EISSN 2667-6370

Turkish Journal of Anaesthesiology & Reanimation

Volume 52 • Issue 6 • December 2024

Official journal of the TURKISH SOCIETY OF ANAESTHESIOLOGY AND REANIMATION

galenos Publishing House

turkjanaesthesiolreanim.org

Turkish Journal of Anaesthesiology & Reanimation

Turkish Journal of Anaesthesiology & Reanimation

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr **Publisher Certificate Number:** 14521

Publishing Date: December 2024
E-ISSN: 2667-6370
International scientific journal published bimonthly.

Turkish Journal of Anaesthesiology & Reanimation

Please refer to the journal's webpage (**https://turkjanaesthesiolreanim.org/**) for "Ethical Policy", "Instructions to Authors" and "Instructions to Reviewers".

The editorial and publication process of the Turkish Journal of Anaesthesiology and Reanimation are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing. Turkish Journal of Anaesthesiology and Reanimation is indexed in **PubMed Central, Web of Science - Emerging Sources Citation Index, Scopus, DOAJ, TUBITAK ULAKBIM TR Index, China National Knowledge Infrastructure (CNKI), EMBASE, EmCare, CINAHL, ProQuest** and **Gale**.

The journal is published online.

Owner: Ali Fuat Erdem on behalf of the Turkish Anesthesiology and Reanimation Association

Responsible Manager: Zekeriyya Alanoğlu

Turkish Journal of Anaesthesiology & Reanimation

Contents

Review Article

Original Articles

Index

DOI: 10.4274/TJAR.2024.241657

Review Article
Pain

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2024;52(6):200-206

Acute Pain Management in Peripheral Artery Disease: A Holistic, Beyond-Opioids, Individualized Multimodal Approach

Maria P. Ntalouka[1], Athanasios Chatzis[1], Petroula Nana[2], Konstantinos Spanos[2], Metaxia Bareka[1], Miltiadis Matsagkas[2], Eleni Arnaoutoglou[1]

[1]University of Thessaly Faculty of Medicine; Larissa University General Hospital, Department of Anaesthesiology, Larissa, Greece
[2]University of Thessaly Faculty of Medicine; Larissa University General Hospital, Department of Vascular Surgery, Larissa, Greece

Cite this article as: Ntalouka MP, Chatzis A, Nana P, et al. Acute Pain Management in Peripheral Artery Disease: A Holistic, Beyond-Opioids, Individualized Multimodal Approach. *Turk J Anaesthesiol Reanim.* 2024;52(6):200-206.

Abstract

Peripheral artery disease (PAD) is quite prevalent, and its incidence will increase with aging of population. Pain is a key diagnostic feature of symptomatic PAD and has been linked to disease progression and poor quality of life. Symptom improvement is of utmost importance in PAD; therefore, optimal and comprehensive pain therapy is mandatory. However, the management of acute pain in PAD remains challenging due to the lack of high-quality evidence, the complex pathophysiological mechanisms of pain, and the high comorbidity of patients. On the other hand, inadequate pain control leads to several pathophysiological deviations, such as the aggravated neuroendocrine stress response, which may be detrimental in patients with PAD. Experts suggest that the management of acute pain in patients with vascular diseases should be oriented toward the underlying pathophysiological mechanisms of each modality and should follow a multifactorial approach. Although the exact pain pathways in PAD are still poorly understood and more probably multifactorial, they may be key to an effective, individualized, patient-centered, multimodal pain strategy. The aim of this review was to provide a holistic, beyond-opioids, individualized multimodal pain approach for patients with PAD.

Keywords: Acute pain, multimodal treatment, pain, pain management, peripheral artery disease

Main Points

- Management of patients with acute pain due to peripheral artery disease (PAD) is challenging due to high comorbidity and complex pathophysiology.
- Multimodal pain management is the cornerstone of optimal treatment of acute PAD-induced pain.
- The neuropathic component of pain is of utmost importance.
- Opioids are the gold standard treatment for severe pain.
- Multimodal analgesia, invasive techniques, and non-pharmaceutical interventions are effective and safe approaches for the management of acute pain due to PAD.

Introduction

Peripheral artery disease (PAD) is defined as the clinical spectrum of chronic vascular insufficiency due to widespread arterial atherosclerosis that predominantly affects the segments of the lower limb (aortoiliac, femoropopliteal, and infrapopliteal).[1-4] Although its incidence varies, more than 200 million patients worldwide are affected by PAD.[1,3] The infrapopliteal arterial form is the most prevalent, with a reported incidence of up to 20%.[1,3] As the population continues to age, the incidence of PAD will increase, severely affecting the quality of life and longevity of patients. However, because PAD is often asymptomatic, it may remain underdiagnosed, underrecognized, or undertreated.

Corresponding author: Maria P. Ntalouka, e-mail: maria.ntalouka@icloud.com

Received: June 27, 2024 Accepted: November 26, 2024

Pain is a key diagnostic feature of symptomatic PAD, and it has a major impact on quality of life and everyday function. Worsening pain has been linked to disease progression.[4-8] Hence, optimal and comprehensive pain treatment in patients with PAD is mandatory. However, pain management in this population proves to be challenging due to the lack of high-quality evidence, the underlying complex pathophysiological mechanisms of pain, and the high comorbidity-including ischemic heart disease, impaired renal function, and diabetes mellitus-which further complicate the provision of therapeutic pain interventions.[5] On the other hand, inadequate pain control leads to several pathophysiological deviations such as the aggravated neuroendocrine stress response and the activation of the autonomic nervous system (ANS), which may prove to be detrimental in patients suffering from PAD.[5] Although the exact pain pathways and mechanisms in symptomatic PAD are multifactorial and still poorly understood, they are considered to be valuable assets that will lead to an effective, individualized, and patient-centered, multimodal pain strategy.

The first part of this review presents a short overview of the clinical manifestations, pathophysiology, and etiology of pain in patients with PAD. We then provide a holistic, beyond-opioids, individualized multimodal pain approach for acute pain in patients with PAD based on the relevant pain pathways.

Pain Manifestations of PAD

Although PAD is usually asymptomatic in the early stages, up to 50% of patients progress to symptomatic disease in which pain prevails. The key diagnostic characteristics of painful PAD are chronic and gradually worsening pain frequency and intensity, with exacerbations of acute pain. Pain characteristics have been linked to disease progression, while clinical manifestations vary from intermittent claudication (IC) to critical limb ischemia (CLI). Of note, CLI without treatment can cause tissue and limb loss.[4,5,7-9]

IC, otherwise known as stable PAD, presents as cramp-like pain in the muscle group distal to the atherosclerotic lesions. Buttock and thigh claudication indicate aortoiliac segment disease, whereas calf claudication indicates femoropopliteal segment disease. IC pain follows a characteristic pattern: (i) pain is absent at rest, as there is adequate blood supply for the tissues; (ii) is triggered by exercise and develops progressively due to muscle ischemia; and (iii) is eased by a short period of rest. In the vast majority of patients, IC pain recurs with the same pattern and at a similar walking distance.[1,2,5] However, some patients may not present with the classic features of IC, but they may fall under the "leg pain/carry on" or "leg pain on exertion and rest" symptoms. Leg pain that occurs with exertion but does not force the patient to stop walking is known as "leg pain/carry on", while pain that is consistently triggered by activity but may be present at rest is known as "leg pain on exertion and rest".[2]

On the other hand, CLI is characterized by severe pain at rest, which is worse on elevation and only relieved by dependency.[1,2,5] Pain is the result of inadequate tissue perfusion and is often more intense at night, due to the absence of the effects of gravity on blood flow. Thus, it is relieved by hanging the lower extremity off the bed or by standing up and walking. Rest pain in CLI may be accompanied by tissue loss ranging from ulcers to frank necrosis and gangrene, which may lead to major amputation and resultant stump pain, phantom limb pain, or post-amputation mechanical back pain.[1,2,4,5,7,8]

Pathophysiology and Etiology of Pain in PAD

The pathophysiology of pain in PAD is multifactorial, complex, and not fully understood. Based on the latest proposed classification, PAD pain may be nociceptive, neuropathic, or mixed, where nociceptive and neuropathic elements coexist (Table 1).[4,5,7-10] Identification of the primary pathophysiological pathway in each stage of PAD is fundamental for the constitution of an appropriate treatment strategy (Table 2).[4,5,7,8,10,11]

Nociceptive pain is mediated through nociceptive receptors, which are located in the outer and middle layers of the wall of large and medium-sized arteries. These receptors may be activated by dilation or dissection, whereas the painful stimulus is often further enhanced by stimulation of the ANS fibers that cover large vessels, such as the aorta. Moreover, in patients with PAD, nociceptive pain further escalates because of the destruction of tissues by chronic inflammation, which in turn activates the somatosensory nervous system.[5,9] This surge of inflammatory mediators, including cytokines and chemokines, triggers nociceptors and subsequently downregulates their threshold, a phenomenon known as peripheral sensitization. This state of increased responsiveness is responsible for the activation of the threshold of pain pathways from non-painful or lower threshold stimuli and for the perceived aggravated response to noxious stimulation.[5]

Neuropathic pain is the result of a lesion or disease of the somatosensory nervous system. This may have an impact on the function or structure of the somatosensory nervous system, leading to sensory loss and an increased responsiveness to noxious and innocuous stimuli. Neuropathic pain is a critical component of CLI and indicates the long-term nature of the underlying disease. Experts suggest that alterations in ion channels, G-protein-coupled receptors, neurotransmitters, and central activation constitute the main pathophysiological components of neuropathic pain.[5]

Table 1. Pathophysiological Classification of Pain in Patients with PAD	
Primary pathophysiological mechanism of pain	**PAD stage**
Nociceptive	Ischemia (acute ischemia or early-stage PAD) Ischemia (end-stage PAD) Stump pain Mechanical back pain after limb amputation
Neuropathic	Ischemia (end-stage PAD) Stump pain
Mixed	Ischemia (end-stage PAD) CRPS: stump pain, phantom limb pain, mechanical back pain after limb
PAD, peripheral artery disease; CRPS, complex regional pain syndrome	

Table 2. Etiology of Acute Pain in Patients with PAD	
Acute pain	
Acute lower extremity ischemia	Atherosclerotic plaque rupture
Acute exacerbations of chronic pain	
IC, CLI	Atherosclerosis with progressive disease deterioration
Limb amputation	
Stump pain	Exposure of large and different tissue surfaces to a multitude of nociceptors under strong noxious stimulation
Phantom limb pain	Central sensitization
Mechanical back pain	Exacerbation of pre-existing conditions, prolonged recumbency, and early stages of prosthesis use
PAD, peripheral arterial disease; IC, intermittent claudication; CLI, critical limb ischemia	

Moving on to mixed pain, both advanced IC and CLI, where both neuropathic and nociceptive pain elements coexist with severe chronic inflammation, constitute a typical example.[5,9] In addition, patients with PAD may suffer from mixed pain after lower limb amputation. Following limp amputation, an interaction of the sympathetic nervous system with the first-order sensory neuron is established, which leads to central sensitization, which is the increased responsiveness of the brain and spinal cord nociceptors to normal or below-normal intensity of afferent stimulus. The aforementioned changes, with subsequent modifications of vascular network reactivity, indicate the existence of central/complex regional pain syndromes (CRPS), which play a key role in phantom limb pain.[5]

It should be highlighted that in 2016, the term nociplastic pain was defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage that causes peripheral nociceptors activation or evidence of disease or lesion of the somatosensory system causing the pain".[12] According to the latest literature, this fairly new concept of pain appears in chronic pain conditions. From a pathophysiological point of view, three main mechanisms have been recognized: supraspinal, spinal, and peripheral mechanisms. However, no study has indicated the implication of oncoplastic pain in any stage of PAD.[12]

Proposed Stepwise Pain Management for PAD

According to experts, managing the multifaceted nature of pain in PAD is challenging and hence requires a multifactorial approach. Of note, in addition to the proposed pain management strategy, optimal management of PAD seems to be of paramount importance for the adequate alleviation of pain. Nevertheless, when the exacerbations of chronic pain are considered, treatment of the neuropathic element of pain is considered to be rather essential.[5,6]

Based on the current literature, it is recommended that optimal pain management should be individualized according to the patient, his/her comorbidities, the underlying pathophysiology of the pain, and the respective clinical entity (PAD). Holistic multifactorial analgesia based on pharmaceutical agents, invasive techniques, and non-pharmacological methods appears to prevail because it targets several sites throughout the pain pathways, providing better analgesic effects.

Pharmaceutical Pain Management

The model of Channels-Enzymes-Receptors Targeted Analgesia (CERTA), a multimodal pain strategy, is proposed for optimal pharmaceutical pain management.[2] Based on CERTA, a pain treatment strategy is adopted according to the pathophysiological pathways of pain in each stage of PAD. This model utilizes a variety of analgesic agents, depending on pain pathways, in low doses in terms of maximum safety and therapeutic efficacy for each agent. CERTA intends to be a stepwise therapeutic intervention with the titration of several opioids and non-opioid analgesics as the intensity of pain increases. Tables 3-5 summarizes the proposed pharmaceutical pain management strategies according to pain intensity and the primary pathophysiological element.[10,13-19]

It should be noted that the use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with PAD requires extreme vigilance because of the high probability that there might be several contraindications for administration,

including comorbidities, bleeding predisposition, or active bleeding.[5,6,14,17,18] Moreover, in contrast to intravenous or oral NSAIDs, topical or transdermal NSAIDs achieve analgesia through local infiltration and subsequently increase the concentration of the drug up to 4-7 times in the target tissues compared with plasma concentrations. Pharmaceutical forms intended for topical use are considered ideal for patients with impaired renal function or elderly patients prone to elevated plasma concentrations of the drug, as well as for patients with multiple comorbidities, such as patients with gastric ulcer and cardiovascular diseases, in which the use of oral NSAIDs is contraindicated.[14,17,18]

Table 3. Pharmaceutical Pain Management in Mild Pain (NRS 1-3/VAS 1-3, Step 1)

Nociceptive	Paracetamol (1 g) Paracetamol SL 0.5gr x2 NSAIDs: ibuprofen, 400 mg; naproxen, 500 mg; diclofenac, 50 mg; celecoxib, 200 mg NSAIDs: diclofenac topical gel 1% (maximum dose: 2 gr upper extremities, 4 gr lower extremities), solution 1.5% (maximum dose: 40 drops), transdermal patch 1.3% (1 patch)
Neuropathic Mixed/CRPS	Lidocaine: transdermal patch 4-5% (up to 3 patches), lidocaine 2.5% + prilocaine 2.5% gel (up to 20 gr in 200 cm^2) Capsaicin: transdermal patch 3.75-8% (up to 4 patches)

NRS, numerical rating scale; VAS, visual analogue scale; PO, oral administration; SL, sublingual administration; NSAIDs, non-steroidal anti-inflammatory drugs; CRPS, complex regional pain syndrome

Table 4. Pharmaceutical Pain Management for Moderate Pain (NRS 4-6/VAS 4-6#, Step 2)

Nociceptive	Paracetamol (1 g) NSAIDs: ibuprofen IV 400-800 mg, diclofenac NSAIDs: diclofenac topical gel 1% (maximum dose: 2 gr upper extremities, 4 gr lower extremities), solution 1.5% (maximum dose: 40 drops), transdermal patch 1.3% (1 patch)
Neuropathic Mixed/CRPS	Ketamine: IV 0.1-0.3 mg kg^{-1} (single dose in 10-15 minutes) or IV 0.15 mg kg^{-1} h^{-1} (continuous infusion), or IN 0.7-1 mg kg^{-1} Gabapetin 50 mg or pregabalin 25 mg (GABA) Duloxetine PO 30 mg (SNRIs) Amitriptyline PO 10-25 mg (TCAs)

#Nitric oxide (NO; 50% O_2 + 50% N_2O, inhaled), while other forms of analgesia are installed.
NRS, numerical rating scale; VAS, visual analogue scale; IV, intravenous administration; PO, oral administration; NSAIDs, non-steroidal anti-inflammatory drugs; CRPS, complex regional pain syndrome; GABA, gabapentinoids; SNRIs, selective norepinephrine receptor inhibitors; TCAs, tricyclic antidepressants

Table 5. Pharmaceutical Pain Management in Patients with Severe Pain (NRS ≥7/VAS ≥7#, Step 3)

