Manni M, Rollo G, Meccariello L, Vicente CI, Ceccarini P, Ruggiero C, Caraffa A. Tranexamic acid in peritrochanteric femoral fracture: is it a safe drug or not? *Folia Med (Plovdiv)* 2018; 60:67-78.
33. Suero EM, Westphal R, Citak M, Hawi N, Liodakis E, Krettek C, Stuebig T. Robotic technique improves entry point alignment for intramedullary nailing of femur fractures compared to the conventional technique: a cadaveric study. *J Robot Surg* 2018; 12:311-5.
34. Liebergall M, Ben-David D, Weil Y, Peyser A, Mosheiff R. Computerized navigation for the internal fixation of femoral neck fractures. *J Bone Joint Surg Am* 2006; 88:1748-54.
35. Hayda RA, Hsu RY, DePasse JM, Gil JA. Radiation exposure and health risks for orthopaedic surgeons. *J Am Acad Orthop Surg* 2018; 26:268-77.
36. Matityahu A, Duffy RK, Goldhahn S, Joeris A, Richter PH, Gebhard F. The great unknown—a systematic literature review about risk associated with intraoperative imaging during orthopaedic surgeries. *Injury* 2017; 48:1727-34.
37. Honl M, Schwieger K, Gauck CH, Lampe F, Morlock MM, Wimmer MA, Wimmer MA, Hille E. Pfannenposition und Orientierung im Vergleich. *Orthopäde* 2005; 34:1131-6.
38. Myden CA, Anglin C, Kopp GD, Hutchison CR. Computer-assisted surgery simulations and directed practice of total knee arthroplasty: educational benefits to the trainee. *Comput Aided Surg* 2012; 17:113-27.
39. Takai H, Mizuta K, Murayama M, Nakayama D, Kii S, Hayai C, Takahashi T. Comparing the usefulness of a fluoroscopic navigation system in femoral trochanteric fracture for orthopaedic residents with the conventional method. *Injury* 2020; 51:1840-5.
40. Lee HW, Song SJ, Bae DK, Park CH. The influence of computer-assisted surgery experience on the accuracy and precision of the postoperative mechanical axis during computer-assisted lateral closing-wedge high tibial osteotomy. *Knee Surg Relat Res* 2019; 31:15.

Post-traumatic instability of the first metatarsophalangeal joint: a novel surgical technique of capsular reconstruction in a young kickboxer

Gianni Caizzi, Michele Coviello, Andrea Franchini, Flavia Riefoli, Florianna Palmiotto, Biagio Moretti

¹Department of Basic Medical Science, Neuroscience and Sensory Organs, Azienda Ospedaliero Universitaria Consorziale Policlinico, Bari, Italy

ABSTRACT

Aim To report a novel surgical technique of capsular reconstruction of post-traumatic instability of the first metatarsophalangeal joint (MTPJ).

Methods The clinical case is related to a 24-year-old male athlete whose clinical symptoms began with pain and spontaneous dislocation of the left first MTPJ during a kickboxing fight. He received conservative treatment (cryotherapy and rest) at first. Afterwards, he referred persistent hallux instability associated with moderate pain, despite normal anatomic alignment with no evidence of first ray deformity. Plain traditional x-rays of the left foot, magnetic resonance imaging (MRI), static and dynamic ultrasonography (US) and clinical tests were performed in order to diagnose capsular ligamentous structure lesions.

Results The plain x-rays showed *hallux abductus* angle of 3°. The MRI and US demonstrated a rupture of the lateral capsular ligamentous structures and detachment of the abductor tendon. The pull out medium-lateral of the capsule with the abductor suture was performed as a treatment for dynamic hallux varus deformity. At six-month follow up, the patient walked without lameness with complete active and passive range of motion and with a stable first MTPJ.

Conclusion The patient presented with the post traumatic instability of the first metatarsophalangeal joint treated with a novel surgical technique of capsular reconstruction. The patient returned to the full weight-bearing in only 2 months of rehab. To the best of our knowledge, the surgical correction proposed has not been previously described.

Key words: hallux varus, joint instability, metatarsophalangeal joint

Corresponding author:

Michele Coviello
Department of Basic Medical Science,
Neuroscience and Sensory Organs,
Azienda Ospedaliero Universitaria
Consorziale Policlinico
Piazza Giulio Cesare, 11, 70124 Bari, Italy
Phone: +39 393 816 5088;
Fax: +39 080 501 5702;
E-mail: michelecoviello91@gmail.com
Gianni Caizzi ORCID ID: <https://orcid.org/0000-0002-6048-0494>

Original submission:

03 June 2022;

Revised submission:

04 July 2022;

Accepted:

04 August 2022

doi: 10.17392/1505-22

Med Glas (Zenica) 2023; 20(1): 95-100

INTRODUCTION

Acquired hallux varus is an uncommon occurrence in foot pathology. The most common cause is iatrogenic following bunionectomy (1). Another less common etiology is trauma (1). The first metatarsal phalangeal joint (MTPJ) post-traumatic instability is a rare condition. Injury produces the rupture of the capsular-ligamentous structure of the joint (2). Hallux varus is studied as a triplane deformity consisting of medially deviated hallux in a varus rotation with the contraction of the interphalangeal joint (IPJ) (1). Trauma mechanism is typically in hyper plantarflexion-adduction of the hallux. Similar foot lesions in male boxers and professional and amateur dancers were described (2-3). Clinically, instability is complained as a sub-dislocation or dislocation of the hallux during active or passive range of motion (ROM), especially during dorsi-flexion (4).

Big toe and the first MTPJ are essential in load transfer while walking. Stability of the joint is guaranteed by the capsular-ligamentous complex; particularly, the abductor maintains alignment of the hallux, and it has a “lever” effect on the first metatarsal, it pushes the first metatarsal towards the second one acting in a parallel line with this bone and using the metatarsal head as a fulcrum. The hallux adductor balances the action of the abductor, with its two transverse and oblique ends (4).

Different techniques to reconstruct the joint stabilizers were described (1).

The aim of this study was to present a novel surgical technique to treat the first metatarsal phalangeal instability successfully managed in a young male kickboxer. To the best of our knowledge, the surgical correction proposed has not been previously described.