Nociceptive	In addition to Step 2, the following steps are repeated: Morphine IV 0.05-0.1 mg kg^{-1} Fentanyl IV 0.5-1.0 μg kg^{-1} Ketamine: IV 0.1-0.3 mg/kg (single dose in 10-15 minutes) or IV 0.15 mg kg^{-1} h^{-1} (continuous infusion), or IN 0.7-1 mg kg^{-1} Lidocaine IV 1-2 mg kg^{-1} (single dose over 10 minutes, 200 mg maximum dose) or IV 0.5-3 mg kg^{-1} h^{-1} (continuous infusion, based on ideal body weight, 200 mg maximum dose) Dexmetatomidine IV 0.5-1.0 μg kg^{-1} (loading dose in 10 minutes) or IV 0.5-2 μg kg^{-1} h^{-1} (continuous infusion) or IN 1-2 μg kg^{-1}
Neuropathic Mixed/CRPS	In addition to Step 2, the following steps are repeated: $MgSO_4$ IV 70 mg kg^{-1} (in 4 hours with an average flow of 25 mL hr) Dexamethasone IV 8 mg with simultaneous administration of 250 mL 10% mannitol Morphine IV 0.05-0.1 mg kg^{-1} Fentanyl IV 0.5-1.0 μg kg^{-1} Lidocaine IV 1-2 mg kg^{-1} (single dose over 10 minutes, 200 mg maximum dose) or IV 0.5-3 mg kg^{-1} h^{-1} (continuous infusion, based on ideal body weight, 200 mg maximum dose) Dexmetatomidine IV 0.5-1.0 μg kg^{-1} (loading dose in 10 minutes) or IV 0.5-2 μg kg^{-1} h^{-1} (continuous infusion) or IN 1-2 μg kg^{-1}

#Nitric oxide (NO; 50% O_2 + 50% N_2O, inhaled) while other forms of analgesia are installed.
NRS, numerical rating scale; VAS, visual analogue scale; IV, intravenous administration; IN, intranasal administration

Invasive Techniques

If the above therapeutic interventions fail and the pain intensity remains high (numerical rating scale-*NRS* score or visual analog scale score>7), the use of invasive techniques in the form of peripheral nerve block (PNB) is mainly recommended in patients with CRPS.[15] Moreover, PNB attenuate the sympathetic tone and produce significant vasodilation, two important features in PAD-related ischemic pain. For patients with stump and phantom limb pain after amputation, PNB with the addition of clonidine to the local anaesthetic solution remains the gold standard. In patients undergoing below the knee amputation, the block of the sciatic nerve is sufficient, in contrast to the one above the knee amputation where the block of the femoral nerve is necessary.[5]

Non-pharmaceutical Pain Management

The implementation of non-pharmaceutical interventions is strongly recommended in parallel with pharmaceutical measures and always depends on the patient's age, developmental status, prevailing conditions, and severity of the current clinical condition (Table 6).[14,19]

Intermittent Pneumatic Compression

Although high-quality data are lacking, intermittent pneumatic compression (IPC) could serve as a safe and effective alternative for patients with non-operable PAD in an attempt to alleviate the symptoms, including pain, of PAD and CLI. It appears that IPC can reduce pain intensity and increase pain-free walking distance in patients who are not suitable candidates for open or endovascular surgical treatment and in those who require palliative care. The main idea behind this favorable profile of IPC is that implementation of IPC can improve venous outflow and arterial flow and can increase the shear stress and release of nitric oxide by the endothelium, leading to vasodilation and decreased peripheral resistance.[20,21]

Lifestyle Changes

Nutrition and Diet Therapy

Although high-quality data are still missing, it seems that the Mediterranean diet, along with nuts and polyunsaturated fats, may be associated with a lower incidence of PAD, while it may improve blood flow and reduce pain in patients with established PAD.[22] Overall, adherence to a healthy diet, rich in antioxidants, in an attempt to reduce chronic inflammation, oxidative stress, and endothelial dysfunction has been associated with improved outcomes in PAD.[22] Moreover, it has been reported that oral antioxidants such as vitamin E, vitamin C, beta-carotene, ginkgo biloba, cocoa, and flavonoids may lead to longer pain-free walking distances in patients suffering from chronic PAD.[22,23] However, there is a paucity of data regarding their value in the acute phase of the disease.

Table 6. Non-pharmaceutical Interventions

Adequate time available for history taking and patient interaction	Music therapy
Reassurance and attentive listening	Aromatherapy
Empathy	Discussion with a psychologist or cognitive therapy
Eye contact	Massage
Use of wheelchair or wheeled bed	Acupuncture
Resting body position and/or resting of the suffering limb	Transcutaneous electrical nerve stimulation
Tools for distraction: television, tablet applications, virtual reality, and book reading	Infiltration and/or massage of trigger points

Smoking Cessation

Smoking can increase the levels of potent vasoconstricting peptides, such as endothelin-1, for approximately 15 minutes.[22] Long-term increased endothelin-1 levels can reduce muscle blood flow and compromise vasodilation.[23] Thus, smoking cessation is associated with a decreased risk of progression from PAD to CLI, improved walking ability, and decreased claudication symptoms.[22,23] However, a direct association between smoking cessation and ischemic pain exacerbation has not been established.[22]

Supervised Exercise Therapy

Exercise training, including aerobic and strength training, as tolerated with gradually increased physical activity or exercise to near-maximal claudication levels, has been proven to be beneficial to ischemic pain management due to enhanced perfusion, muscle oxygen extraction capacity, regulation of vessels, and vascular endothelium function.[22] Compared with home-based training, supervised exercise therapy (SET) is a more effective strategy for the management of symptomatic PAD.[22] SET is defined as 30-60 min of treadmill or track walking to the point of pain, followed by rest. SET walking programs are the recommended first-line therapy for claudication.[22] Self-directed walking programs are recommended as second-line treatment when SET is not applicable. According to the results of the ERASE trial, SET combined with revascularization in patients with aortoiliac or femoropopliteal PAD demonstrated increased maximum walking distance, pain-free walking distance, and better quality of life.[22,23] However, SET is contraindicated for patients with ischemic pain at rest, and there is a paucity of data regarding its value in the acute phase of the disease. Lastly, regarding high- or low-intensity exercises, there is no available evidence to support their value in terms of better outcome.[22]

Figure 1 summarizes the proposed algorithm for a stepwise and multimodal pain approach for PAD.

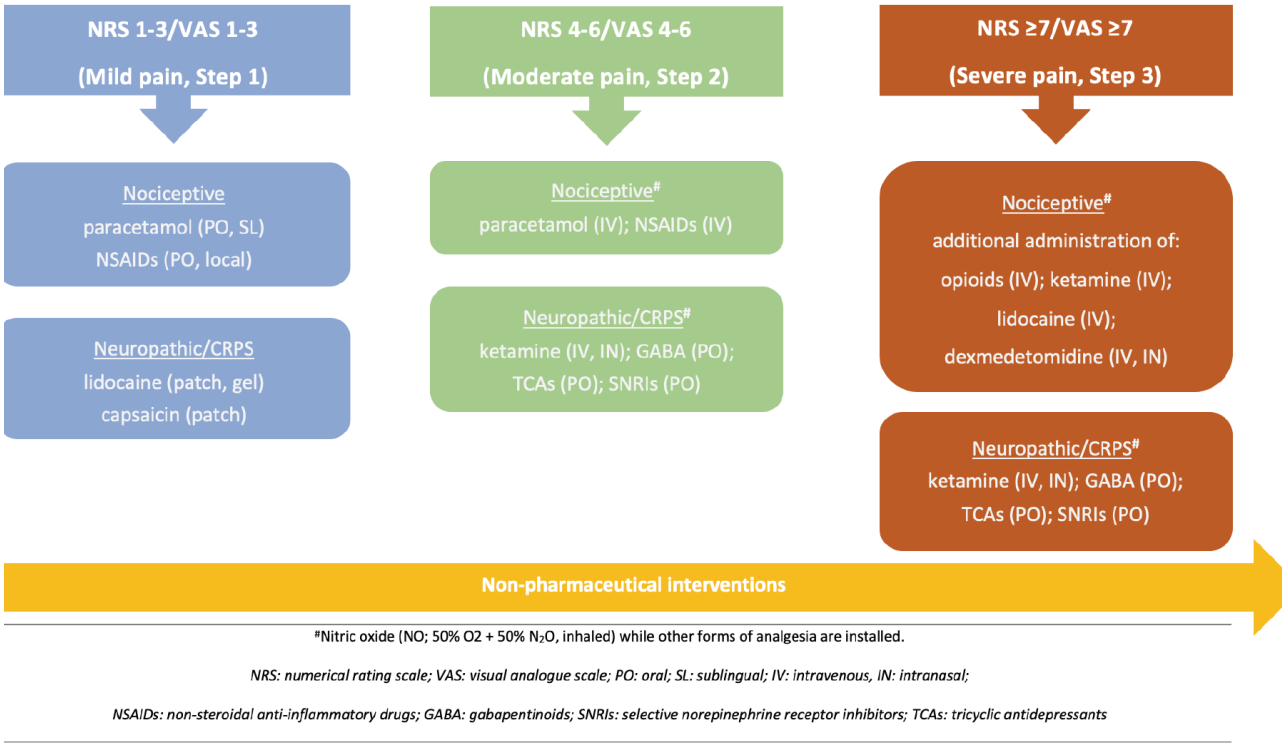

Figure 1. Algorithm for stepwise pain management in PAD.

PAD, peripheral artery disease.

Conclusion

PAD is prevalent, and pain is a key diagnostic feature of symptomatic PAD. Inadequate pain control may be detrimental to patients with PAD. Hence, optimal and comprehensive pain therapy is mandatory. However, the management of acute pain in PAD remains challenging. An individualized, patient-centered, multimodal pain strategy based on the underlying pathophysiological mechanisms of each stage of PAD, including lifestyle modifications, is key to a holistic and effective pain approach for patients suffering from PAD.

Footnotes

Author Contributions: Surgical and Medical Practices - M.P.N., A.C., P.N., K.S., M.B., M.M., E.A.; Concept - M.P.N., M.M., E.A.; Design - M.P.N., A.C., P.N., K.S., M.B., M.M., E.A.; Data Collection and/or Processing - M.P.N., A.C., P.N., K.S., M.B., M.M., E.A.; Analysis and/or/Interpretation - M.P.N., A.C., P.N., K.S., M.B., M.M., E.A.; Literature Review - M.P.N., E.A.; Writing - M.P.N., A.C., P.N., K.S., M.B., M.M., E.A.

Declaration of Interests: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Sonnenschein K. No pain, no gain in PAD. *Vasa.* 2021;50(6):483. [CrossRef]
2. Campia U, Gerhard-Herman M, Piazza G, Goldhaber SZ. Peripheral artery disease: past, present, and future. *Am J Med.* 2019;132(10):1133-1141. [CrossRef]
3. Primary Panel; Abramson BL, Al-Omran M, et al. Canadian Cardiovascular Society. 2022 Guidelines for peripheral arterial disease. *Can J Cardiol.* 2022;38(5):560-587. [CrossRef]
4. Ramsingh J, Kingsmore D. Peripheral vascular disease. In: Touyz RM, Delles C, eds. Textbook of Vascular Medicine. 1st ed. Glasgow: Springer; 2019:473-484. [CrossRef]
5. Seretny M, Colvin LA. Pain management in patients with vascular disease. *Br J Anaesth.* 2016;117(Suppl 2):ii95-ii106. [CrossRef]
6. Johansen K. Pain due to vascular causes. In: Ballantyne JC, Fishman SM, Rathmell JP, eds. Bonica's Management of Pain. 5th ed. China: Wolters Kluwer; 2018:1860-1884. [CrossRef]
7. Acute Leg Ischemia. In: Wahlberg E, Olofsson P, Goldstone J. Emergency vascular surgery a practical guide. 1st ed. USA: Wolters Kluwer; 2007:119-133. [CrossRef]
8. Fritz D. Vascular emergencies. In: Stone KC, Humphries RL, eds. CURRENT Diagnosis & Treatment Emergency Medicine, 7e. USA: McGraw-Hill Medical; 2011:687-706. [CrossRef]

9. Vadivelu N, Whitney CJ, Sinatra RS. Pain pathways and acute pain processing. In: Sinatra RS, de Leon-Casacola O, Ginsberg B, Viscusi E. Acute Pain Management. 1st ed. USA: Cambridge University Press; 2009:3-20. [CrossRef]
10. Jones MR, Prabhakar A, Viswanath O, et al. Thoracic outlet syndrome: a comprehensive review of pathophysiology, diagnosis, and treatment. *Pain Ther*. 2019;8:5-18. [CrossRef]
11. Bradley S, Quenzer F, Wittler M. Ruptured visceral artery aneurysms: a deadly cause of epigastric pain. *Clin Pract Cases Emerg Med.* 2019;3:132-136. [CrossRef]
12. Bułdyś K, Górnicki T, Kałka D, et al. What do we know about nociplastic pain? *Healthcare (Basel)*. 2023;11(12):1794. [CrossRef]
13. Cisewski DH, Motov SM. Essential pharmacologic options for acute pain management in the emergency setting. *Turk J Emerg Med.* 2019;19:1-11. [CrossRef]
14. Pain Assessment and Management Initiative. Pain Management and Dosing Guide. Available online: https://pami.emergency.med.jax.ufl.edu/resources/dosing-guide/. Accessed on January 9, 2022 [CrossRef]
15. Casale R, Atzeni F, Sarzi-Puttini P. The therapeutic approach to complex regional pain syndrome: light and shade. *Clin Exp Rheumatol*. 2015;33(1 Suppl 88):126-139. [CrossRef]
16. Hachimi-Idrissi S, Dobias V, Hautz WE, et al. Approaching acute pain in emergency settings; European Society for Emergency Medicine (EUSEM) guidelines-part 2: management and recommendations. *Intern Emerg Med.* 2020;15:1141-1155. [CrossRef]
17. EMRA. Pharmacology of Pain. Available online: https://www.emra.org/books/pain-management/pharmacology-of-pain. Accessed on January 9, 2022. [CrossRef]
18. EMRA. Neuropathic pain. Available online: https://www.emra.org/books/pain-management/neuropathic-pain. Accessed on January 9, 2022 [CrossRef]
19. Pak SC, Micalos PS, Maria SJ, Lord B. Nonpharmacological interventions for pain management in paramedicine and the emergency setting: a review of the literature. *Evid Based Complement Alternat Med.* 2015;2015:873039. [CrossRef]
20. Nickles MA, Ennis WJ, O'Donnell TF Jr, Altman IA. Compression therapy in peripheral artery disease: a literature review. *J Wound Care*. 2023;32(Suppl 5):25-30. [CrossRef]
21. Alvarez OM, Wendelken ME, Markowitz L, Comfort C. Effect of high-pressure, intermittent pneumatic compression for the treatment of peripheral arterial disease and critical limb ischemia in patients without a surgical option. *Wounds*. 2015;27(11):293-301. [CrossRef]
22. Woo K, Murphy C, Gregg E, Moralejo J, LeBlanc K, Brandys T. Management of pain in people living with chronic limb threatening ischemia: highlights from a rapid umbrella review. *J Wound Ostomy Continence Nurs*. 2024;51(5):371-376. [CrossRef]
23. King RW, Canonico ME, Bonaca MP, Hess CN. Management of peripheral arterial disease: lifestyle modifications and medical therapies. *J Soc Cardiovasc Angiogr Interv*. 2022;1(6):100513. [CrossRef]

DOI: 10.4274/TJAR.2024.241676

Original Article
Intensive Care

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2024;52(6):207-212

The Anticipated Organ Donation Approach Increases the Number of Organ Donors

Erwan d'Aranda[1], Valérie Arsonneau[2], Didier Demory[2,3]

[1]Sainte Anne Military Teaching Hospital, Intensive Care Unit, Toulon, France
[2]CHITS Sainte-Musse Hospital, Local Organ Procurement Organization, Toulon, France
[3]CHITS Sainte-Musse Hospital, Intensive Care Unit, Toulon, France

Cite this article as: d'Aranda E, Arsonneau V, Demory D. The Anticipated Organ Donation Approach Increases the Number of Organ Donors. *Turk J Anaesthesiol Reanim.* 2024;52(6):207-212.

Abstract

Objective: Deficiency of organs for transplantation is a significant public health issue. French learned societies accept intensive care unit admission for patients with catastrophic neurological prognosis to optimize organs prior to probable brain death. We evaluated the implementation of a specific ethical care procedure for these patients.

Methods: A descriptive before-after study was conducted, comparing the 2009-2012 period to the 2013-2016 period, during which this procedure was applied.

Results: The number of patients increased from 145 to 186 (+28.3%) and the number of harvested organs increased from 323 to 485 (+50.1%). The anticipated organ donation approach was initiated 135 times. Of the 117 meetings with families, 83 (71%) consented to organ donation. Fifty-three (64%) patients were brain dead, and 49 (92%) of these patients had 194 organs harvested.

Conclusion: The anticipated approach increased the number of donors and organs suitable for grafts. The application of a specific protocol for managing untreatable catastrophic neurological patients improved communication between hospital staff and families and respected patient autonomy by offering options for either organ donation or palliative care.

Keywords: Brain death, intensive care, organ donors, organ procurement, tissue donors

Main Points

- Implementing a specific protocol for managing catastrophic neurological patients resulted in an increase in actual donors and organ donors.
- This protocol respects patients' autonomy and facilitates relationships with their families.
- This protocol could help reduce the shortage of transplant recipients.

Introduction

The shortage of transplanted organs is a significant medical and social issue, as transplantation is often the best therapeutic option for end-stage organ failure.[1] One donor has the potential to impact the lives of six others. Organ donation is a national priority in France, with several "graft plans" implemented by the French Bio-medicine Agency, the national organ procurement organization (OPO), to increase public and healthcare staff awareness.[2] There is no age limit for organ donors, and with improved medical management, the criteria for potential organ donor selection have been expanded since 2003.[3] In 2016, 9.9% of the donors were alive, 90.1% were deceased, and 95.2% were brain dead.[4] Over the past 20 years, the etiology of death has changed, with traumatic brain injuries accounting for over 50% of deaths in the 1990s and over 60% of deaths today attributed to stroke. In 2016, 3,676 patients were identified as potential organ donors, but only 1,770 patients became actual organ donors, resulting

Corresponding author: Erwan d'Aranda, e-mail: erwan.daranda@gmail.com

Received: July 16, 2024 Accepted: September 22, 2024

in 5,891 solid organ transplantations. Although impressive, the annual number of organ transplants is low compared with the 15,465 patients on the waiting list, which continues to grow.[4] Patients with renal failure are the most numerous on the waiting list, and they are increasingly older, which decreases their chances of transplantation. An increase in potential donors is necessary.

Given the lack of grafts and longer waiting lists, the use of marginal transplants has increased, particularly in elderly patients. Intensive care unit (ICU) admission of patients with catastrophic neurological prognosis presents ethical and economic challenges for ICU teams. The legitimacy of this care was established in 2010. French intensivist approved ICU admission of patients with severe coma after infarction or cerebral hemorrhage in the absence of therapeutic resources and when progression toward brain death is likely for exclusive organ donation.[1,5] This is an anticipated organ donation approach. Implementation in hospitals requires new practices to identify potential donors, select patients, and communicate with families. We evaluated the implementation of a specific ethical care procedure for patients with catastrophic brain injuries.

Methods

The study protocol consisted of a retrospective analysis of an anonymised database without any direct human involvement. In accordance with the French law at the time of the study, the protocol received approval (approval number: 8.4.17, no.: 376) from the local ethics review board on April 8, 2017, at the military teaching hospital Sainte Anne, Toulon, France.

We conducted a retrospective cohort study in a local OPO located in Centre Hospitalier Intercommunal de Toulon, France, which works with four regional hospitals. We compared two periods: 2009-2012, during which an anticipated organ donation approach was not in place, and 2013-2016, during which a specific protocol was initiated. We included all patients diagnosed with complete brain death or who were included in the anticipated organ donation approach. The collected data included demographics (age), number of potential organ donors, number of actual organ donors, number and type of organs retrieved, and evolution after identification of potential organ donors or after inclusion in the anticipated organ donation approach.

Anticipated Organ Donation

The aim of this approach is to admit patients to the ICU who do not have brain death but have a high probability of subsequent brain death. These patients require a specific protocol to avoid initiating an anticipated procedure if there is an obvious obstacle to organ donation, if the patient cannot be medically treated (e.g., no beds available in the ICU), or if the patient is not progressing toward brain death. We performed step-by-step screening in the emergency unit, stopping the procedure when any step resulted in a "no" (Figure 1). We screened patients with catastrophic brain injuries after infarction or cerebral hemorrhage, in an absence of therapeutic resources, and after multidisciplinary ethics discussions to make treatment withdrawal decisions.

The local OPO was contacted to coordinate the protocol. We evaluated whether the patient had a high probability of progressing toward brain death. We used locally defined criteria to identify a brain state preceding the "imminent brain death" state by 24-48 hours. These selection criteria evolved during the implementation of the procedure and included either a Glasgow coma score <5 without confounding factors and the absence of bilateral corneal reflex or the disappearance of three brainstem reflexes; an initial Glasgow coma score <7 with at least one negative element on computed tomography: obliterated basal cisterns, subfalcine herniation superior to 15 mm, hematoma

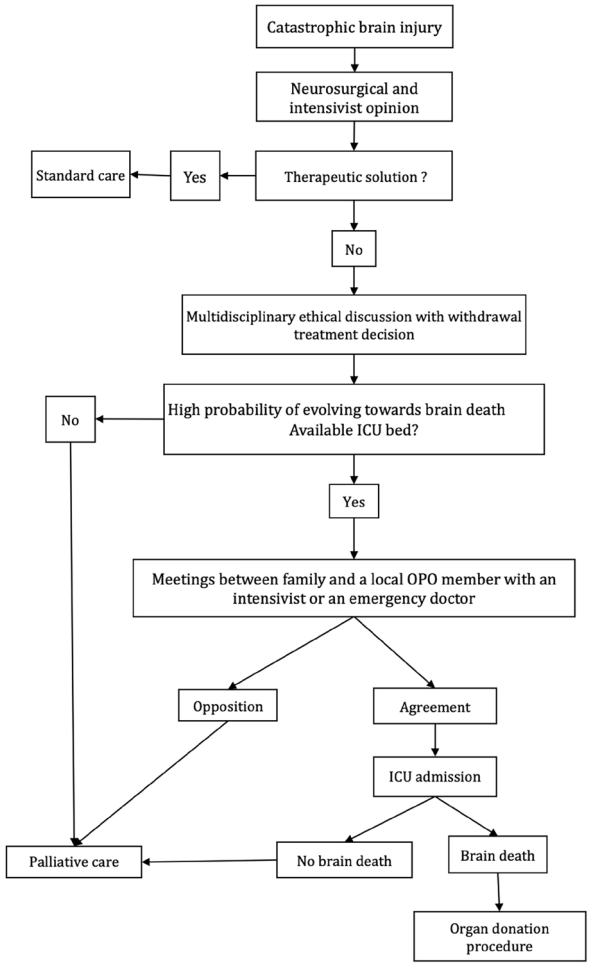

Figure 1. Step-by-step screening of a patient with catastrophic brain injury.

superior to 65 mL, or intraventricular hemorrhage with bleeding inside V3 or V4.

We subsequently evaluated whether the patient was a potential organ donor by reviewing their medical and surgical history, performing a clinical examination, and assessing kidney and liver function. If a bed was available in the ICU within 6 hours, the patient was included in the anticipated approach. The family was contacted to confirm that there was no opposition to organ donation under French law. A local OPO member met with an intensivist or an emergency doctor. Patients without opposition were admitted to the ICU for nontherapeutic care, which only included organ preservation and patient comfort. We allowed 48 hours for brain death diagnosis. For patients whose families objected to organ donation, or if there were no free beds in the ICU or no brain death after 48 hours, palliative care was initiated. The local OPO member established a moral contract with the family to inform them and make decisions within a reasonable timeframe.

Management of Potential Organ Donors

The management of potential organ donors was guided by international guidelines.[2,6] In the absence of evidence of cortical function and brainstem reflexes with no confounding factors, an apnea test was performed with continuous positive airway pressure at 10 cm H_2O. The ancillary testing methods for determining brain death were cerebral angiography and electroencephalography.

Statistical Analysis

Quantitative data are provided as numbers, means (standard deviation), or percentages. All analyses were performed with Excel 2011 (Microsoft, USA).

Results

We identified 331 potential organ donors with brain death over 8 years. Of these, 210 became actual donors, resulting in 808 organs being transplanted. Table 1 presents the number of organ donors during the first and second periods and the anticipated approach during the second period. A mean of 36.5 potential organ donors per year before 2012 and 46.5 per year beginning in 2012 represented a gain of 28.3%. The number of actual organ donors increased from 22.75 per year to 29.75 per year, representing a gain of 30.7%. The number of solid organs transplanted increased by 50.1% from a mean of 80.75 transplantations per year to 121.25 transplantations per year. The number of annual renal grafts is shown in Figure 2.

During 2013-2016, the anticipated organ donation approach was initiated 135 times. A flow chart of patient evolution is provided in Figure 3. Among the 53 patients who died, 49 (92%) were actual donors.

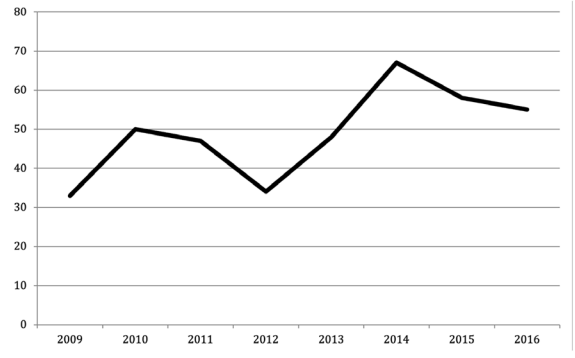

Figure 2. Number of renal grafts per year.

Table 1. Organ Donation Data for the Two Periods and the Anticipative Approach

Group	All patients	All patients	Evolution between the two periods	Only patients requiring the anticipated approach
Period	2009-2012	2013-2016		2013-2016
Age	56.6	58.2		67.5
Potential organ donors	145	186	+28.3%	
Organ donors	91	119	+30.7%	49
Organs transplanted	323	485	+50.1%	194
Kidney	164	228	+39%	98
Liver	68	103	+51.5%	43
Heart	33	42	+27.3%	20
Lung	53	102	+92.5%	29
Pancreas	5	10	+100%	4

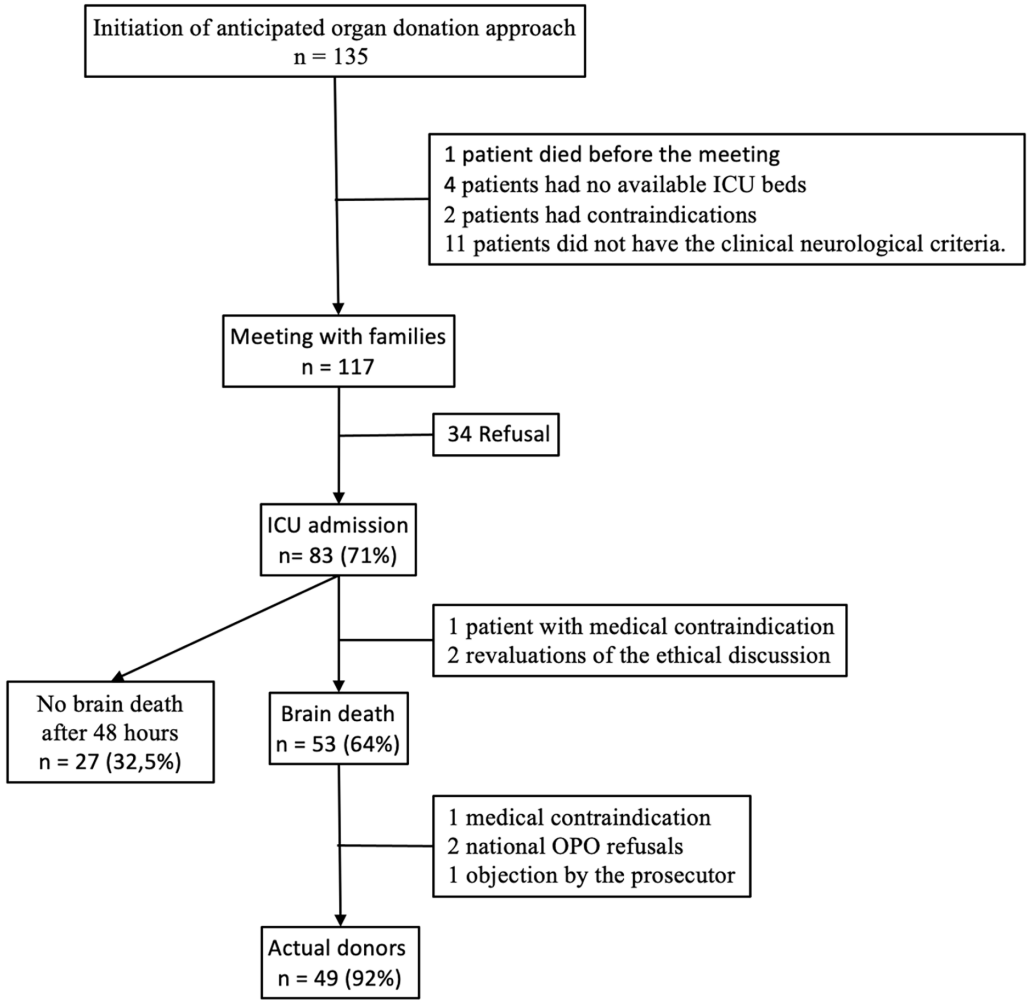

Figure 3. Flow chart of patient evolution with an anticipated organ donation approach during the 2013-2016 period.

ICU, intensive care unit; OPO, organ procurement organization

Discussion

Our study demonstrates that the anticipated organ donation approach increased the number of actual organ donors and the number of organs harvested, particularly kidneys. The number of potential donors increased by 28.3% between the two periods, whereas the national increase was 12.2%.[4]

The anticipated approach is initiated early after neuroaggression and is often implemented in the hospital emergency room after an initial clinical and paraclinical workup, including cerebral and transcranial Doppler ultrasonography. Identifying an untreatable cerebral lesion and making a decision after a multidisciplinary ethics discussion regarding the therapeutic intensity of palliative care will orient the patient toward the anticipated approach. Identifying early clinical and paraclinical data to predict subsequent brain death is essential for preventing unnecessary organ care. Retrospective studies have created scores to predict brain death, but no prospective studies have defined pertinent predictive criteria. de Groot et al.[7] defined the principle of "imminent brain death" as "a mechanically ventilated, deeply comatose patient admitted to an ICU with irreversible catastrophic brain damage of known origin".[3] This condition requires a Glasgow coma score of 3 and progressive absence of at least three of six brainstem reflexes, or a score of E0M0B0R0 on the Full Outline of UnResponsiveness scale. Although this stage suggests a final evolution toward brain death, it is rarely detected in the emergency department before ICU admission. The condition is more frequently detected within 48 hours of ICU admission due to hematoma, ischemic edema, or hydrocephalus. No clinical argument has been established to predict the occurrence of brain death with sensitivity, and imagery data alone cannot predict it.[8,9] The evolution of the results of repeated neurological examinations, cerebral imagery, and transcranial Doppler ultrasonography over

time, while eliminating confounding factors, enables clinicians to predict subsequent brain death. Although no usable predictive score is available in current clinical practice, data from the literature and successful experience have enabled us to select the criteria used in our protocol.

The anticipated organ donation approach is a proactive solution to organ donation[10,11] and involves all players from the emergency department to the ICU. Player involvement relies on the conviction that taking the time to confirm brain death can help resolve public health problems. de Groot et al.[7] reported that professional practices have been modified in recent years. When brain death is anticipated, communication with families regarding the possibility of organ donation.

In our local OPO during the 2013-2016 period, 62% of the meetings with families occurred before the diagnosis of brain death was confirmed. Out of the 117 anticipated approaches performed, more than two-thirds of patients were admitted to the ICU, and over half of them donated organs. This overall proportion is close to that recorded in patients with brain death. Our approach increased the number of patients listed as brain dead in a population base, and the grafts confirmed our results. Experience with this technique acquired over time should result in an increase in the number of organs available for grafting. The next step is to fine-tune the predictive criteria and reduce errors secondary to procedure implementation. The refusal rate observed by our team was lower than that observed annually in France (29% vs. 33.7%).[4]

The interest of a standardized "anticipated approach" procedure is to enable all healthcare staff to identify potential donors beginning in the emergency room and to respect ethics and good practices during end-of-life situations. The algorithm for the care of untreatable catastrophic neurological patients is an aid for physicians, enabling them to resolve ethical problems between respecting the wishes of patients and public health given the shortage of grafts. The local OPO does not intervene in multidisciplinary discussions regarding the intensity of patient therapy but only intervenes after the decision to perform palliative care. In our experience, the local OPO is a real added value, as it improves the experience of the healthcare team and families by coordinating the data of different players. Potential patients were screened by specially trained personnel. These situations are emotionally stressful for families, and the healthcare team must be capable of proposing adapted and coherent care. Invasive treatment must not be continued if the patient is not ultimately brain dead or if there is a contraindication. This approach can reduce the number of available organs for patients on waiting lists. The positive evolution of the number of patients and organs harvested in our study should encourage teams to develop this anticipated approach. Implementation of this approach in hospitals requires the writing of a specific procedure that describes the steps involved in this type of care. The families are included in this donor approach.

The absence of proof of brain death is considered a failure by the healthcare team and family. Since 2014, France has authorized the harvesting of organs from patients who died of cardiac arrest after the discontinuation of active ICU therapy (Maastricht 3). Patients under 65 years of age who are included in the procedure can be donors despite the absence of proof of brain death. Therefore, an "ethical" continuity exists in these procedures that makes it possible to reduce the number of failures in the donor procedure.