PATIENT AND METHODS

Patient and study design

A 24-year-old male athlete without other medical issues complained about pain and instability of the left hallux. The patient denied the use of drugs, smoking or alcohol. He referred foot injury in June 2020 during a kickboxing fight. His hallux was forced in flexion and adduction stuck on the ground. The patient reported medial hallux sub-

dislocation with pain, which spontaneously reduced within a few days. He went to the emergency department, where he received conservative treatment (cryotherapy and rest) at first. Afterwards, he referred persistent hallux instability associated with moderate pain, despite normal anatomic alignment with no evidence of first ray deformity.

Physical examination revealed a medial dislocation of the hallux during the switch in extension, both in passive and active ROM. The orthopaedic team planned further consultations and instrumental diagnostic investigations.

Methods

Vascular and neurologic examinations were performed and completed with a 10-cm visual analogue scale (VAS) (5), the short-form 36-item health survey (SF-36) (6), and the American Orthopedic Foot and Ankle Society ankle-hindfoot scale (AOFAS) (7). Imaging studies included a traditional X-ray (anteroposterior, lateral) in order to measure *hallux abductus* angle, MRI and static and dynamic ultrasonography (US) to investigate capsular ligamentous structure lesions. The latter was performed with the dynamic varus stress tests by a senior orthopaedic surgeon experienced in dynamic musculoskeletal ultrasound. The pull out medium-lateral of the capsule with the abductor suture was indicated as the treatment of choice for the dynamic hallux varus deformity. It was completed in September 2020.

After patient discussion about treatment options, risks and potential complications, as well as the postoperative management, the patient signed an informed consent. A written informed consent for the publication of their clinical details and/or clinical images was also obtained.

Surgical treatment

The patient was taken to the operating room and placed in a supine position. The surgical procedure was performed with troncular anaesthesia and using a pneumatic thigh tourniquet. The leg was sterilized up to the knee. Skin incision was made in line with the first interdigital space, just lateral to the first MTPJ. A dissection was performed down to the lateral structures of the joint. An inveterate lesion of the lateral capsule showing hypertrophic and fibrotic was reported. The detachment of the abductor tendon was identified (Figure 1). Varus

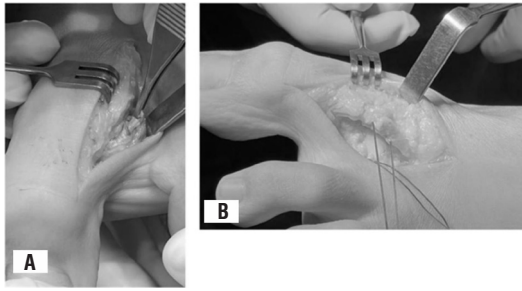


Figure 1. Surgical technique. A) Frontal view of detachment of abductor tendon; B) lateral view of detachment of abductor tendon (Policlinico Bari, September 2020)

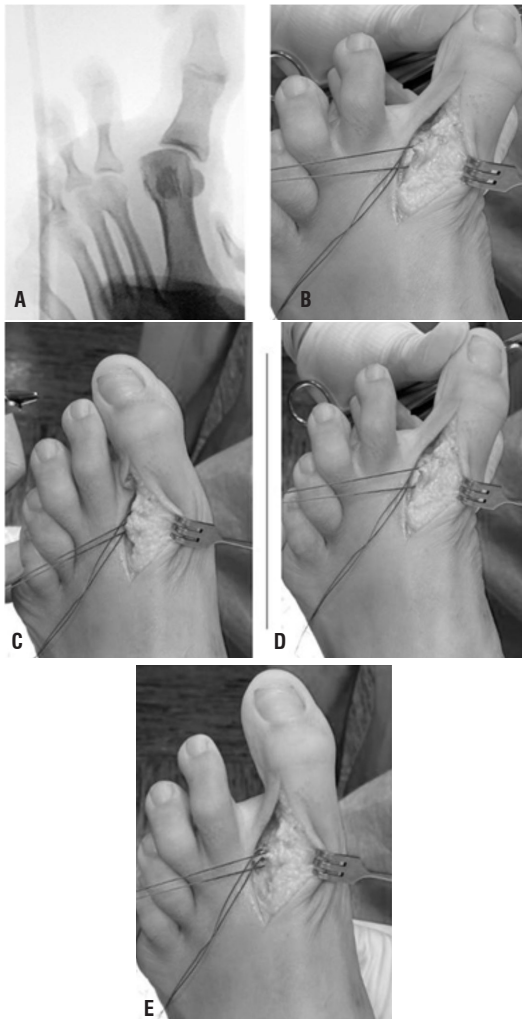


Figure 2. Intra-operative stress test and preparation of the lateral capsule. A) Varus stress test instability repeated under fluoroscopy; B) lateral capsule prepared with Vicryl 2.0 suture; C) tensioning of the system; D) varus stress test of the lateral capsule; E) valgus stress test of the lateral capsule (Policlinico Bari, September 2020)

stress test was repeated under fluoroscopy (Figure 2). Lateral capsule was prepared with Vicryl 2.0 suture (Ethicon Inc., Ohio, USA), and the tensioning of the system was tested (Figure 2). A pull out was made with a slotted Kirshner (K) wire, from

the metatarsal head following lateral-to-medial direction. The wire was locked with a button over the skin (Figure 3). Stability was checked with the varus-valgus stress tests under fluoroscopy - no instability found. Abductor tendon was re-inserted on the base of the proximal phalanx. Capsule was further tensioned with another Vicryl 2.0 suture. Then, C-arm images were performed once more: the hallux stability in varus stress test was confirmed. Hallux was splinted in syndactyly with the second toe and the patient had non-weight-bearing postoperative care regimen for 3 weeks. Skin sutures were removed 15 days postoperatively.