The anticipated approach involves older patients who, for the most part, are stroke victims with multiple pathological histories. Most of these cases are "imperfect" donors, for whom the question of so-called "expanded criteria" organs. The use of grafts obtained from donors with expanded criteria is no longer in question,[12] with the development of organ preservation techniques by machine perfusion[13] enabling access to grafts for many patients who cannot be otherwise operated on.

Study Limitations

We acknowledge several limitations of our study. First, we conducted a retrospective cohort study with limited available demographic and clinical data or reasons for family refusal. In addition, the initiation of the anticipatory approach was due to the medical team and their awareness of the detection and inclusion of these rapidly deteriorating patients for whom no care was previously offered, which may have underestimated our results. Finally, the criteria used to detect early a possible transition to a state of brain death within 48 hours were based on limited published data and the local experience of practitioners, which may have led to the exclusion of potential donors.

Conclusion

The anticipated organ donation approach increases the number of organs available for transplantation, helping to address the public health issue of organ shortage. Implementing this approach requires a written protocol tailored to each hospital for the care of patients with untreatable catastrophic neurological injuries, as well as local OPO training and increased awareness among healthcare personnel. The anticipated approach respects patient autonomy by offering the option of organ donation or palliative care and aligns with the development of practices that facilitate communication between healthcare personnel and families. This procedure benefit from scientific advances in the early determination of predictive criteria for brain death and reinforces harvesting procedures after cardiocirculatory arrest.

Ethics

Ethics Committee Approval: The study protocol consisted of a retrospective analysis of an anonymised database without any direct human involvement. In line with the French law prevailing at the time of the study, the protocol received approval (approval no.: 8.4.17, no.: 376) from the local ethics review board on April 8, 2017, at Ministere De La Defense/H.I.A. Sainte Anne.

Informed Consent: This study protocol consisted of a retrospective analysis of an anonymised database

Footnotes

Author Contributions: Surgical and Medical Practices - D.D., E.d'A.; Concept -V.A., D.D., E.d'A.; Design - V.A., D.D., E.d'A.; Data Collection and/or Processing - V.A., E.d'A.; Analysis and/or/Interpretation - V.A., D.D., E.d'A.; Literature Review - V.A., D.D., E.d'A.; Writing - V.A., D.D., E.d'A.

Declaration of Interests: The authors declare no conflicts of interest.

Funding: No funding was received for conducting this study.

References

1. Citerio G, Cypel M, Dobb GJ, et al. Organ donation in adults: a critical care perspective. *Intensive Care Med.* 2016;42(3):305-315. [CrossRef]
2. Ministère du travail, de la santé, et des solidarités. Greffes et dons d'organes : plans d'actions 2022-2026. Ministère du travail, de la santé, et des solidarités. Published on July 15, 2024. Accessed July 15, 2024. https://sante.gouv.fr/soins-et-maladies/autres-produits-de-sante/article/greffes-et-dons-d-organes-plans-d-actions-2022-2026. [CrossRef]
3. Metzger RA, Delmonico FL, Feng S, Port FK, Wynn JJ, Merion RM. Expanded criteria donors for kidney transplantation. *Am J Transplant.* 2003;3(Suppl 4):114-125. [CrossRef]
4. Agence de la biomédecine. Le rapport médical et scientifique 2022. Published September 17, 2023. Accessed on July 15, 2024. https://www.agence-biomedecine.fr/Le-rapport-medicalet-scientifique-2022est-en-ligne [CrossRef]
5. Bollaert PE, Vinatier I, Orlikowski D, Meyer P. Stroke management by intensivist in adults and children (subarachnoid hemorrhage excluded, new-born excluded). Société de réanimation de langue francaise experts recommendations. *Réanimation.* 2010;19(6):471-478. [CrossRef]
6. Kotloff RM, Blosser S, Fulda GJ, et al. Management of the potential organ donor in the icu: society of critical care medicine/American college of chest physicians/association of organ procurement organizations consensus statement. *Crit Care Med.* 2015;43(6):1291-1325. [CrossRef]
7. de Groot YJ, Jansen NE, Bakker J, et al. Imminent brain death: point of departure for potential heart-beating organ donor recognition. *Intensive Care Med.* 2010;36(9):1488-1494. [CrossRef]
8. Galbois A, Boëlle PY, Hainque E, et al. Prediction of evolution toward brain death upon admission to ICU in comatose patients with spontaneous intracerebral hemorrhage using simple signs. *Transpl Int.* 2013;26(5):517-526. [CrossRef]
9. Humbertjean L, Mione G, Fay R, et al. Predictive factors of brain death in severe stroke patients identified by organ procurement and transplant coordination in Lorrain, France. *Transpl Int.* 2016;29(3):299-306. [CrossRef]
10. Dalal AR. Philosophy of organ donation: Review of ethical facets. *World J Transplant.* 2015;5(2):44-51. [CrossRef]
11. Domínguez-Gil B, Murphy P, Procaccio F. Ten changes that could improve organ donation in the intensive care unit. *Intensive Care Med.* 2016;42(2):264-267. [CrossRef]
12. Tomita Y, Tojimbara T, Iwadoh K, Nakajima I, Fuchinoue S. Long-term outcomes in kidney transplantation from expanded-criteria donors after circulatory death. *Transplant Proc.* 2017;49(1):45-48. [CrossRef]
13. Kaths JM, Paul A, Robinson LA, Selzner M. Ex vivo machine perfusion for renal graft preservation. *Transplant Rev Orlando Fla.* 2018;32(1):1-9. [CrossRef]

DOI: 10.4274/TJAR.2024.241526

Original Article
Intensive Care

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2024;52(6):213-222

Evaluation of Delirium Risk Factors in Intensive Care Patients

Selin Erel[1], Eda Macit Aydın[2], Bijen Nazlıel[3], Lale Karabıyık[1,2]

[1]Gazi University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Ankara, Turkey
[2]Gazi University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Division of Intensive Care, Ankara, Turkey
[3]Gazi University Faculty of Medicine, Department of Neurology, Ankara, Turkey

Cite this article as: Erel S, Macit Aydın E, Nazlıel B, Karabıyık L. Evaluation of Delirium Risk Factors in Intensive Care Patients. *Turk J Anaesthesiol Reanim.* 2024;52(6):213-222.

Abstract

Objective: The negative effects of delirium in intensive care unit (ICU) patients necessitate the identification and management of risk factors. This study aimed to determine the incidence of delirium and its associated modifiable and non-modifiable factors in the ICU setting to provide valuable insights for better patient care and outcomes.

Methods: Patients admitted to the ICU underwent delirium screening twice daily. Comprehensive records of modifiable and non-modifiable risk factors were maintained throughout the ICU stay.

Results: The incidence of delirium was 32.5%. Age [odds ratio (OR) 1.04, confidence interval (CI) 1.02-1.06, $P < 0.001$)]. Illiteracy (OR 4, CI 1.19-13.35, $P=0.02$), hearing impairment (OR 3.37, CI 1.71-7.01, $P=0.001$), visual impairment (OR 3.90, CI 2.13-7.15, $P < 0.001$), hypertension (OR 2.56, CI 1.42-4.62, $P=0.002$), Sequential Organ Failure Assessment score (OR 1.21, CI 1.08-1.36, $P=0.001$), Acute Physiology and Chronic Health Evaluation II score (OR 1.20, CI 1.12-1.28, $P < 0.001$), presence of a nasogastric catheter/drain (OR 2.15, CI 1.18-3. 90, $P=0.01$), tracheal aspiration (OR 3.63, CI 1.91-6.90, $P < 0.001$), enteral nutrition (OR 2.54, CI 1.12-5.76, $P=0.02$), constipation (OR 1.65, Cl 1.11-2.45, $P=0.02$), oliguria (OR 1.56, Cl 1.06-2.28, $P=0.02$), midazolam infusion (OR 3. 4, Cl 1.16-10.05, $P=0.02$), propofol infusion (OR 2.91 Cl 1.03-8.19, $P=0.04$), albumin use (OR 2.39, Cl 1.11-5.14 $P=0.02$) and steroid use (OR 2.17, Cl 1.06-4.40, $P=0.03$) were found to be independent risk factors for delirium.

Conclusion: This study highlights several risk factors contributing to delirium, such as age, sensory impairment, educational level, procedural interventions, and medications. Oral nutrition and mobilization are effective strategies for reducing delirium incidence in the ICU.

Keywords: Cognition disorders**,** critical care, delirium, incidence, risk

Main Points

- Delirium is prevalent within intensive care unit (ICU) environments, and the incidence of hypoactive type delirium is higher than expected.
- Various risk factors contribute to delirium, including age, sensory impairment, education level, procedural interventions, and drugs.
- Strategies such as oral nutrition and mobilization can help reduce delirium incidence in the ICU.

Introduction

Delirium is a mental syndrome with a sudden onset in hospitalized patients, characterized by impaired cognitive function, and is more common in intensive care units (ICU).[1,2] This syndrome has many consequences, including prolonged hospital stays, elevated mortality rates, escalated healthcare costs, and a surge in the workload of healthcare providers.[3,4] Therefore, increasing the awareness of medical personnel regarding this syndrome in critically ill patients is of great importance for effective delirium management.[5]

The prevalence of delirium in ICUs is 22-84% and is higher and more variable than that in ward patients.[6,7] This variability may be due to the study design, differences in data collection, method of diagnosing delirium,

Corresponding author: Selin Erel, e-mail: selinerel@yahoo.com

August 06, 2024 October 10, 2024

patient characteristics, environmental conditions, and use of sedatives and analgesics. There are three classic types of delirium: hyperactive, hypoactive, and mixed. The diagnosis of hypoactive and mixed subtypes of delirium might be overlooked. However, these clinical subtypes may still be present in approximately one-third of all critically ill patients admitted to the ICU.[8,9]

Delirium is a multifactorial syndrome. The risk factors are classified as modifiable or non-modifiable. Advanced age, comorbidities, and visual impairment are examples of non-modifiable factors. Electrolyte and metabolic abnormalities, drugs, infection, pain, anaesthesia and surgery, intensive care interventions, malnutrition, mobilization, and lack of environmental stimulation are among the most common modifiable factors.[10,11] During the coronavirus disease-2019 pandemic, delirium was observed more frequently due to the mandatory stricter implementation of isolation measures in ICUs. Benzodiazepine use and absence of family visits were modifiable risk factors for delirium in this patient group.[12]

Early recognition of delirium is important for all intensive care patients. Identifying risk factors associated with delirium and closely monitoring high-risk patients are crucial to ensure effective management and care. The primary approach to delirium prevention involves addressing and eliminating modifiable risk factors. However, in situations where delirium is accompanied by severe agitation, pharmacological treatment may be necessary to ensure patient safety and enhance comfort.[13,14] Although drugs such as antipsychotics, benzodiazepines, and dexmedetomidine have been used to treat delirium symptoms, current guidelines do not support their routine use.[11,13-16]

In this prospective observational study, we aimed to determine the overall incidence of delirium, including hypoactive and mixed types that may be clinically overlooked, and to identify the associated modifiable and non-modifiable risk factors in ICU patients.

Methods

After obtaining ethics committee approval from the Gazi University Faculty of Medicine Clinical Research Ethics Committee (decision no.: 588, date: 10.9.2018), this prospective observational study was conducted between September 2018 and May 2019 at the Gazi University, Departments of Anaesthesiology ICU, Neurology, and General Surgery. All three tertiary ICUs involved in this study follow an arena-style design, which allows for optimal monitoring and patient care in a centralized setting.

Patients aged >18 years of age who were hospitalized in the ICU for >48 hours were included in the study. Patients who lacked proficiency in Turkish, failed to comply with the diagnostic test (Richmond Agitation and Sedation Score: RASS ≤-4), or had a documented medical history of Alzheimer's disease and/or dementia were excluded from the study (Figure 1).[17] Diagnosis of Alzheimer's disease, based on medical records before ICU admission. After ICU admission, patients with appropriate clinical conditions were screened using the Mini-mental test.

The evaluations were performed by the same anaesthesiologist, ensuring consistency across all patient assessments. This researcher was responsible for conducting twice-daily delirium screening tests at 8:00 am and 8:00 pm using the Confusion Assessment Method for the ICU to screen for delirium.[18] Demographic data (age, gender, body mass index, education level, and comorbidities), ICU type (anaesthesia, neurology, and general surgery), ward type before ICU admission, duration of hospital stay before ICU admission, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and Sequential Organ Failure Assessment (SOFA) score were recorded.

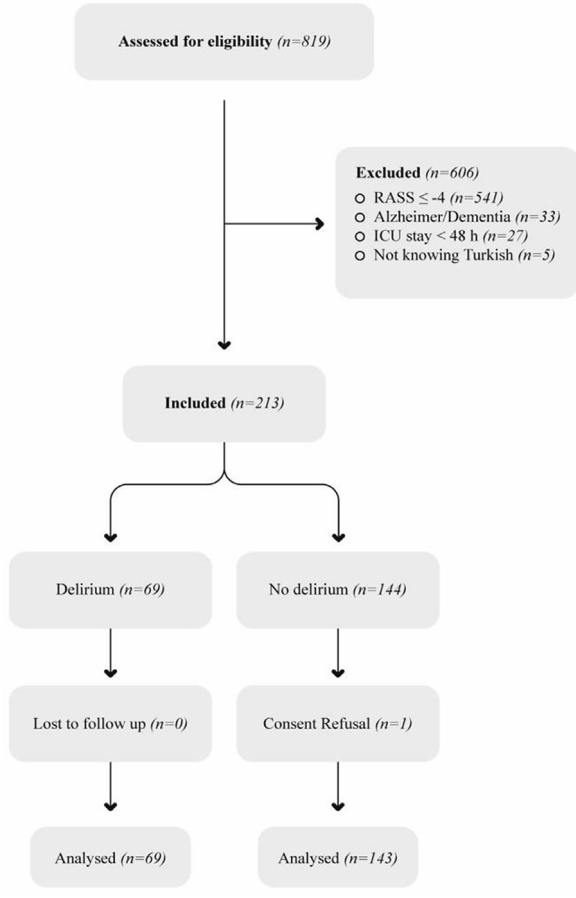

Figure 1. Flow chart of the study.

RASS; Richmond agitation and sedation score; ICU, intensive care unit.

The daily follow-up records included the presence of medical devices (such as endotracheal tubes, nasogastric tubes, and catheters), duration of mechanical ventilation, drug infusions, pain scores [using the visual analogue scale (VAS)], hemodynamic changes, oxygen requirements, shock status, electrolyte and acid-base imbalances, number of administered drugs, family visits, method of nutrition, urine output, frequency of defecation, infection status, and administration of sedative drugs. Patients diagnosed with delirium were continuously monitored. Follow-up involved tracking the specific drug treatments, total duration of delirium, and delirium relapse. Additionally, the length of ICU stay and discharge or mortality status of the patients were recorded.

To ensure objective data collection, the records were maintained by an independent investigator who was not involved in patient follow-up or treatment. Routine patient care, including the management of delirium and other medical conditions, was provided by intensivist who were not a part of the study, ensuring that treatment protocols were unaffected by the research procedures.

Statistical Analysis

The Statistical Package for the Social Sciences version 22.0 (SPSS Inc. Chicago, USA) was used to analyze the study data. The descriptive statistics section evaluates categorical variables as numbers and percentages and continuous variables as mean ± standard deviation. The conformity of continuous variables to a normal distribution was evaluated using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). The Mann-Whitney U test was used to compare data that did not conform to the normal distribution. Pearson's chi-square test was used to compare independent groups for categorical variables. Univariate logistic regression analysis was used to identify factors associated with delirium. The regression analysis results are presented as OR and 95% CI. The statistical significance level was set at $P < 0.05$.

Results

In total, 212 patients from the anaesthesia, general surgery, and neurology ICUs were followed up. The most common indication for ICU admission was postoperative monitoring and care. An overview of admission indications categorized by ICU type is provided in Table 1.

The overall incidence of delirium in all ICUs was 32.5%. The mean age of the patients was 57.5 years, and 49.5% were male (Table 2). Among the patients diagnosed with delirium, 49.3% were hypoactive, 36.2% were hyperactive, and 14.5% were mixed-type. Delirium emerged on an average of 2.1±1.9 days and patients who experienced delirium remained in this state for an average of 5.8±6.4 days.

A significant difference was found between the patient groups when comparing the reasons for ICU admission and incidence of delirium ($P < 0.001$). Delirium occurred in 43.5% (n = 10) of patients admitted for respiratory failure, 50% (n = 2) of those with renal failure, 21.7% (n = 5) of trauma patients, 19.3% (n = 16) of postoperative patients, 64.3% (n = 9) of those with multiorgan dysfunction, 46.9% (n = 15) of patients with cerebrovascular incident, 75% (n = 3) of patients with sepsis, 4.3% (n = 1) of patients with intoxication, and 25% (n = 4) of those with acute abdomen.

Age (OR 1.04, CI 1.02-1.06, $P < 0.001$), illiteracy (OR 4, CI 1.19-13.35, P=0.024), hearing impairment (OR 3.37, CI

Table 1. Indications for Admission to the Anaesthesiology, General Surgery, and Neurology ICUs

Indications for admission	Anaesthesiology n (%)	General Surgery n (%)	Neurology n (%)	Total n (%)
Postoperative	32 (38.6)	51 (61.4)	0 (0)	83 (39.2)
Cerebrovascular incident	5 (15.6)	1 (3.1)	26 (81.3)	32 (15.1)
Respiratory failure	19 (82.6)	2 (8.7)	2 (8.7)	23 (10.8)
Posttrauma/accident	23 (100)	0 (0)	0 (0)	23 (10.8)
Acute abdomen	2 (12.5)	12 (75.0)	2 (12.5)	16 (7.5)
Multiorgan dysfunction	5 (35.7)	7 (50)	2 (14.3)	14 (6.6)
Intoxication	7 (100)	0 (0)	0 (0)	7 (3.3)
Kidney failure	3 (75.1)	1 (25)	0 (0)	4 (1.9)
Sepsis	3 (75)	1 (25)	0 (0)	4 (1.9)
Post CPR	2 (66.7)	1 (33.3)	0 (0)	3 (1.4)
Cardiac instability	1 (50)	1 (50)	0 (0)	2 (0.9)
Liver failure	0 (0)	1(100)	0 (0)	1 (0.5)
Total	102 (48.1)	78 (36.8)	32 (15.1)	212

ICU, intensive care unit; CPR, cardiopulmonary resuscitation.

1. 71-7.01, *P*=0.001), visual impairment (OR 3.90, CI 2.13-7.15, *P* < 0.001), and hypertension (OR 2.56, CI 1.42-4.62, *P*=0.002) were found to be risk factors. Increased SOFA (OR 1.21, CI 1.08-1.36, *P*=0.001) and APACHE II (OR 1.20, CI 1.12-1.28, *P* < 0.001) scores at admission were found to be risk factors for delirium (Table 1).

Patients with delirium had a longer mean length of ICU stay (12.2±12.4 days) than those without delirium (6.4±5.5 days) (*P* < 0.001). The length of ICU stay was found to be a risk factor for delirium (OR 1.10, CI 1.05-1.15, *P* < 0.001). No significant correlation was observed between the number of days spent in the hospital before ICU admission and the development of delirium in the ICU.

The mortality rate was significantly higher in patients with delirium (24.6%) than in those without (4.9%) (*P* < 0.001) (Table 2).

Table 2. Non-modifiable Risk Factors and Demographic Characteristics of Delirium

Properties	Deliriuma	No Deliriuma	Total	*P*
ICU n (%)				
Anaesthesia ICU	36 (52.2)	66 (46.2)	102 (48.1)	
General surgery ICU	21 (30.4)	57 (39.9)	78 (36.8)	0.4[1]
Neurology ICU	12 (17.4)	20 (14.0)	32 (15.1)	
Gender n (%)				
Male	34 (49.3)	71 (49.7)	105 (49.5)	0.95[1]
Female	35 (50.7)	72 (50.3)	107 (50.5)	
Age (mean ± SD)	67.0±16.5	52.4±19.4	57.5±19.7	<0.001[2]
Body mass index (mean ± SD)	25.9±6.5	26.0±6.8	25.9±6.7	0.99[2]
Education level (%)				
Illiterate	9 (13.0)	9 (6.3)	18 (8.5)	
Primary school graduate	31 (44.9)	57 (39.9)	88 (41.5)	
Secondary school graduate	13 (18.8)	15 (10.5)	28 (13.2)	0.03[1,*]
High school graduate	8 (11.6)	30 (21.0)	38 (17.9)	
University graduate	8 (11.6)	32 (22.4)	40 (18.9)	
Comorbidities, n (%)				
Visual impairment	41 (59.4)	39 (27.3)	80 (37.7)	<0.001[1,*]
Hearing impairment	23 (33.3)	18 (12.6)	41 (19.3)	<0.001[1,*]
Smoking	20 (29.0)	31 (21.7)	51 (24.1)	0.24
Ex-smoker	23 (33.3)	31 (21.7)	54 (25.5)	0.06
Alcohol	6 (8.7)	10 (7.0)	16 (7.5)	0.6
Hypertension	42 (60.9)	54 (37.8)	96 (45.3)	0.002[1,*]
Epilepsy	3 (4.3)	2 (1.4)	5 (2.4)	0.18
Lung disease	14 (20.3)	16 (11.2)	30 (14.2)	0.07
Heart disease	18 (26.1)	19 (13.3)	37 (17.5)	0.02[1,*]
Liver disease	3 (4.3)	5 (3.59)	8 (3.8)	0.76
Diabetes	18 (26.1)	32 (22.4)	50 (23.6)	0.55
Malignancy	27 (39.1)	53 (37.1)	80 (37.3)	0.77
Trauma history	7 (10.1)	22 (15.4)	29 (13.7)	0.29
Transferring wards n (%)				
Emergency room	37 (53.6)	65 (45.5)	102 (48.1)	
Other	23 (33.4)	39 (27.2)	62 (29.3)	
Postoperative	7 (10.1)	34 (23.8)	41 (19.3)	0.21[1]
External center	2 (2.9)	5 (3.5)	7 (3.3)	
SOFA score (mean ± SD)	4.3±2.5	2.9±2.7	3.4±2.8	<0.001[2,*]
APACHE II score (mean ± SD)	16.9±5.4	11.9±5.0	13.6±5.7	<0.001[2,*]
Pre-ICU hospital length of stay (mean ± SD)	5.9±12.5	4.6±17.1	5.0±15.7	0.8
Mortality	17 (24.6)	7 (4.9)	24 (11.3)	<0.001[1,*]

[1]Pearson chi-square test, [2]Mann-Whitney U test, [a]Column percentage, [*]*P* < 0.05
ICU, intensive care unit; SD, standard deviation; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation.

Table 3. Modifiable Risk Factors for Delirium Development

	Delirium[a] n (%)	No Delirium[a] n (%)	Univariate OR (95% CI Lower Bound-Upper Bound)	*P*[1]
Interventions				
Nasogastric catheter	32 (46.4)	41 (28.7)	2.15 (1.18-3.90)	0.01*
Urinary catheter	65 (94.2)	128 (89.5)	0.25 (0.12-0.51)	0.26
Wound drain	14 (20.3)	52 (36.4)	2.89 (1.39-6.02)	0.01*
Tracheal aspiration	30 (43.5)	25 (17.5)	3.63 (1.91-6.90)	<0.001*
Central catheter	23 (33.3)	33 (23.1)	1.66 (0.88-3.14)	0.11
Arterial catheter	13 (18.8)	17 (11.9)	0.68 (0.27-1.69)	0.17
Pneumatic device	5 (7.2)	14 (9.8)	2.39 (0.74- 7.65)	0.54
Nutrition				
Enteral nutrition	14 (20.3)	13 (9.1)	2.54 (1.12-5.76)	0.02*
Oral enteral nutrition	11 (15.9)	59 (41.3)	0.27 (0.13-0.55)	<0.001*
Parenteral nutrition	12 (17.4)	23 (16.1)	0.91 (0.42-1.9)	0.8
Ventilation				
Mechanical ventilation	24 (34.8)	21 (14.7)	3.09 (1.57-6.10)	0.001*
Oxygen requirement	55 (79.7)	82 (57.3)	2.92 (1.49-5.73)	0.001*
Hypoxia	3 (4.3)	5 (3.5)	2.05 (1.03-4.08)	0.76
CPAP	3 (4.3)	5 (3.5)	0.7 (0.18-3.43)	0.04*
Intubation	16 (23.2)	18 (12.6)	2.09 (0.99-4.42)	0.05
Transfusion	14 (20.3)	40 (28.0)	1.71 (0.36-8.00)	0.22
ES transfusion	10 (14.5)	31 (21.7)	0.64 (0.17-2.36)	0.21
FFP transfusion	9 (13.0)	21 (14.7)	1.21 (0.32-4.61)	0.74
Platelet transfusion	3 (4.3)	2 (1.4)	0.31 (0.05-1.91)	0.18
Drugs				
Midazolam infusion	9 (13.0)	6 (4.2)	3.4 (1.16-10.05)	0.02*
Midazolam bolus	7 (10.1)	7 (4.9)	2.19 (0.7-6.52)	0.15
Propofol infusion	9 (13.0)	7 (4.9)	2.91 (1.03-8.19)	0.04*
Vasopressor	9 (13.0)	8 (5.6)	2.53 (0.93-6.87)	0.06
Insulin	14 (20.3)	20 (14.1)	0.64 (0.3-1.3)	0.25
Albumin	16 (23.2)	16 (11.2)	2.39 (1.11-5.14)	0.02*
Steroid	18 (52.6)	20 (47.4)	2.17 (1.06-4.40)	0.03*
Urine output				
Normal	39 (56.5)	103 (72.0)	0.50 (0.27-0.92)	0.02*
Anuric/Oligouric	30 (43.5)	40 (28.0)	1.56 (1.06-2.28)	
Defecation frequency				
<3 days	20 (15.4)	22 (29.0)	0.44 (0.22-0.88)	0.02*
>3 days	49 (71.0)	121 (84.6)	1.65 (1.11-2.45)	
Hemodynamic instability				
Hypotension	11 (15.9)	10 (7.0)	2.5 (1.01-6.26)	0.04*
Hypertension	18 (26.1)	19 (13.3)	2.20 (1.11-4.74)	0.02*
Blood glucose level				
Hypoglycemics	4 (5.8)	4 (2.8)	0.59 (0.28-1.25)	
Hyperglycemic	15 (21.7)	21 (14.8)	1.4 (0.30-6.50)	0.22
Growth in culture	39 (56.5)	44 (30.8)	2.92 (1.61-5.29)	<0.001*
Blood culture (+)	18 (26.1)	20 (14.0)	2.17 (1.06-4.40)	0.03*
Urine culture (+)	15 (21.7)	14 (9.8)	2.56 (1.15-5.66)	0.01*
ETA culture (+)	15 (21.7)	7 (4.9)	5.39 (2.08-13.96)	<0.00*
Wound site culture (+)	12 (17.4)	20 (14.0)	1.29 (0.59-2.82)	0.516
Sepsis	13 (18.8)	7 (4.9)	4.51 (1.71-11.89)	0.001*
History of previous surgery	26 (37.7)	84 (58.7)	0.42 (0.23-0.76)	0.004*
History of previous anaesthesia	23 (33.3)	78 (54.5)	0.41 (0.22-0.75)	0.004*

[1]Pearson chi-square test, [a]column percentage, *$P < 0.05$

CPAP, continuous positive airway pressure; ES, erythrocyte suspension; FFP, fresh frozen plasma; ETA, endotracheal aspirate; OR, odds ratio; CI, confidence interval.

During ICU stay, the presence of a nasogastric catheter and/or drain (OR 2.15, CI 1.18-3.90, *P*=0.012), tracheal aspiration (OR 3.63, CI 1.91-6.90, *P* < 0.001), and the frequency of aspiration (OR 1.35, CI 1.22-1.50, *P* < 0.001) were identified as risk factors for delirium. Patients with delirium were aspirated an average of 3.9±0.5 times a day, whereas those without delirium had an average of 0.6±0.1 aspirations per day. No significant association was found between the presence of a urinary catheter and the emergence of delirium (*P*=0.26) (Table 3).

In the comparison of feeding methods, enteral feeding was identified as a risk factor for delirium (OR 2.54, CI 1.12-5.76, *P*=0.025), whereas oral feeding was found to significantly decrease the incidence of delirium (OR 0.27, CI 0.13-0.55, *P*<0.001). However, no significant association was observed between parenteral nutrition and delirium emergence (*P*=0.81).

A defecation time of >3 days (OR 1.65, CI 1.11-2.45, *P*=0.02) and anuria/oliguria (OR 1.56, CI 1.06-2.28, *P*=0.02) were identified as risk factors for delirium.

Midazolam administration (OR 3.4, CI 1.16-10.05, *P*=0.02) and propofol infusion (OR 2.91, CI 1.03-8.19, *P*=0.04) were associated with an increased risk of delirium.

Albumin and steroid use was observed in 23.2% and 26.4% of patients with delirium, respectively. Albumin (OR 2.39, CI 1.11-5.14, *P*=0.02) and steroids (OR 2.17, CI 1.06-4.40, *P*=0.03) were found to be risk factors for delirium.

Hemodynamic instability was also identified as a risk factor for delirium, hypotension (OR 2.5, CI 1.01-6.26, *P*=0.04), and hypertension (OR 2.20, CI 1.11-4.74, *P*=0.021), increasing the risk of delirium.

On the other hand, mobilization was found to decrease the risk of delirium (OR 0.38, CI 0.20-0.73, *P*=0.003).

Irregular night sleep and sleep quality deterioration increase the risk of delirium. Among the patients with delirium, 56.5% described their night sleep as poor, 17.4% as moderate, and 26.1% as good (*P* < 0.001).

No statistically significant correlations were found between the frequency of family visits, dialysis, continuous renal replacement therapy, pain score, average number of daily medications taken, electrolyte levels, and delirium.

The mean VAS score was 1.97±0.29 in patients who developed delirium, compared to 2.26±0.18 in those who did not. No significant relationship was observed between pain scores and the development of delirium (*P*=0.16).

However, a significant relationship was observed between blood carbon dioxide level and delirium. Hypoxia (OR 2.05, CI 1.03-4.08, *P*=0.03) and hypercarbia (OR 2.0, CI 1.05-4.28, *P*=0.03) were identified as risk factors for delirium. No significant association was observed between hyperoxia and delirium in the present study.

Of the 69 patients with delirium, 43.5% received treatment for delirium. Pharmacological treatment was administered to 58.3% of patients in the anaesthesia, 41.7% in neurology, and 19.0% in general surgery ICUs. There was a statistically significant difference in the administration of pharmacological treatment for delirium between the different ICUs (*P*=0.015).

In 13 patients with delirium (39.4%), dexmedetomidine was used, while haloperidol was administered in 12 patients (36.4%), antipsychotics in 2 patients (6.1%), a combination of dexmedetomidine and haloperidol in 4 patients (12.1%), and a combination of haloperidol and antipsychotics in 2 patients (6.1%). No significant differences were observed between these pharmacological treatments in terms of the success of delirium management or mortality (*P*=0.8 and *P*=0.7, respectively). The treatments were continued for an average of 3.7±3.3 days during delirium management.

Discussion

In the present study, the incidence of delirium was 32.5% among the 212 patients. The incidence of delirium, a multifactorial syndrome, varies due to various contributing factors. These variations can be attributed to differences in demographic profiles, varying levels of illness severity, distinct ICU features, and the utilization of diverse delirium screening tests in intensive care patients.

The type of ICU setting significantly affects the incidence, risk factors, and prognosis of delirium. The study was conducted across three different ICUs, each serving different patient populations. However, this variability may have positively influenced the results and increased the generalizability of the study. The prevalence of delirium may be higher in branch ICUs. For example, in one study, the incidence of delirium in non-intubated intensive care unit patients was only 20%, whereas in another study, this rate was found to be 83% in patients on mechanical ventilation.[18,19] In a comprehensive meta-analysis of 42 studies that focused on delirium in ICU patients, the overall incidence was 31.8%.[2] Remarkably, the incidence in our study is consistent with that reported in the literature.

According to the results of our study, advanced age, visual and hearing impairments, hypertension and heart disease, illiteracy, and high APACHE II and SOFA scores during hospitalization were found to be the "non-modifiable risk factors" for delirium. Nasogastric catheter, wound drain, enteral nutrition, mechanical ventilation, oxygen requirement, midazolam and propofol infusion, albumin,

and steroid use, decreased urine output and defecation frequency, hemodynamic instability, and infection were "modifiable risk factors" for the development of delirium (Table 3).