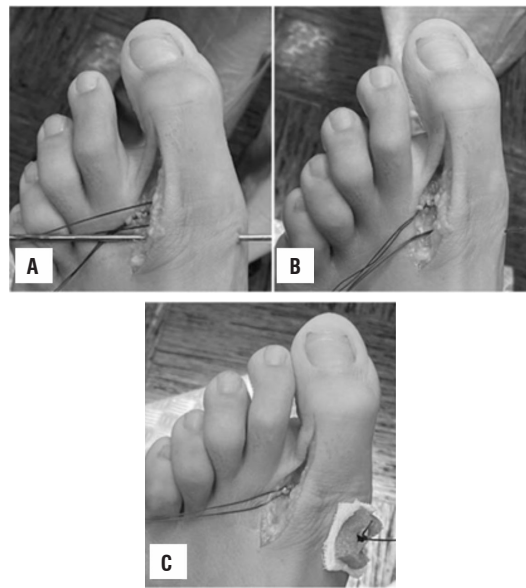


Figure 3. Pull-out technique. A) Slotted K-wire was passed through the base of the first metatarsal; B) the Vicryl suture was inserted medially; C) the button was used to fix the pull out (Policlinico Bari, September 2020)

RESULTS

Before surgery, vascular and neurologic examinations were unremarkable. The clinical scores were: VAS 6.5, SF-36 physical and mental components 31 and 33 respectively, and AOFAS scored 35. Palpatory pain was mainly localized on the lateral side of the first MTPJ. Traditional X-ray (Figure 4) showed correct alignment of the first MTPJ. The *hallux abductus* angle was 3°. Magnetic resonance imaging (Figure 4) and static and dynamic ultrasonography detected a rupture of the lateral capsular ligamentous structures and a detachment of the abductor tendon (Figure 4).

Three weeks after the surgery, splint was removed but syndactyly was maintained. Weight-bearing was indicated with talus shoes. Flexion and

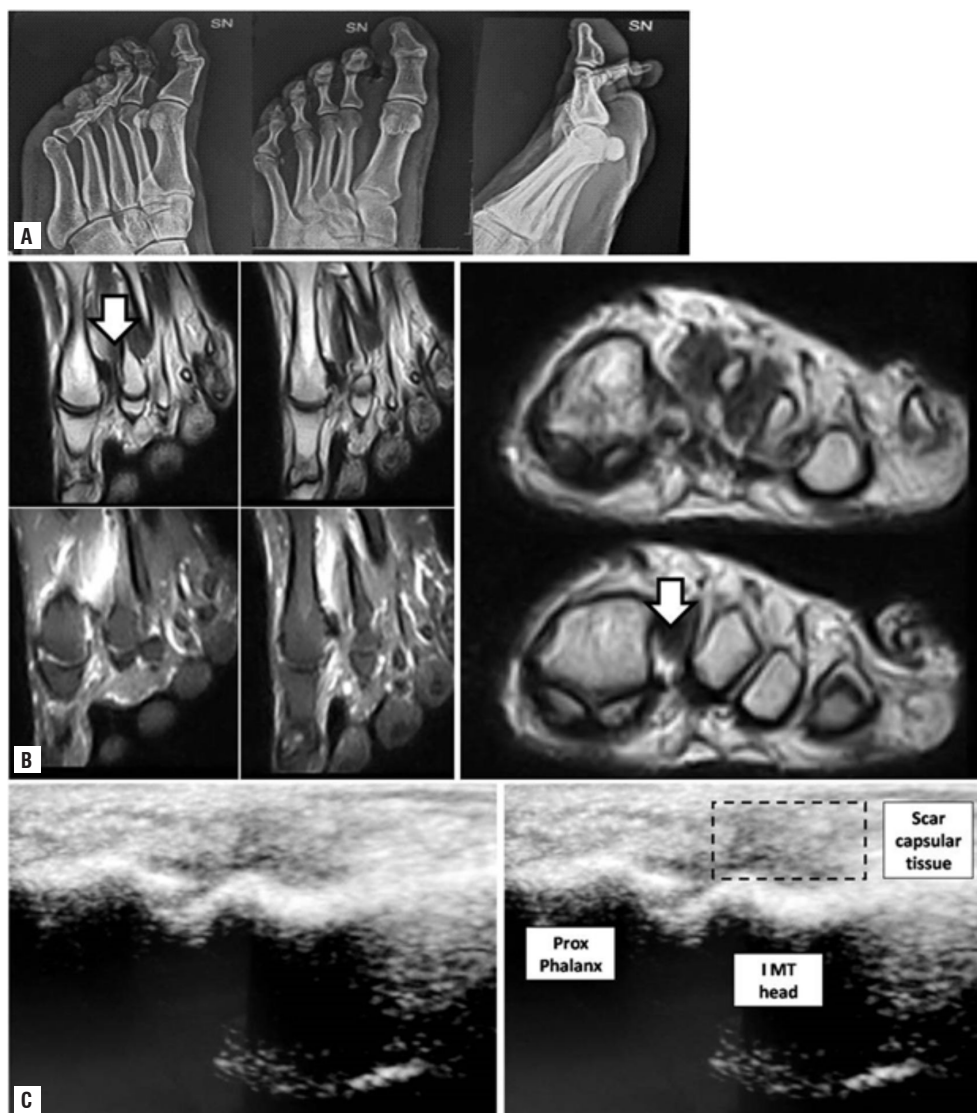


Figure 4. Pre-operative lesion. A) Traditional X-ray showed correct alignment of the first MTPJ with the *hallux abductus* angle 3°; B) magnetic resonance imaging of the abductor tendon detachment; C) ultrasonography of the lateral capsular ligamentous structures rupture (Policlinico Bari, August 2020)

extension were completed and granted in syndactyly. The VAS was 3, SF-36 measured 45 and 43, AOFAS scored 65.

After 2 months, the button was removed and full weight-bearing was gradually started. The clinical scores improved again with ROM complete.

After another 30 days, the syndactyly and the talus shoes were removed. The patient walked freely. It was advisable to abstain from sporting activity for another 30 days. The patient returned to check after six months, he walked without lameness. The surgical scar was normochromic and normotrophic. No residual anatomical deviation maintained (Figure 5). Complete active

and passive ROM with mild pain at maximum degrees of the interphalangeal joint was possible. The joint appeared stable. The patient referred he resumed cautiously running and regularly walking on toes. Hallux elastic taping and syndactyly with the second toe while playing sports was recommended. After six months, the visual analogue scale pain score improved from a pre-operative score of 6.5 to 2; the short-form 36-item health survey physical component and mental component scores improved from 31 and 33, to 55 and 52 points, respectively; the American Orthopedic Foot and Ankle Society score increased from 35 to 81 points.