Despite being frequently overlooked in ICU patients, delirium has a significant impact on outcomes, increased length of ICU stay, and increased mortality rates.[2,3,10] In our study, we found that patients who did not experience delirium had an average ICU stay of 6.4 days. On the other hand, those who developed delirium were hospitalized for a much longer period of 12.2 days, and mortality was observed to be higher in these patients. Various studies have also shown that delirium can lead to mortality rates ranging from 25% to 33%, even in ward patients, and can increase mortality in the intensive care unit by 1.5 times.[10,20] The association between delirium and mortality may be attributed to direct mechanisms such as neuroinflammation, neurotransmitter imbalance, and cerebral metabolic disturbances, all of which can lead to long-term neuronal damage. Indirectly, delirium contributes to increased mortality through complications like aspiration pneumonia, pressure ulcers, and the use of physical restraints. Prolonged hospital and intensive care unit stays due to delirium further elevate the risk of hospital-acquired complications.[21]

The elevated mortality observed in patients with delirium can also be explained by higher APACHE II and SOFA scores, which are predictive models for multiple physiological parameters and organ systems. As a multifactorial syndrome, delirium is inherently linked to higher scores on these assessments, reflecting an increased risk of adverse outcomes. Multicentre studies and meta-analyses have demonstrated a correlation between elevated APACHE II scores and increased delirium risk.[22,23] In our study, we observed a higher frequency of delirium with increasing APACHE II scores. The mean APACHE II score was 5 points higher in patients with delirium than in those without delirium. In a study conducted by Salluh et al. [24], the median SOFA score was 4 in patients with delirium and 3 in the non-delirium group. Similarly, in our study, the mean SOFA score of the patients with and without delirium was 4.3 and 2.9, respectively. In our study, the expected mortality rate for patients with delirium based on APACHE II scores was approximately 25%, whereas the expected mortality rate based on SOFA scores was 10%, which is consistent with the findings in the literature. The elevated mortality rate in the delirium group is consistent with these expectations.[25,26] These results emphasize the critical importance of heightened vigilance for delirium in patients with higher APACHE II and SOFA scores, which are significant predictors of poor clinical outcomes in this population.

Advanced age, particularly when accompanied by visual and hearing impairments, is recognized as a significant risk factor for delirium.[27,28] Individuals with vision or hearing loss are up to three times more likely to develop delirium. However, the use of assistive devices for these impairments in hospitalized elderly patients can prevent delirium and reduce its duration.[2,28] In this study, we also found that advanced age and the presence of visual or hearing impairments were risk factors for delirium. We also determined that there was a remarkable relationship between the development of delirium and education level and that the lowest incidence was among university graduates. These findings suggest that susceptibility to delirium increases as cognitive function declines.

Bellelli et al. [29] showed the effect of interventional procedures such as nasogastric tubes, central venous catheters, and urinary catheters on delirium. Additionally, in a multicenter delirium epidemiology in critical care-DECCA study including 975 patients, a relationship was found between central venous catheters, arterial catheters, urinary catheters, and delirium.[26] In agreement with the literature, we found similar results regarding the relationship between nasogastric and wound drain catheter use and delirium. Moreover, a noteworthy finding of our study was the association between the number of aspirations performed during the day and the risk of delirium. However, we did not observe a significant association between the use of urinary catheters and delirium. This discrepancy could be attributed to the high frequency of urinary catheter use in our patients.

Urinary retention and constipation are recognized risk factors for delirium. Smonig et al.[30] demonstrated an increased incidence of delirium in patients in whom defecation was absent for more than 5 days. In line with these findings, our study revealed a similar trend, indicating a higher incidence of delirium in patients who did not defecate for more than 3 days and had decreased urine output.

Infection and sepsis are significant risk factors for delirium. The pathophysiological mechanisms involved in these conditions include neuroinflammation and microglial activation resulting from infection as well as impaired cerebral perfusion and neurotransmitter imbalance. These factors are believed to contribute to delirium.[31] In the present study, we found a higher prevalence of microbiological growth in the blood, urine, and endotracheal aspirate cultures of patients with delirium, supporting these hypotheses.

Malnutrition is a risk factor for delirium, particularly in the elderly population of ICU patients, and enteral nutrition is effective in reducing delirium by preventing malnutrition.[32] Few studies have compared oral and enteral nutrition in the existing literature. In the present study, we discovered a protective effect of oral nutrition against the development of delirium. Specifically, compared with oral enteral nutrition, enteral nutrition with a feeding tube increased the risk of delirium by 2.5-fold.

In our study, we noticed a 2.9-fold increase in the likelihood of delirium by 2.9 times among patients who received an infusion for sedation. Zaal et al.[33] found that intravenous infusion increased the risk of delirium by 4% on the subsequent day in ICU patients. However, this effect was not observed with the bolus. Consistent with these findings, our study revealed that administering sedatives as a bolus had no impact on delirium emergence, whereas infusion increased the risk of delirium by 3.4 times.

Corticosteroids can disrupt behavioral and cognitive functions by affecting serotonergic neurotransmitters within the intracellular space. Our study also found that steroid use increased the risk of developing delirium.

We observed a significant 2.3-fold increase in delirium among patients who received albumin replacement. However, it is uncertain whether this risk is caused directly by albumin administration or hypoalbuminemia. Hypoalbuminemia can potentially contribute to delirium through two mechanisms. Low albumin levels may have adverse effects on hemodynamics by reducing intravascular oncotic pressure. Low oncotic pressure may compromise hemodynamic stability and predispose patients to delirium. Second, hypoalbuminemia may influence the pharmacokinetics of drugs that affect cognitive function. The drugs used in clinical practice rely on albumin for transport and distribution. Hypoalbuminemia alters the availability and concentration of these drugs, potentially influencing their effectiveness and adverse effects. Such disruptions in drug metabolism and distribution may have implications for cognitive function and, consequently, contribute to the emergence of delirium.

In this study, we did not find any significant association between blood glucose levels, electrolyte disorders, and the emergence of delirium. Although several studies have suggested a connection between metabolic and serum electrolyte disorders and delirium, no consensus has been reached on this matter.[10,12]

Hypoxic ischemic encephalopathy can cause severe neuronal and cortical damage, particularly if left untreated, and may present as hypoactive and mixed delirium during the early stages of cerebral hypoxia and hypercarbia. Therefore, it is important to identify hypoxia-induced delirium in patients. In our study, there was no association between delirium and hyperoxia, whereas hypoxia and hypercarbia were associated with an increased risk of delirium.

To prevent the onset of delirium, it is crucial to address the factors that limit patient movement and prioritize mobilization through regular physical therapy with at least three sessions per day.[10] Although the incidence of delirium increased among patients with movement restraints in our study, the results were not statistically significant. However, mobilization had a protective effect against the development of delirium.

In the pain agitation/sedation, delirium, immobility, and sleep disruption guidelines, the use of bright light should be minimized because of its potential impact on delirium.[16] Our findings support this recommendation, as we demonstrated that decreased sleep quality is associated with a 4.6-fold increased risk of delirium. The lighting systems in these units may play a role in affecting sleep quality, thereby contributing to the development of delirium.

High pain scores are a risk factor for the development of delirium, and the use of analgesics is recommended.[16] However, in our study, no relationship was found between the average pain score and the development of delirium. This is attributed to analgesic practices that did not allow VAS scores to exceed three points.

In a previous study, patients with delirium were reported to have a hospitalization duration of approximately 11 days before ICU admission.[34] However, in our study, the duration of hospitalization before ICU admission for patients with delirium was shorter (5.9 days. Despite this discrepancy, our study demonstrated that the frequency of delirium increased with the duration of hospitalization before ICU admission.

Ely et al.[18] reported a higher incidence of delirium in patients receiving mechanical ventilation. Similarly, 53.3% of patients on mechanical ventilators developed delirium. In addition, intubation and oxygen requirement were significant risk factors. However, continuous positive airway pressure, tracheostomy, and reintubation were not found to be associated with delirium. It is possible that the lack of a significant association between these latter factors could be attributed to the relatively small number of patients in these subgroups.

Delirium has multiple causes, including a history of hypertension, vasopressor use, and hemodynamic instability, which increase the risk. In this study, we also found that hemodynamic instability, hypertension history, and vasopressor use were associated with delirium in intensive care patients.

It is stated that delirium in the ICU usually begins on the second day of hospitalization and lasts for an average of 3 days.[34] Similarly, delirium developed on the second day after admission, and the average duration of delirium was 5.8 days in our study.

In the pharmacologic management of delirium, various agents, including antipsychotics-particularly haloperidol-alpha-2 agonists, such as dexmedetomidine, antidepressants, and acetylcholinesterase inhibitors, have been explored in the literature.[16] In our study, dexmetatomidine and haloperidol were the most frequently used treatments, yet

no significant difference was observed in terms of patient outcomes like discharge rates or mortality. Combinations of these drugs were used in a small subset of patients, although the lack of statistical significance in outcomes suggests that a larger sample size is needed to explore potential additive or synergistic effects. Current guidelines favor dexmedetomidine for its sedative properties without respiratory depression, making it a preferable option in certain ICU settings.[13,14] However, the observed variability in treatment success underscores the need for individualized approaches based on patient condition.

Study Limitations

A primary limitation of this study was the twice-daily delirium assessment schedule, which, while providing consistent monitoring, may have led to an underestimation of the true incidence of transient delirium, especially in patients with fluctuating cognitive states. More frequent assessments, such as every four to six hours, may provide a more accurate representation of the prevalence of delirium in critical care settings. If patients had been evaluated more frequently throughout the study, the recorded incidence of delirium might have been higher. Additionally, in this study, the cognitive status of patients after discharge from the ICU was not assessed. Our assessment did not include factors such as the extent of care delivered by healthcare providers and patient relatives and the potential increase in hospital costs.

Conclusion

Nearly half of the delirium cases in this study were hypoactive and often under-recognized. Timely identification of patients is essential for improving outcomes. The study also identified several risk factors, including advanced age, sensory impairments, educational status, hypertension, heart disease, hemodynamic instability, catheter use, infection, sedative infusions, constipation, albumin and steroid use, enteral nutrition, mechanical ventilation, prolonged intensive care unit stays, and elevated SOFA and APACHE II scores. Addressing these factors early can help reduce the incidence of delirium in the ICU.

Ethics

Ethics Committee Approval: This prospective observational study was approved by the Gazi University Faculty of Medicine Clinical Research Ethics Committee (decision no.: 588, date: 10.9.2018).

Informed Consent: Written informed consent was obtained from each patient.

Footnotes

Author Contributions: Surgical and Medical Practices - E.M.A., B.N.; Concept - B.N., L.K.; Design - B.N., L.K; Data Collection and/or/Processing -S.E., E.M.A., B.N., L.K.; Analysis and/or/Interpretation-S.E., L.K.; Literature Review-S.E.; Writing - S.E., L.K.

Declaration of Interests: The authors declare no conflicts of interest.

Funding: No funding was received for conducting this study.

References

1. European Delirium Association; American Delirium Society. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. *BMC Med.* 2014;12:141. [CrossRef]
2. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ.* 2015;350:h2538. [CrossRef]
3. Ely E, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med.* 2001;27(12):1892-1900. [CrossRef]
4. Caplan GA, Teodorczuk A, Streatfeild J, Agar MR. The financial and social costs of delirium. *Eur Geriatr Med.* 2020;11(1):105-112. [CrossRef]
5. Lange S, Mędrzycka-Dąbrowska W, Friganović A, Religa D, Krupa S. Patients' and relatives' experiences of delirium in the intensive care unit-a qualitative study. *Int J Environ Res Public Health.* 2022;19(18):11601. [CrossRef]
6. Van den Boogaard M, Schoonhoven L, Maseda E, et al. Recalibration of the delirium prediction model for ICU patients (PRE-DELIRIC): a multinational observational study. *Intensive Care Med.* 2014;40(3):361-369. [CrossRef]
7. Brummel NE, Jackson JC, Pandharipande PP, et al. Delirium in the ICU and subsequent long-term disability among survivors of mechanical ventilation. *Crit Care Med.* 2014;42(2):369-377. [CrossRef]
8. Peterson JF, Pun BT, Dittus RS, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc.* 2006;54(3):479-484. [CrossRef]
9. Gao Y, Gong S, Zhou W, Li X, Gan X. Frequency and risk factors of subsyndromal delirium in the intensive care units: a prospective cohort study. *Neuropsychiatr Dis Treat.* 2023;19:1003-1016. [CrossRef]
10. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014;383(9920):911-922. [CrossRef]
11. Mart MF, Williams Roberson S, Salas B, Pandharipande PP, Ely EW. Prevention and management of delirium in the intensive care unit. *Semin Respir Crit Care Med.* 2021;42(1):112-126. [CrossRef]
12. Pun BT, Badenes R, La Calle GH, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med.* 2021;9(3):239-250. [CrossRef]
13. Stollings JL, Kotfis K, Chanques G, Pun BT, Pandharipande PP, Ely EW. Delirium in critical illness: clinical manifestations, outcomes, and management. *Intensive Care Med.* 2021;47(10):1089-1103. [CrossRef]
14. Korenoski A, Li A, Kane-Gill SL, Seybert AL, Smithburger PL. Pharmacologic management of delirium in the ICU: a review of the literature. *J Intensive Care Med.* 2020;35(2):107-117. [CrossRef]
15. Van Den Boogaard M, Slooter AJ, Brüggemann RJ, et al. Effect of haloperidol on survival among critically Ill adults with a high risk of delirium: the REDUCE randomized clinical trial. *JAMA.* 2018;319(7):680-690. [CrossRef]
16. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med.* 2018;46(9):e825-e873. [CrossRef]
17. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med.* 2002;166(10):1338-1344. [CrossRef]

18. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. 2001;286(21):2703-2710. [CrossRef]
19. Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Elseviers M, Bossaert L. A comparison of the CAM-ICU and the NEECHAM Confusion Scale in intensive care delirium assessment: an observational study in non-intubated patients. *Crit Care*. 2008;12(1):R16. [CrossRef]
20. Pranata R, Huang I, Lim MA, Yonas E, Vania R, Kuswardhani RAT. Delirium and mortality in coronavirus disease 2019 (COVID-19) - a systematic review and meta-analysis. *Arch Gerontol Geriatr*. 2021;95:104388. [CrossRef]
21. Aung Thein MZ, Pereira JV, Nitchingham A, Caplan GA. A call to action for delirium research: Meta-analysis and regression of delirium associated mortality. *BMC Geriatr*. 2020;20(1):325. [CrossRef]
22. Krewulak KD, Stelfox HT, Leigh JP, Ely EW, Fiest KM. Incidence and prevalence of delirium subtypes in an adult ICU: a systematic review and meta-analysis. *Crit Care Med*. 2018;46(12):2029-2035. [CrossRef]
23. Van Eijk MM, Van den Boogaard M, Van Marum RJ, et al. Routine use of the confusion assessment method for the intensive care unit: a multicenter study. *Am J Respir Crit Care Med*. 2011;184(3):340-344. [CrossRef]
24. Salluh JI, Soares M, Teles JM, et al. Delirium epidemiology in critical care (DECCA): an international study. *Crit Care*. 2010;14(6):R210. [CrossRef]
25. Satoh T, Isozaki O, Suzuki A, et al. 2016 Guidelines for the management of thyroid storm from The Japan Thyroid Association and Japan Endocrine Society (First edition). *Endocr J*. 2016;63(12):1025-1064. [CrossRef]
26. Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med*. 1998;26(11):1793-1800. [CrossRef]
27. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263-306. [CrossRef]
28. Van Rompaey B, Elseviers MM, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Bossaert L. Risk factors for delirium in intensive care patients: a prospective cohort study. *Crit Care*. 2009;13(3):R77. [CrossRef]
29. Bellelli G, Morandi A, Di Santo SG, et al. "Delirium Day": a nationwide point prevalence study of delirium in older hospitalized patients using an easy standardized diagnostic tool. *BMC Med*. 2016;14(1):106. [CrossRef]
30. Smonig R, Wallenhorst T, Bouju P, et al. Constipation is independently associated with delirium in critically ill ventilated patients. *Intensive Care Med*. 2016;42(1):126-127. [CrossRef]
31. van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. *Lancet*. 2010;375(9716):773-775. [CrossRef]
32. Song L, Gong Q, Li B, et al. Influence of effective enteral nutrition support on delirium in ICU patients with mechanical ventilation. *Food Sci Technol*. 2021;42:e78921. [CrossRef]
33. Zaal IJ, Devlin JW, Hazelbag M, et al. Benzodiazepine-associated delirium in critically ill adults. *Intensive Care Med*. 2015;41(12):2130-2137. [CrossRef]
34. Zaal I, Tekatli H, Van der Kooi A, et al. Classification of daily mental status in critically ill patients for research purposes. *J Crit Care*. 2015;30(2):375-380. [CrossRef]

DOI: 10.4274/TJAR.2024.241636

Original Article
Orthopaedic Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2024;52(6):223-230

Efficacy of Preoperative Pericapsular Nerve Group Block in Patients with Hip Fracture and its Effect on the Success of Spinal Anaesthesia: A Retrospective Study

Burcu Kaplan, Eyyüp Sabri Özden, Mustafa Soner Özcan, Filiz Alkaya Solmaz, Pakize Kırdemir

Süleyman Demirel University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Isparta, Turkey

Cite this article as: Kaplan B, Özden ES, Özcan MS, Alkaya Solmaz F, Kırdemir P. Efficacy of Preoperative Pericapsular Nerve Group Block in Patients with Hip Fracture and its Effect on the Success of Spinal Anaesthesia: A Retrospective Study. *Turk J Anaesthesiol Reanim.*2024;52(6):223-230.

Abstract

Objective: We intended to research the efficacy of pericapsular nerve group (PENG) block performed with preoperative ultrasonography (USG) in patients who underwent hip fracture repair under spinal anaesthesia and whether it affects the success of spinal anaesthesia.