Figure 5. Clinical image of the 6-month follow-up. **A)** The surgical scar clinically normochromic and normotrophic; **B)** no residual hallux anatomical deviation; **C)** walking on toes in lateral view; **D)** walking on toes in anterior view (Policlinico Bari, March 2021)

DISCUSSION

First metatarsophalangeal instability can be considered as a consequence of non-adequate management and treatment of initial injury. Few cases were described in literature, and a guideline of treatment and rehabilitation is not available yet (1-3).

Mullis and Miller described the adductor hallucis tendon reattachment via drill holes in the proximal phalanx and suturing the tendon on itself. This provided adequate reduction of the varus; however, weight-bearing was gradually resumed in the 7th postoperative week and full return to activity was achieved 4 months postoperatively (4). Labovitz and Kaczander presented a case involving a traumatic avulsion of the *abductor hallucis* tendon leading to hallux varus. A T-shaped capsulotomy was performed laterally, a wedge of capsule excised, and the proximal and distal aspects were tagged with suture (1). Ryan et al. described a traumatic hallux varus: patient initially injured his foot during a wrestling contest; he reported lateral collateral ligament of the 1st MTPJ lesion (8). Soft tissue anchor, as in supraspinatus tendon repair (9), alone was used to stabilize the joint in the transverse plane and augment the lateral capsule and collateral ligament (8). Residual pain and instability likely due to osteoarthritis are a fearful complication to be avoided (10-11).

Lui TH reported a case of traumatic hallux varus due to avulsion fracture of the lateral side of the proximal phalanx base hitting from a door (12).

Lateral instability of the first metatarsophalangeal joint was believed to be due to adductor hallucis function disruption. Surgical treatment consisted in minimally invasive extensor hallucis brevis (EHB) tenodesis using a tendon graft. The hallux varus deformity was then corrected by tensioning of the graft and the first metatarsal was transfixed with a 1.6mm K-wire as in transverse midshaft metacarpal fractures technique (13). The graft was sutured to the abductor hallucis under tension. The medial capsule was stripped from the bone with a small periosteal elevator. The K-wire was removed, and the patient walked weight-bearing with wooden base sandal 4 weeks after the operation. The patient could resume normal shoe gear 2 months after the operation (12).

In conclusion, the post traumatic instability of the first metatarsophalangeal joint is a rare condition. Our surgical correction has never been described before. The procedure included the pull out of the lateral capsule guaranteed the restoration of joint stability with a short-term surgery. Moreover, the treatment was simple and replicable. It was important to identify the intraoperative lesion and adequately prepare the capsule for the pull out. The patient returned to the full weight-bearing in only 2 months of rehab.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

1. Labovitz JM, Kaczander BI. Traumatic hallux varus repair utilizing a soft-tissue anchor: a case report. *J Foot Ankle Surg* 2000; 39:120-3.
2. Loosemore M, Lightfoot J, Palmer-Green D, Gatt I, Bilzon J, Beardsley C. Boxing injury epidemiology in the Great Britain team: a 5-year surveillance study of medically diagnosed injury incidence and outcome. *Br J Sports Med* 2015; 49:1100-7.
3. Rinonapoli G, Graziani M, Ceccarini P, Razzano C, Manfreda F, Caraffa A. Epidemiology of injuries connected with dance: a critical review on epidemiology. *Med Glas (Zenica)* 2020; 17:256-64.
4. Mullis DL, Miller WE. A disabling sports injury of the great toe. *Foot Ankle* 1980; 1:22-5.
5. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med* 2001; 8:1153-7.
6. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. *Health Econ* 1993; 2:217-27.
7. Ibrahim T, Beiri A, Azzabi M, Best AJ, Taylor GJ, Menon DK. Reliability and validity of the subjective component of the American Orthopaedic Foot and Ankle Society clinical rating scales. *J Foot Ankle Surg* 2007; 46:65-74.
8. Ryan PM, Johnston A, Gun BK. Post-traumatic dynamic hallux varus instability. *J Clin Orthop Trauma* 2014; 5:94-8.
9. Solarino G, Solarino G, Bortone I, Vicenti G, Bizzoca D, Coviello M, Maccagnano G, Moretti B, D'Angelo F. Role of biomechanical assessment in rotator cuff tear repair: arthroscopic vs mini-open approach. *World J Orthop* 2021; 12:991-1000.
10. Ripani U, Manzarbeitia-Arroba P, Guijarro-Leo S, Urrutia-Graña J, De Masi-De Luca A. Vitamin C may help to reduce the knee's arthritic symptoms. outcomes assessment of nutraceutical therapy. *Med Arch* 2019; 73:173-7.
11. Moretti L, Maccagnano G, Coviello M, Cassano GD, Franchini A, Laneve A, Moretti B. Platelet rich plasma injections for knee osteoarthritis treatment: a prospective clinical study. *J Clin Med* 2022; 11:2640.
12. Lui TH. Stabilization of first metatarsophalangeal instability with plantar plate tenodesis. *Foot Ankle Surg* 2008; 14:211-4.
13. Pasquino A, Tomarchio A, De Cruto E, Conteduca J, Longo D, Russi V, Pica G, Meccariello L, Rollo G. Comparing hand strength and quality life of locking plate versus intramedullary k wire for transverse midshaft metacarpal fractures. *Med Glas (Zenica)* 2021; 18:316-21.

Spinal cord stimulation in chronic pain treatment – first experiences in Bosnia and Herzegovina

Tatjana Bućma^{1,2}, Ostoja Savić³, Tatjana Boškić¹, Lena Arambašić Topić¹, Igor Sladojević², Snježana Novaković Bursać¹

¹Institute for Physical Medicine and Rehabilitation "Dr. Miroslav Zotović", ²School of Medicine, University of Banja Luka, ³University Clinical Center of Republic of Srpska; Banja Luka, Bosnia and Herzegovina

ABSTRACT

Aim To describe results of spinal cord stimulation technique when the conventional multidisciplinary treatment of neuropathic or mixed pain failed.

Methods The research was conducted at the Institute for Physical Medicine and Rehabilitation "Dr. Miroslav Zotović", Banjaluka. Ten patients, who had chronic pain resistant to other therapeutic options and a failed back surgery, were sent for an evaluation. Each patient underwent a 4-week evaluation by a team of medical specialists, psychologist and social workers. Additional diagnostic methods (MRI of the lumbosacral spine, electromyoneurography of lower extremities, cognitive assessment tests) were also performed to establish a proper indication for implantation of the system for spinal cord stimulation. Leads of a system for spinal cord stimulation were implanted percutaneously or surgically at the epidural space. Functional outcome measures (visual analogue scale, Oswestry index, anxiety and depression scales) were taken before the implantation of the system and on several followups.

Results Four patients did not meet criteria for the inclusion in the study (two were not ready, two showed psychopathological symptoms). One patient had a percutaneous lead implant, but it was removed after six months due to paresthesia. The remaining five had surgically implanted epidural leads and showed significant improvement in pain control, Oswestry index had lower values, and all except one patient had improvement registered by anxiety and depression scales.

Conclusion. Short-term and long-term follow up showed a long lasting pain reduction and improvement of functionality in all patients.

Key words: electric stimulation therapy, failed back surgery syndrome, treatment outcome

Corresponding author:

Tatjana Bućma
Department of Physical Medicine and
Rehabilitation "Dr Miroslav Zotović"
Slatinska 11, 78000 Banjaluka,
Bosnia and Herzegovina
Phone: +387 65 531 141;
E-mail: tatjana.bucma@gmail.com
ORCID ID: <https://orcid.org/0000-0002-4388-4681>

Original submission:

17 June 2022;

Accepted:

27 July 2022

doi: 10.17392/1507-22

INTRODUCTION

Spinal cord stimulation (SCS) is a neuromodulation technique that reduces pain by the use of electrical energy to stimulate the dorsal horns of the spinal cord. Perception of pain reduces the quality of life, which leads to anxiety and/or depression, highlighting a significant correlation between pain and the psychological status of the patient. It has been shown that SCS could reduce chronic pain and improve the quality of life (1). Brinzeu et al. showed that two years after the first SCS implantation close to 60% of the patients retained a significant pain reduction and 74% showed improvement in pain scores with significant decreases in drug and non-drug pain treatments (2).

Numerous studies propose Failed Back Surgery Syndrome (FBSS) as the first indication for SCS system implantation. The SCS was proved to be more efficient in the lumbar segment treatment than repeated surgery (1,2). A few years later, studies confirmed that the SCS was more superior to the conservative medical treatment for 6, 12, and 24 months in reduction of leg pain (>50%), improvement of the function and quality of life (3). A significantly larger number of patients with the SCS system and an optimal medical therapy have reduction of pain >50% in the lumbar region in the 6th month from the procedure, compared to patients who received only the medical therapy (4).

The SCS was introduced as a pioneer therapeutic option in Bosnia and Herzegovina in 2018. The aim of this study was to describe the results of SCS in chronic pain reduction and improvement of functional status and symptoms of anxiety and depression when the conventional multidisciplinary treatment of neuropathic or mixed pain failed.

PATIENTS AND METHODS

Patient and study design

Ten patients were referred to an evaluation for the system implantation by the neurosurgeons at the Institute for Physical Medicine and Rehabilitation "Dr. Miroslav Zotović", Banjaluka (Institute), Bosnia and Herzegovina, in the period February 2018 - June 2021, and no indication was found for a repeated surgical treatment of patients. All patients had had results of magnetic resonance imaging (MRI) of lumbar spine and

electromyoneurography (EMNG) of lower extremities beforehand.

Before the final evaluation, the patients spent four weeks at the outpatient hospital for the treatment of chronic pain in the Institute, where any previously undertaken method for the chronic pain treatment (medical or physical therapy, acupuncture, mesotherapy, psychosocial support) was carefully analyzed. If any of these methods had not been applied, and there was a possibility for its justified application, that treatment was applied as well. When a possibility for successful treatment by some other method was ruled out, a team consisting of specialists in neurosurgery, physical medicine and rehabilitation, psychiatry, anesthesiology and clinical pharmacy, together with a psychologist and a social worker conducted evaluation of the patient's eligibility for the implantation of the system for SCS. Also, the listed contraindications for SCS implantation (inserted pacemaker or some other type of implantable cardiac defibrillator, serious diseases such as immunodeficiency or coagulation disorders, problems with addiction, the changed morphology of the spinal column) had to be taken into the account.

The neurosurgeon obtained insight into the morphological condition of the spinal column, as well as the functional condition of nerves of the lower extremities, while psychiatrist and psychologist carried out a series of tests, among which was the Montreal cognitive assessment/test for rapid cognitive assessment (MoCA test) that determined no diagnostically significant deficits of cognitive abilities (7).

Before the final decision was made, the patients were given detailed information about the implantation procedure, the method of handling the system, what to expect, and they were enabled to contact patients that had already had the system implanted.

The preparation of the patient for the procedure began only after all team members agreed that there was an indication for the implantation of the SCS system in chronic pain treatment.

All patients received patient information and signed an informed consent form that had been approved by the Ethics Committee of the Institute for Physical Medicine and Rehabilitation "Dr. Miroslav Zotović" (Approval number 116-15-12894-1/19).

Methods

There were two options for the selection of a proper lead for spinal cord stimulation. The implantation of percutaneous lead was carried out in local anesthesia, and the lead was implanted into the epidural space alongside the dorsal horns of the spinal cord controlled by C-arm X-ray and with the estimation of a level compared to the pain propagation. The battery with the pulse generator was left externally for four weeks when the system's efficacy was evaluated- whether the pain's intensity was reduced by at least 50% and if the quantity of analgesic medical therapy reduced significantly. The programming of the system was performed with smaller changes during this phase, when the patient was trained to handle the system (turning on and off, and increasing the intensity of the impulse). All the remaining parts of programming and patient follow-up in the following years were in the scope of the trained members of the team. After identifying good results of the implanted system in pain management, the second part of the procedure was the implantation of the permanent RestoreSensor SureScan MRI neurostimulator (Medtronic, Minneapolis, Minnesota, United States) in general anesthesia in the subcutaneous space of the anterolateral abdominal wall.