Methods: The files of 100 patients were analysed, and 60 patients were enrolled in the study. The patients were assigned into two groups: Group P (n = 30) consisted of patients who underwent USG-guided PENG block before the start of surgery and the control group (Group C; n = 30) consisted of patients in whom tramadol infusion was initiated. All patients received 10 mg IV bolus tramadol as rescue analgesia when numeric rating scale (NRS)>3. From the files of the patients, before PENG block application, after PENG block application, during positioning before spinal anaesthesia, the NRS values at the time of the patient's discharge from the operating room and at 2nd, 4th, 12th and 24th hour NRS values, spinal anaesthesia duration and number of attempts, and perioperative total tramadol consumption were obtained.

Results: In group P, NRS values were found to be significantly lower after PENG block application, during positioning before spinal anaesthesia, and at the postoperative discharge, 2nd, 4th, 12th and 24th hours. In addition, group P had a lower duration of spinal anaesthesia, a lower number of spinal anaesthesia attempts and a lower total perioperative tramadol consumption.

Conclusion: The results demonstrated that preoperative PENG block facilitated positioning for spinal anaesthesia, shortened the application time, increased the first-attempt success rate, decreased pain scores, and reduced the need for postoperative opioids.

Keywords: Hip fracture, opioid use, pericapsular nerve group block, spinal anaesthesia

Main Points

- The advantage of the pericapsular nerve group (PENG) block is that it can be applied in the supine position for a patient with pain that worsens with movement, and three nerve blocks can be performed with a single needle insertion.
- PENG block performed on hip fracture patients in the preoperative care unit can provide effective analgesia in patients during preoperative transfer and spinal anaesthesia positioning.
- We found that it provided lower numeric rating scale values in the postoperative period and reduced opioid use and associated side effects.
- When the number of spinal anaesthesia attempts was compared among the groups, the success rate of the first attempt was statistically significantly higher in Group P with 64%.

Introduction

The aim of surgical treatment in hip fracture patients is to provide long-term mobility and the best possible function while aiming for low disability and mortality rates.[1] However, the recommended type of anaesthesia is still open to debate.[2] Among the regional anaesthesia techniques, unilateral hipobaric spinal anaesthesia in lateral decubitus

Corresponding author: Eyyüp Sabri Özden, e-mail: dreyupsabri@gmail.com

Received: June 27, 2024 Accepted: October 17, 2024

position is a popular choice because it can be applied in the surgical position and causes fewer hemodynamic changes.[3]

It is essential to note that uncontrolled pain, which has the potential to have both physiological and psychological negative effects, can make it challenging to provide a suitable position for spinal anaesthesia and may affect the procedure's success.[4,5] Effective pain control with regional analgesia can lead to faster recovery, shorter hospital stays, and cost-related benefits. Additionally, regional blocks applied under ultrasonography (USG) guidance have fewer side effects.[6,7]

The pericapsular nerve group (PENG) block was first developed for postoperative analgesia in total hip arthroplasty in 2018.[8] One of the key benefits of the USG-guided PENG block is that it can be applied in the supine position for a patient with pain that increases with movement. This makes it a particularly suitable option for those who experience discomfort when moving around. Additionally, it is possible to perform a block for the articular branches of the femoral, obturator and accessory obturator nerves with a single needle entry, which is a useful advantage.[9]

The aim of our study was to assess the efficacy of PENG block in patients undergoing hip fracture surgery with spinal anaesthesia. Our primary objective was to demonstrate that the PENG block improves the success of spinal anaesthesia in the first attempt by reducing pain during spinal anaesthetic positioning and shortening the administration time. Our secondary objective was to demonstrate that PENG block reduces postoperative pain, opioid use, and side effects.

Methods

This retrospective study was performed after approval from the Clinical Research Ethics Committee of Süleyman Demirel University Faculty of Medicine (decision no.: 281570, dated: 10.06.2022). Between December 2021 and June 2022, 100 patients aged 18 and above in the American Society of Anesthesiologists' (ASA) I-II-III risk group underwent hip fracture surgery using spinal anaesthesia at Süleyman Demirel University Faculty of Medicine Hospital. A statistical power analysis was conducted using data from similar studies as a reference. With an effect size of d=1.02 and an alpha error of 20%, the number of patients estimated to deliver the population with 80% power was calculated as 52. When patients who did not meet the study criteria were removed, a total of 60 patients, 30 with PENG block and 30 without block, were enrolled in the study. The data available from the files of all patients were included in the analysis. Patients with a history of chronic pain, previous hip joint surgery, failed PENG block application, and missing data in medical records were not included in the study (Figure 1).

Upon arrival at the preoperative care unit (PCU), patients were briefed about the procedure and written informed consent was obtained after an explanation. Standard ASA monitoring was then conducted following the acquisition of consent. Patients who demonstrated full cooperation were instructed about the numeric rating scale (NRS), and pain scores were registered on the pain follow-up form. In the absence of contraindications, all patients were administered a single dose of paracetamol (1 g). Following the assessment

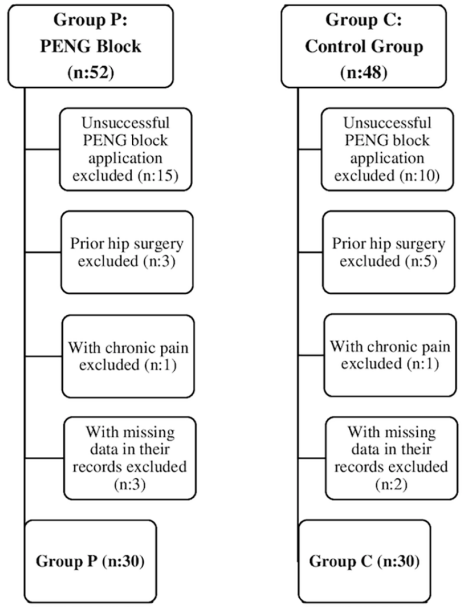

Figure 1. Patient flow chart of 100 patients undergoing hip surgery.

PENG, pericapsular nerve group.

of the pain score in the PCU, a preemptive PENG block was performed or, alternatively, 10 mg tramadol was given intravenously as a single dose, followed by an infusion of 10 mg/hour, depending on the clinical condition of the patient. In group PENG (P), the linear USG probe for block was positioned in a direction parallel to the imaginary line crossing from the anterior inferior iliac spine and the iliopubic eminence. Using in-plane technique, an 80 mm peripheral block needle was inserted and 20 mL of 0.25% bupivacaine was injected to complete the block. In the control group (C), 10 mg intravenous bolus tramadol was given to patients who did not prefer block followed by 10 mg hr infusion in the PCU.

The NRS scores of all patients were registered and if the NRS score was >3, a 10 mg IV bolus of tramadol was given with a waiting period of 30 minutes before starting the surgical intervention. Following a 30-minute after the block, the patient was transferred to the operating room table.

In the absence of specific circumstances, patients underwent unilateral hypobaric spinal anaesthesia with a 25 G - 90 mm cutting-edge disposable spinal needle and received 1.5 mL of 0.5% bupivacaine (7.5 mg), 1.5 mL of distilled water, and 0.25 mL of fentanyl (12.5 µg). The number of attempts, success of dural puncture, and time of skin incision were noted on the anaesthesia follow-up form. Furthermore, the level of spinal anaesthesia was established by pinprick test at the 5th minute.

Demographic data of the patients, surgical procedure and duration, the patient's postoperative discharge site, heart rate, mean arterial pressure (MAP), and peripheral saturation (SpO_2), values obtained before PENG block application, after PENG block application, during lateral decubitus positioning before spinal anaesthesia, after spinal anaesthesia and at postoperative discharge were recorded and evaluated. Similarly, NRS values before PENG block application, after PENG block application, during positioning before spinal anaesthesia, at the time of the patient was discharged from the operating room and at 2nd, 4th, 12th and 24th hours postoperatively, the duration of spinal anaesthesia (the time between the onset of spinal anaesthesia and skin incision), and the number of spinal anaesthesia attempts were noted and assessed. In addition, total perioperative tramadol consumption and postoperative complications (e.g., nausea and vomiting, hypotension, quadriceps muscle weakness, infection, haematoma, local anaesthetic toxicity), were noted and reviewed, from hospital information system data, anaesthesia tracking forms, operative notes, perioperative pain monitoring forms, and discharge notes.

Statistical Analysis

This article presents the results of a statistical analysis of the data by using the Statistical Package for Social Science version 24. Qualitative data are presented as numerical values and percentages, while quantitative data are presented as means and standard deviations. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determined the normality of the continuous variables. The Student's t-test was used to evaluate the statistical significance of differences between two independent groups of normally distributed variables. The Mann-Whitney U test was employed to analyse the data obtained from two independent variable groups that did not have normal distribution. Finally, the chi-square test was applied to analyse categorical data.

Results

The demographic and perioperative clinical characteristics and surgical durations of the cases were compared, in Table 1 ($P > 0.05$).

Table 1. Demographic Data of Patients, Preoperative Clinical Characteristics and Distribution of Surgery Durations According to Groups

Variables	Group P (n = 30)	Group C (n = 30)	Total (n = 60)	*P*
Age*	74.60±19.71	76.97±11.70	75.78±16.11	0.574
BMI* (kg m^{2-1})	24.11±4.22	22.93±4.86	23.52±4.21	0.283
Gender†				
Male	15 (50.0%)	12 (40.0%)	27 (45.0%)	0.436
Female	15 (50.0%)	18 (60.0%)	33 (55.0%)	
ASA†				
1	6 (20.0%)	4 (13.3%)	10 (16.7%)	0.661
2	10 (33.3%)	13 (43.3%)	23 (38.3%)	
3	14 (46.7%)	13 (43.3%)	27 (45.0%)	
Surgical duration (min)	109.83±27.99	119.83±28.51	114.83±28.35	0.176

Data are shown as mean ± SD, number (%), *t-test on independent variables, †chi-square test, $P < 0.05$: Statistically significant
BMI, body mass index; ASA, American Society of Anesthesiologists Physical Condition Classification; min, minutes; SD, standard deviation.

The number of patients requiring postoperative intensive care was five (8.3%), while the number of patients followed up in the ward was 55 (91.7%) ($P > 0.05$). Perioperative heart rate, MAP, and SpO_2 values were not significantly different between the groups ($P > 0.05$) (Figures 2, 3).

The NRS values before PENG block application were similar ($P > 0.05$). However, the NRS values after PENG block application, during positioning before spinal anaesthesia, and at the postoperative discharge, 2nd, 4th, 12th and 24th hours were found significantly lower in Group P than in Group C (Figure 4).

A statistically significant reduction in the duration of spinal anaesthesia and the number of attempts was observed in Group P ($P < 0.001$ and $P=0.022$, respectively) (Table 2).

A comparison of the number of spinal anaesthesia attempts between the groups revealed a statistically significant higher success rate on the first attempt in Group P, at 64% ($P=0.023$) (Table 3).

Nausea-vomiting and hypotension were observed only in Group C in a total of 6 patients and were statistically significant ($P < 0.05$). No instances of haematoma, bleeding, unintentional nerve injury, quadriceps muscle weakness, wound infection, local anaesthetic toxicity, or headache were observed in both groups.

A comparison of the tramadol consumption between the groups revealed that Group P exhibited a lower consumption rate ($P < 0.001$) (Table 4).

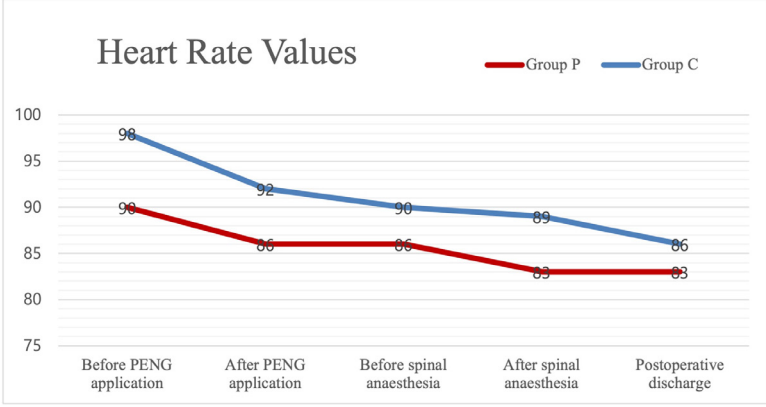

Figure 2. Heart rate values. Data are shown as mean. The Student's t-test was used in the analysis of the independent variables

PENG, pericapsular nerve group

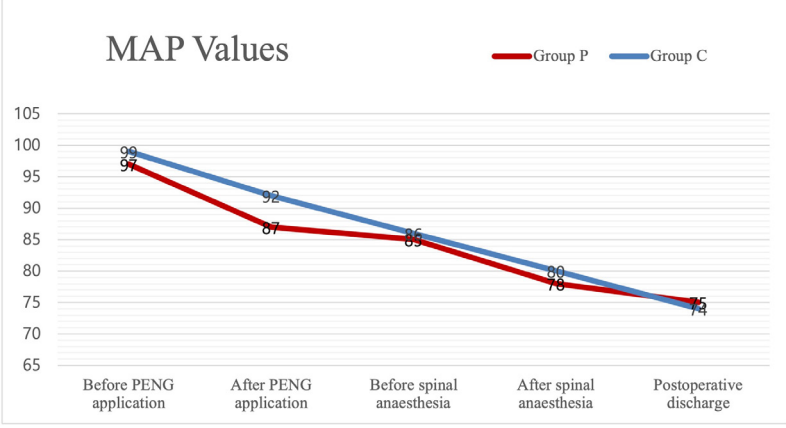

Figure 3. MAP values. Data are shown as mean. The Student's t-test was used in the analysis of the independent variables

MAP, mean arterial pressure; PENG, pericapsular nerve group

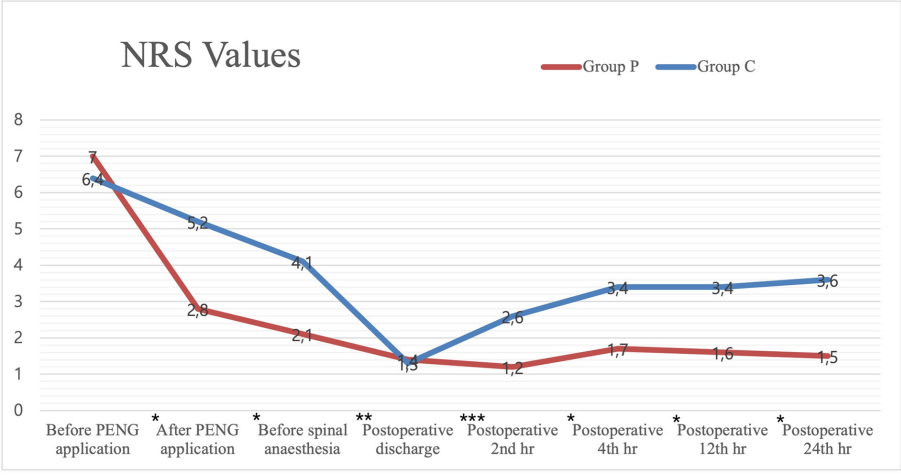

Figure 4. NRS values. Data are shown as mean. Mann-Whitney U test was used in the analysis of the variables

NRS, numerical rating scale, *$P < 0.001$, **$P=0.012$, ***$P=0.001$

Table 2. Distribution of Spinal Anaesthesia Duration and Number of Attempts Between Groups

Spinal anaesthesia	Group P	Group C	*P*
Duration (min)	13.63±2.49	18.13±3.08	<0.001
Attempts	1.63±0.96	2.27±1.11	0.022

Data are shown as mean ± SD, t-test was used in the analysis of the variables, $P < 0.05$: Statistically significant
SD, standard deviation; min, minutes.

Table 3. Distribution of the Number of Spinal Anaesthesia Attempts Between Groups

Attempts	Group P (n = 30)	Group C (n = 30)	Total (n = 60)	*P*
1†	19 (64%)	8 (27%)	27 (45%)	0.023*
2‡	5 (17%)	12 (40%)	17 (28%)	
3	4 (13%)	5 (17%)	9 (15%)	
4	2 (6%)	4 (13%)	6 (10%)	
5	0 (0%)	1 (3%)	1 (2%)	

Data are shown as number (%), chi-square test was used in the analysis of the variables, *significant at 0.05 level according to exact chi-square test, †post-hoc test is significant for attempts 1, ‡post-hoc test is significant for attempts 2, $P < 0.05$: Statistically significant.

Table 4. Perioperative Tramadol Consumption Amount by Groups

Tramadol consumption (mg)	Group P (n = 30)	Group C (n = 30)	*P*
Total	14.00±30.240	272.67±32.582	<0.001

Data are shown as mean ± SD, Mann-Whitney U test was used in the analysis of the variables, $P < 0.05$: Statistically significant
SD, standard deviation.