The procedure for the implementation of surgical leads was performed in general anesthesia, when the surgical leads were implanted into the epidural space under the control of the C-arm, and neurostimulator was implanted into the subcutaneous space of the anterolateral abdominal wall. The programming was performed four days after the surgical procedure.

To manage post-operative pain, the following scheme was used: a day before the surgery gabapentin 600 mg in the evening, also 600 mg on day zero in the evening, and then it was gradually weaned off. Morphine (3-5 mg) was also administered on day zero as a total daily dose. The next day, 1.25 g of metamizole sodium was administered every 6 hours intravenously to manage acute postoperative pain until pain was completely alleviated. Patients' acute pain was managed this way and the system was turned on the fourth day to program.

All the patients were preoperatively monitored (a period of eligibility evaluation for the implantation of the system) for pain intensity according

to visual analogue scale (VAS) (8) and Oswestry Disability Index (9) for the functionality assessment. Values of VAS were recorded by a nurse, and the assessment of the Oswestry Disability Index by an occupational therapist.

The psychologist performed the testing with personality inventory scale Beck Anxiety Inventory (BAI) (10) and Beck Depression Inventory (BDI) (11), and interpreted the results as previously described (10,11).

The VAS, Oswestry Disability Index, BAI and BDI tests were again done on discharge (two weeks after the surgical procedure). On the last follow-up, the VAS value was redefined (based on the pain records, which were recorded by patients, and intensity average, when the system for SCS was on/off and for how long).

RESULTS

Initially, there were 10 patients with FBSS, but four of them did not meet the inclusion criteria. Two patients (one male and one female), after establishing the proper indication, withdrew from the procedure because they did not feel ready; two patients (two females) were excluded because of the presence of psychopathological symptoms in a degree that represents a contraindication for the procedure.

Six patients who were involved in the implantation process had different duration of complains, several number of surgical procedures, and a different level of implanted electrodes (Table 1).

All patients with surgically implanted leads participated in the follow-up, while one female patient with percutaneous leads was excluded from the monitoring because the system was removed after six months due to difficulty tolerating the paresthesia, despite numerous attempts to set new program parameters. All other patients had no intraoperative, postoperative, as well as any other long-term complications.

Most patients showed the same values of VAS in the follow-up after a half to two and a half years, just like in the follow-up after two weeks, except the patient in case III, who described comorbidity with changes in the spinal cord, which cannot be excluded as the cause of the mentioned pain, although those values are still in the range of good results. The patient in case IV also had a mild increase of pain intensity according to VAS, but

Table 1. Data on patients who had spinal cord stimulation (SCS) system implanted due to failed back surgery syndrome (FBSS)

Case	Age	Gender	Complaints	Former surgical procedures (year)	Month/ year of im- plantation	Level and method
I	74	F	Lumbar area pain spreading down the right leg since 2008	Interhemilaminectomy L5-S1 (2008); Interhemilaminectomy L4-L5 (2016); System extracted after six months	02/2018	P Th10/11
II	48	M	Lumbar area pain spreading down the legs, dominantly left, since 2011	hemilaminectomy L4-L5 (2012); spondylodesis and stabilisation L5/S1 (2013); foraminotomia L4, discectomia L4, spondylodesis L4/S1 (2013)	04/2018	H Th9/10
III	55	M	Lumbar spine pain spreading down the right leg since 2010	laminectomy L2-L3, disc extirpation (2010); reductio reg.conus medularis (2010).	09/2018	H Th11/12
IV	58	M	Left side lumbar pain, burning pain in the left thigh and upper third of the lower leg	partial endoscopic discectomia L3/L4 (2016); reoperation of the disc L3L4 (2016); discectomia L3L4, transpedicular stabilisation with fusion (2017)	09/2018	H Th9/10
V	45	M	Lumbar area pain, propagation to both legs, more to the left	hemilaminectomy L5-S1 and deliberation of left S1 radix (2018); hemilaminectomy L5-S1 and deliberation of right S1 radix (2018);	11/2019	H Th9/10
VI	54	F	Lumbar region pain, propagati- on to the left lower extremity	Three surgical procedures for herniated disci L5-S1 with transpedi- cular stabilization (2003, 2004, and 2017).	12/2020	H Th9/10

M, male; F, female; P, percutaneous leads; H, surgical leads

still in the range of good results. These patients used analgesic medication therapy for other pain sources (case VI) or after larger physical activity (case II) or occasionally (opioid) along with the use of co-analgesic medications (gabapentin) (cases III and V) (Table 2). All patients stated that there were periods (during the day, night, or several days consecutively) when they turned the device off because the pain intensity was minor or completely absent.

Table 2. Values of the visual analog scale (VAS) preoperatively, two weeks after the surgery and on follow-up

Case	VAS			
	Preop.	Two weeks postop.	Last follow-up (June 2021)	
I	9/10	5	N/A	
II	9/10	5	4-6	
III	8	0/1	4	
IV	6	0	2	
V	9	4/5	5	
VI	8/9	4	0	

preop., preoperatively; postop., postoperatively; N/A, not available;

Functionality, evaluated by the Oswestry Disability Index, showed improvement in all patients after two weeks (Table 3).

Table 3. Functional status of patients measured through Oswestry Disability Index

Case	Oswestry Disability Index			
	Preop.	Two weeks postop.	Last follow-up (June 2021)	
I	74	36	N/A	
II	84	46	23	
III	64	15	28	
IV	50	10	22	
V	92	46	23	
VI	52	42	21	

preop., preoperatively; postop., postoperatively; N/A, not available;

All patients, except for the patient in case III (55-year-old male had an improvement on BAI and BDI scales, on both or one of them. The patient in the case III did not have the improvement of the condition compared to the preoperative period, along with mild anxiety without depression (Table 4).

Table 4. Anxiety and depression level according to Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) score

Case	BAI		BDI	
	Before implantation of the system	At the last follow-up (June 2021)	Before implantation of the system	At the last follow-up (June 2021)
I	moderate anxiety	N/A	moderate depression	N/A
II	moderate anxiety	moderate anxiety	moderate depression	bordering depression
III	moderate anxiety	moderate anxiety	no depression	no depression
IV	moderate anxiety	mild anxiety	no depression	no depression
V	no anxiety	mild anxiety	no depression	no depression
VI	severe anxiety	moderate anxiety	severe depression	moderate depression

N/A, not available;

DISCUSSION

This paper shows our first results after the implantation of the SCS system in the treatment of chronic pain. Patients with chronic pain do not get detected by the medical professionals nor understood by the environment. Even though SCS was used for several decades in chronic pain management, there is a lack of high-quality studies on the efficacy of SCS within the largest indication areas such as neuropathic pain and persisting pain after the FBSS (12). Taking into account the

recommendations for SCS system implantation (12), six out of ten of our patients with implanted system had FBSS with several spinal surgical procedures, where the time from the last surgical procedure to the system implantation was 1-8 years.

A workgroup of the European Pain Federation (13) established clear criteria for the SCS implantation. All other modalities of chronic pain treatment had to be exhausted and the patient had the cognitive ability to, after detailed explanation, understand the procedure, benefits, possible risks, and how to handle the system. Anatomically, the patient had at least partially preserved fibers of the dorsal columns of the spinal cord.

All of the specific clinical variables identified in previous studies (12) were included in this study. A broad evaluation must have three dimensions – biological, psychological, and social (14,15). Basic dimensions of the preoperative psychological evaluation are psychosocial risk factors, whether the patient understands the entire procedure, and evaluation of patient's expectations regarding the pain reduction (14).

Also, multiannual pain produces psychological changes that may give distorted perception of the patient's condition, which does not lead to a successful result after the implantation of the system (15). Four of our patients who had passed the evaluation and got into the framework of stated indications and criteria, did not obtain the approval for the system's implantation. The results of the psychological evaluation should not prevent the implantation of the system for SCS, but the psychologist and the doctor have to consult each other directly (14). According to our experience, the multidisciplinary approach has shown to be the key element of success.

In one of our patients, the system was extracted after six months due to paresthesia in the pain region, which she could not bear regardless of numerous attempts to set new program parameters. This could be caused by intolerance to the system, which was impossible to confirm preoperatively (16). Two weeks after the implantation of the SCS system other five patients had a significant reduction of pain. All patients had a decrease in pain of over 50% two weeks after the implantation of the system and in some cases complete absence of pain. Billet et al. reported that the average pain levels 12 weeks after SCS

implantation decreased 61% for back pain and 56% for leg pain with 100% reduction in opioid medication use (17).

The support of self-management training of chronic pain may increase the success in adaptation to the use of the SCS for pain treatment (14). Some patients are unsatisfied even when they experienced at least 50% of pain alleviation. Others expect relief of radicular and back pain, while some are unsatisfied by the system itself regardless of the achievement (16). One part of patients may misinterpret the paresthesia as a relief after pain, while others describe it as discomfort and inability to "bear" such sensations. Patients often "forget" pain they had before the implantation of the system and still report strong pain, but they have far bigger functional capacity compared to the pre-implantation conditions (16).

In a study by Kumar et al. patients with FBSS and implanted system reported significant pain reduction in the lower extremity (but not in the lower back), improvement of functionality, and improvement of quality of life (5). The revision was necessary for 31% of patients, most of them in the first year after the system implantation. In our case, except for the first patient's request for the system extraction, no revision was required and there were no side effects after the system implantation.

Patients with FBSS, due to pain and longstanding search for a therapeutic option, usually have symptoms of anxiety and depression. After successful implantation of the SCS system, patients have a moderate increase in BAI and BDI scales (18). This was confirmed in our sample except in one case where there was no improvement after the SCS implantation, along with mild anxiety. It is difficult to estimate whether this condition was a result of expectations that did not realize and emerged concern for the future, or this condition caused aggravation of the condition in the last follow-up compared to two weeks after the surgery.

The main limitation of the study was a small sample. Funding of the SCS implantation is limited to five patients annually, and therefore we could not increase the sample size nor make randomization.

In conclusion, successful implementation of the SCS as a therapeutic modality for chronic pain after FBSS reduces pain, improves functionality, and reduces the symptoms of anxiety and depre-

ssion. A careful preoperative selection of patients, selection of the implantation technique and stimulation parameters reduce chronic pain in patients with FBSS. Multidisciplinary approach is a key element for a successful treatment outcome.

REFERENCES

1. Corallo F, De Salvo S, Cannistraci C, Lo Buono V, Di Cara M, Floridia D, Cerra F, Romeo L, Pria D, Bramanti P, Marino S, Bonanno L. Chronic pain and spinal cord stimulation. *Medicine (Baltimore)* 2020; 99:e20490.
2. Brinzeu A, Cuny E, Fontaine D, Mertens P, Luyet PP, Van den Abeele C, Djian MC; French SCS Study Group. Spinal cord stimulation for chronic refractory pain: Long-term effectiveness and safety data from a multicentre registry. *Eur J Pain* 2019; 23:1031-44.
3. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. *Neurosurgery* 2005; 56:98-107.
4. Daniell JR, Osti OL. Failed back surgery syndrome: a review article. *Asian Spine J* 2018; 12:372-9.
5. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. *Neurosurgery* 2008; 63:762-70.
6. Rigoard P, Desai MJ, North RB, Taylor RS, Anemans L, Greening C, Tan Y, Van den Abeele C, Shipley J, Kumar K. Spinal cord stimulation for predominant low back pain in failed back surgery syndrome: study protocol for an international multicenter randomized controlled trial (PROMISE study). *Trials* 2013;14:376.
7. Kljajević V. Montrealska procena kognicije: srpska verzija. *Aktuelnosti iz neurologije, psihijatrije i graničnih područja* 2009; 17:31-9.
8. Delgado DA, Lambert BS, Boutris N, McCulloch PC, Robbins AB, Moreno MR, Harris JD. Validation of Digital Visual Analog Scale Pain Scoring with a Traditional Paper-based Visual Analog Scale in adults. *J Am Acad Orthop Surg Glob Res Rev* 2018; 2:e088.
9. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine (Phila Pa 1976)* 2000; 25:2940-52.
10. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988;56:893-7.
11. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4:561-71.
12. Thomson S, Huygen F, Prangnell S, De Andrés J, Baranidharan G, Belaïd H, Berry N, Billet B, Cooil J, De Carolis G, Demartini L, Eldabe S, Gatzinsky K, Kallewaard JW, Meier K, Paroli M, Stark A, Winkelmüller M, Stoevelaar H. Appropriate referral and selection of patients with chronic pain for spinal cord stimulation: European consensus recommendations and e-health tool. *Eur J Pain* 2020; 24:1169-81.
13. Gybels J, Erdine S, Maeyaert J, Meyerson B, Winkelmüller W, Augustinsson L, Bonezzi C, Brasseur L, DeJongste M, Kupers R, Marchettini P, Muller-Schwefe G, Nitescu P, Plaghki L, Reig E, Spince-maille G, Thomson S, Tronnier V, Van Buyten JP. Neuromodulation of pain. A consensus statement prepared in Brussels 16-18 January 1998 by the following task force of the European Federation of IASP Chapters (EFIC). *Eur J Pain* 1998; 2:203-9.
14. Stephens KA, Ward A. Patient selection for spinal cord stimulators: mental health perspective. *Curr Pain Headache Rep* 2014; 18:398.
15. Gould HM, D'Eon MS, Grinberg AM, Chakravarthy KV, Castellanos J, Rutledge T. Psychosocial characteristics of candidates for implantable pain devices: validation of an assessment model. *Pain Manag* 2021; 11:159-72.
16. Blackburn DR, Romers CC, Copeland LA, Lynch W, Nguyen DD, Zeber JE, Hoffman MR. Presurgical psychological assessments as correlates of effectiveness of spinal cord stimulation for chronic pain reduction. *Neuromodulation* 2016; 19:422-8.
17. Billet B, Hanssens K, De Coster O, Nagels W, Weiner RL, Wynendaele R, Vanquathem N. Wireless high-frequency dorsal root ganglion stimulation for chronic low back pain: A pilot study. *Acta Anaesthesiol Scand* 2018; 62:1133-8.
18. Blackburn D, Monte R, Zeber J, McIntyre R. Assessment of psychosocial screeners for spinal cord stimulation success. *Practical Pain Mgmt* 2013; 13:35-9.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

Može se desiti i najboljim doktorima.

Sigurna profesija - Osiguranje karijere od profesionalne pogreške.

uniqa.ba



Sigurna profesija

Zaštita medicinskih i srodnih djelatnosti

Želimo Vas uvesti u svijet zaštite, Vas i Vaše medicinske profesije. Vođeni tom idejom naš cjelokupni program zaštite medicinske profesije objedinili smo pod nazivom UNIQA Sigurna profesija - najbolje rješenje za sve neželjene okolnosti na koje nemate uticaja.

Ugovaranjem osiguranja iz programa UNIQA Sigurna profesija ublažit ćete neželjene finansijske posljedice jer vam UNIQA Osiguranje omogućava da djelujete unaprijed i zaštitite svoju karijeru!

Naš program zaštite sadrži sljedeće:

Postavite sebi već danas pitanja koja će jednog dana svakako doći na red:

- ☒ osiguranje od profesionalne odgovornosti
- ☒ osiguranje pravne zaštite
- ☒ osiguranje finansijskog gubitka

Osiguranje od profesionalne odgovornosti

Osiguravajuće pokriće obuhvata rizike koji mogu nastati tokom obavljanja poslova iz djelokruga osigurane, profesionalne djelatnosti za koju je zdravstveni radnik - osiguranik stručno i znanstveno osposobljen unutar ustanove u kojoj djeluje.

Osiguranje uključuje:

- ☒ troškove odbrane i sudskog postupka
- ☒ isplatu odštetnog zahtjeva
- ☒ pokriće koje vrijedi i u slučaju pružanja prve pomoći na području Europe
- ☒ za osigurane slučajeve nastale tokom jedne godine nadoknađuje se najviše dvostruki iznos ugovorenog osiguranog iznosa (agregatni limit).

Osiguranje pravne zaštite u krivičnom i prekršajnom postupku

Osiguranje pravne zaštite je zaštita od troškova koji nastanu kao posljedica radnji i propusta u obavljanju medicinske djelatnosti kao profesionalne djelatnosti.

Osiguravajuća zaštita obuhvata:

- ☒ odbranu kod krivičnih djela i prekršaja nastalih u obavljanju profesionalne djelatnosti navedene na polisi osiguranja
- ☒ odbranu u disciplinskom postupku kao posljedice krivičnog djela ili prekršaja
- ☒ postupak u slučaju ulaganja pravnih lijekova (žalbeni postupak)
- ☒ troškove odbrane i sudskog postupka do ugovorenog osiguranog iznosa
- ☒ jamčevinu
- ☒ osigurane rizike nastale na području cijele Europe

Osiguranje finansijskih gubitaka

Osiguranje prekida rada kod vlasnika privatnih djelatnosti. Osiguran je finansijski gubitak uzrokovan prekidom rada osigurane djelatnosti ili ordinacije kao posljedice:

- ☒ bolesti osigurane osobe
- ☒ nesretnog slučaja osigurane osobe
- ☒ elementarne nepogode (npr. požar, udar groma, oluja, eksplozija, izljev vode iz vodovodnih cijevi, provalna krađa uključujući i vandalizam)
- ☒ karantene uvedene zbog zaraze ili epidemije.

Posjetite UNIQA web stranicu www.uniqa.ba/sigurna-profesija

i informišite se dodatno o Sigurnoj profesiji. Također, putem Lead box "Želite ponudu?" možete poslati upit za punodu sukladno Vašem opisu posla i Vašim potrebama.