Discussion

It has been shown that PENG block, which can be easily applied under USG-guidance before surgery in the supine position without requiring any change in the patient's position, facilitates the application, shortens the duration and increases the success rate in the first attempt by providing a painless positioning to the patient during spinal anaesthesia application in hip fracture patients. Furthermore, this study showed that PENG block reduced postoperative pain, the need for opioids and the frequency of side effects.

Currently, there are no observational and comparative study investigating the duration and the number of spinal anaesthesia attempts with effective pain control using PENG block. In the literature, studies on PENG block are mostly in the form of case reports and case series.[9] Our study is the first retrospective study to show that PENG block improves the success of spinal anaesthesia at the first attempt by reducing pain and shortening the duration of spinal anaesthesia.

A study conducted on more than 10 patients revealed that the average pain score, which was 7.5 before PENG block, decreased to an average of 1.2 when the patients were given spinal anaesthesia.[10] The results of our study indicate that the average pain score, decreased from 7 before the PENG block to 2.8 after PENG block. Additionally, at the time of the lateral decubitus positioning before spinal anaesthesia, the average pain score was as low as 2.1. Consistent with the existing literature, NRS values were significantly decreased after PENG block in Group P.

A randomised controlled study was conducted on 100 patients who underwent open prostatectomy. The effect of the spinal anaesthesia position on success was investigated. There was no significant difference in success between the

two groups, with both demonstrating comparable outcomes. However, the number of attempts required was higher in the group that extended their legs to the table.[11] We investigated the effect of providing pain control and increasing hip and knee flexion by giving the lateral decubitus position on the trial number and duration of spinal anaesthesia. Upon comparison of the data from both groups, the average NRS value was found to be 4.1 in Group C, with the average number of attempts was 2.2 and the average duration of spinal anaesthesia application was 18.1 minutes. In Group P, the average NRS value was 2.1, the average number of attempts was 1.6, and the average duration of spinal anaesthesia application was 13.1 minutes when the lateral decubitus position before spinal anaesthesia was employed. The hypothesis of effective pain control was achieved with a decrease in NRS values, during positioning and spinal anaesthesia application. Spinal anaesthesia success was increased at the first attempt, and application time got shorter in Group P.

In a prospective observational study involving 1647 patients, the initial puncture success rate was found to be 52.9%. The study included patients with an average age of 38 years and a majority of ASA I (1323) and a minority of ASA III (17). It was observed that male gender, difficulty in palpating spinous processes, presence of bone deformities, and lower experience level of the provider increased the number of attempts for a successful dural puncture.[12] The initial puncture success rate of 45% observed in this study was lower than the 52.9% reported in previous studies. This discrepancy is believed to be due to the patient population, which presented greater challenges in administering spinal anaesthesia due to the structural changes of the spine associated with advanced age. The average age of the patients in this study was 74.7 years, and the ASA III patient ratio was 45%. Upon examination of the successful spinal anesthesia rate in the first attempt (Group P: 64%, Group C: 27%), it can be concluded that there is a significant difference between the two groups, confirming the hypothesis that PENG block increases the successful spinal anesthesia rate by facilitating the application of spinal anesthesia. Nevertheless, we also believe that further randomised controlled studies should be conducted in this regard.

Although femoral nerve block and fascia iliaca compartment block (FICB) have been demonstrated to have positive effects on perioperative analgesia, it is necessary to target the obturator nerve and accessory obturator nerve in order to achieve more effective pain control.[13] It has been demonstrated that the blockade of the accessory obturator nerve and femoral nerve from the anterior capsule nerves plays a greater role than previously reported in providing pain control in hip fractures.[14,15] Girón-Arango et al.[8] described a new regional anaesthetic technique, the PENG block, which was shown to result in a significant reduction in patients' pain scores without quadriceps muscle weakness in five hip fracture patients. A randomised controlled study comparing FICB and PENG block in terms of motor function demonstrated that the PENG block was more effective in preserving motor function.[16] Once more, the PENG block was demonstrated to be more efficacious than FICB in terms of postoperative analgesia.[17]

In our study, as in previous studies, pain control was achieved without quadriceps muscle weakness after PENG block.

It has been demonstrated that neuroaxial anaesthesia can reduce perioperative complication risks following total hip arthroplasty, regardless of age group and the presence of cardiopulmonary disease. Furthermore, the incidence of admission to the intensive care unit was lower in patients who received neuroaxial or neuroaxial plus general anaesthesia compared to those who received general anaesthesia in all groups.[18] The rate of intensive care unit admission for patients undergoing hip fracture surgery in the literature is reported to be 32.5%.[19] In our study, we found an intensive care unit admission rate of 8.3%, which we believe is due to the use of unilateral spinal anaesthesia to minimise haemodynamic changes.

The primary factor associated with increased mortality in general anaesthesia and spinal anaesthesia is intraoperative hypotension.[20] A study of 90 patients found that the incidence of hypotension was lower in unilateral spinal anaesthesia (15%) than in bilateral spinal anaesthesia (56%).[21] The administration of spinal anaesthesia in the lateral decubitus position with the fractured extremity positioned above the patient's body due to the severe pain caused by movement in hip fracture patients has been found to prevent the exacerbation of pain on the fractured extremity and to enable the surgery to be performed without the patient needing to change position.

In an article comparing the haemodynamic effects of hypobaric spinal anesthesia in elderly patients over the age 80 of who underwent surgery for femoral neck fractures, it was shown that the use of moderate doses (6-7.5 mg) of bupivacaine provided advantages in terms of the onset and termination of motor block after surgery.[22] Bupivacaine is the most extensively studied local anaesthetic for unilateral spinal anaesthesia, with minimal side effects.[3] Consequently, the study opted for unilateral spinal anaesthesia with a moderate dose (7.5 mg) of bupivacaine. Neither group exhibited any significant alterations in haemodynamic parameters throughout the perioperative period. The combination of bupivacaine with 12.5 µg of fentanyl was selected in order to take advantage of the pain-reducing effect of fentanyl while limiting the use of systemic opioids.

The National Institute for Health and Care Excellence in the United Kingdom recommends that all patients with hip

fractures receive pain management, irrespective of age or cognitive impairment. This should be initiated at admission and continued with paracetamol administered every six hours before and after surgery, with opioids added if pain persists. To prevent the administration of high doses of opioids, it is recommended that peripheral nerve blocks be employed.[23] The results of our study indicated that postoperative NRS values were significantly lower and the total amount of tramadol consumed was significantly less in patients who received PENG block compared to the control group. These findings demonstrate that the PENG block provides effective analgesia and can be employed to reduce opioid consumption.

No serious adverse events, such as permanent nerve damage, haematoma, or local anaesthetic systemic toxicity, were observed in the patients who received a PENG block. In our study, six patients in Group C exhibited nausea, vomiting, and/or hypotension. We hypothesize that this is a side effect of postoperative tramadol use.

Study Limitations

The study was subject to certain limitations, including its retrospective nature, the difficulty in accessing archive documents, the paucity of medical records, and the deficiencies in the history forms. Furthermore, the age of the patient population may have influenced the assessment of NRS values. Furthermore, postoperative analgesic consumption was not quantified using patient-controlled analgesia methods, and the end time of postoperative spinal anaesthesia was not monitored using the Bromage score. This may have resulted in challenges in pain assessment. There is a need for randomised controlled studies showing that preoperative PENG block application in hip fracture patients provides a more comfortable position to the patient during spinal anaesthesia, facilitates the application and increases the success of spinal anaesthesia.

Conclusion

In our study, PENG block facilitated the administration of spinal anaesthesia by reducing pain, especially during patient transfer and spinal anaesthesia positioning, and also shortened the duration of spinal anaesthesia administration, thus increased the success of first attempt spinal anaesthesia. Moreover, PENG block reduced postoperative pain, opioid use, and side effects.

Ethics

Ethics Committee Approval: This retrospective study was performed after approval from the Clinical Research Ethics Committee of Süleyman Demirel University Faculty of Medicine (decision no.: 281570, dated: 10.06.2022).

Informed Consent: Written informed consent was obtained.

Footnotes

Author Contributions: Surgical and Medical Practices - B.K., E.S.Ö., M.S.Ö., F.A.S.; Concept - B.K., E.S.Ö.; Design - B.K., E.S.Ö., F.A.S.; Data Collection and/or Processing - B.K., E.S.Ö., M.S.Ö.; Analysis and/or/ Interpretation - B.K., E.S.Ö., M.S.Ö., F.A.S., P.K.; Literature Review - B.K., E.S.Ö., M.S.Ö.; Writing - B.K., E.S.Ö., F.A.S., P.K.

Declaration of Interests: The authors declare no conflicts of interest.

Funding: No funding was received for conducting this study.

References

1. Kırdemir V, Baykal B. Lower Extremity Injuries. In: Ertekin C, Tavioğlu K, Güloğlu R, Kurtoğlu M, eds. Trauma. Istanbul Medical Publishing; 2005:1102-1124. [CrossRef]
2. Luger TJ, Kammerlander C, Gosch M, et al. Neuroaxial versus general anaesthesia in geriatric patients for hip fracture surgery: does it matter? *Osteoporos Int*. 2010;21(4):555-572. [CrossRef]
3. Büttner B, Mansur A, Bauer M, et al. [Unilateral spinal anesthesia : Literature review and recommendations]. *Anaesthesist*. 2016;65(11):847-865. [CrossRef]
4. Guay J, Parker MJ, Griffiths R, et al. Peripheral nerve blocks for hip fractures. *Cochrane Database Syst Rev*. 2017;5(5):CD001159. [CrossRef]
5. Scurrah A, Shiner CT, Stevens JA, et al. Regional nerve blockade for early analgesic management of elderly patients with hip fracture–a narrative review. *Anaesthesia*. 2018;73(6):769-783. [CrossRef]
6. Bianchi S, Becciolini M, Urigo C. Ultrasound imaging of disorders of small nerves of the extremities: less recognized locations. *J Ultrasound Med*. 2019; 38(11):2821-2842. [CrossRef]
7. Wick EC, Grant MC, Wu CL. Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: a review. *JAMA Surg*. 2017;152(7):691-697. [CrossRef]
8. Girón-Arango L, Peng PW, Chin KJ, et al. Pericapsular nerve group (PENG) block for hip fracture. *Reg Anesth Pain Med*. 2018;43(8):859-863. [CrossRef]
9. Morrison C, Brown B, Lin DY, et al. Analgesia and anesthesia using the pericapsular nerve group block in hip surgery and hip fracture: a scoping review. *Reg Anesth Pain Med*. 2021;46(2):169-175. [CrossRef]
10. Acharya U, Lamsal R. Pericapsular nerve group block: an excellent option for analgesia for positional pain in hip fractures. *Case Rep Anesthesiol*. 2020;2020:1830136. [CrossRef]
11. Afolayan JM, Areo PO, Adegun PT, et al. Comparison of ease of induction of spinal anaesthesia in sitting with legs parallel on the table versus traditional sitting position. *Pan Afr Med J*. 2017;28:223-227. [CrossRef]
12. Shin JJ, McCrum CL, Mauro CS, et al. Pain management after hip arthroscopy: systematic review of randomized controlled trials and cohort studies. *Am J Sports Med*. 2018;46(13):3288-3298. [CrossRef]
13. Short AJ, Barnett JJG, Gofeld M, et al. Anatomic study of innervation of the anterior hip capsule: implication for image-guided intervention. *Reg Anesth Pain Med*. 2018;43(2):186-192. [CrossRef]
14. Buono RD, Padua E, Pascarella G, et al. Pericapsular Nerve Group (PENG) block: an overview. *Minerva Anestesiol*. 2021;87(4):458-466. [CrossRef]
15. Aliste J, Layera S, Bravo D, et al. Randomized comparison between pericapsular nerve group (PENG) block and suprainguinal fascia iliaca block for total hip arthroplasty. *Reg Anesth Pain Med*. 2021;46(10):874-878. [CrossRef]
16. Natrajan P, Bhat RR, Remadevi R, et al. Comparative study to evaluate the effect of ultrasound-guided pericapsular nerve group

block versus fascia iliaca compartment block on the postoperative analgesic effect in patients undergoing surgeries for hip fracture under spinal anesthesia. *Anesth Essays Res*. 2021;15(3):285-289. [CrossRef]

17. Memtsoudis SG, Rasul R, Suzuki S, et al. Does the impact of the type of anesthesia on outcomes differ by patient age and comorbidity burden? *Reg Anesth Pain Med*. 2014; 39(2):112-9. [CrossRef]
18. Çelik F, Dağh R. Risk factors of geriatric patients admitted to intensive care after hip fracture surgery during the COVID-19 Pandemic. *Ahi Evran Med J*. 2021;5(2):152-159. [CrossRef]
19. Enneking K, Le-Wendling L, Ihnatsenka B. Anesthesia for orthopedic trauma. In UpToDate [Internet]. Waltham, 2019.https://medilib.ir/uptodate/show/100073[CrossRef]
20. Salem FB, Grat L, Gahbiche M. Rachianesthésie unilatérale et bénéfice hémodynamique des faibles doses de bupivacaïne hyperbare. *Ann Fr Anesth Reanim*. 2003;22(2):145-146. [CrossRef]
21. Khatouf M, Loughnane FJ, Boini S, et al. Unilateral spinal anaesthesia in elderly patient for hip trauma: a pilot study. *Ann Fr Anesth Reanim*. 2005; 24(3):249-254. [CrossRef]
22. Prakash S, Mullick P, Kumar SS, et al. Factors predicting difficult spinal block: A single centre study. *J Anaesthesiol Clin Pharmacol*. 2021;37(3):395-401. [CrossRef]
23. Ftouh S, Morga A, Swift C, et al. Management of hip fracture in adults: summary of NICE guidance. *BMJ*. 2011;342:d3304. [CrossRef]

DOI: 10.4274/TJAR.2024.241771

Original Article
Perioperative Care

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2024;52(6):231-239

Effect of Low-dose Ketamine on Inflammatory Markers, Perioperative Analgesia, and Chronic Pain in Patients Undergoing Laparoscopic Inguinal Hernia Surgery: A Prospective, Randomized, Double-blind, Comparative Study

Shivani Vijayakumar Hallikeri, Renu Sinha, Bikas Ranjan Ray, Ravindra Kumar Pandey, Vanlal Darlong, Jyotsna Punj, Virinder Kumar Bansal, Renu Saxena

All India Institute of Medical Sciences, Department of Anaesthesiology, Pain Medicine and Critical Care, New Delhi, India

Cite this article as: Hallikeri SV, Sinha R, Ray BJ, et al. Effect of Low-dose Ketamine on Inflammatory Markers, Perioperative Analgesia, and Chronic Pain in Patients Undergoing Laparoscopic Inguinal Hernia Surgery: A Prospective, Randomized, Double-blind, Comparative Study. *Turk J Anaesthesiol Reanim.* 2024;52(6):231-239.

Abstract

Objective: The neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are indicators of postoperative inflammatory response. Low-dose ketamine has analgesic and anti-inflammatory properties. Inguinal hernia surgery is associated with a higher incidence of chronic pain.

Methods: Sixty patients aged 18-60 years; American Society of Anesthesiologists status I and II who were scheduled for laparoscopic inguinal hernia surgery were included. After the induction of general anaesthesia, a ketamine 0.5 mg kg-1 bolus, followed by a 0.2 mg kg^{-1} h^{-1} infusion (group K) or saline bolus and infusion (group S) was administered until the end of the surgery. Blood samples were collected at various time intervals. Fentanyl requirement, hemodynamics, verbal analog scale (VAS), emergence delirium, recovery, postoperative nausea and vomiting, and chronic pain were recorded.

Results: Median (interquartile range) NLR was 4.63 times increased at 2 hours postoperatively from the baseline in group S [2.07 (1.72-2.79) to 7.91 (5.74-14.7)] as compared to 2.53 times increase in group K [1.85 (1.4-2.61) to 5.45 (2.89-7.61)] (P=0.02). The increase in median PLR from baseline to 2 hours postoperatively was greater in group S (2.98 times) than in group K (1.94 times) (P=0.02). The NLR and PLR were comparable on POD1 between the groups. Fentanyl requirement was significantly higher in group S compared to Group K both intraoperatively, (P=0.01) and two hours postoperatively (P=0.047). More patients had chronic pain and VAS scores in group S than in group K (13 vs 5, P=0.05).

Conclusion: Low-dose ketamine reduces postoperative inflammatory response, decreases perioperative opioid requirement, and reduces incidence of chronic pain after laparoscopic inguinal hernia surgery with no significant side effects.

Keywords: Chronic pain, inflammatory markers, inguinal hernia, ketamine, neutrophil lymphocyte ratio, platelet lymphocyte ratio

Main Points

- Low-dose intravenous ketamine bolus followed by infusion reduces inflammatory response, as observed by a significantly lower increase in neutrophil lymphocyte ratio and platelet lymphocyte ratio values at 2 hours postoperatively from baseline in laparoscopic inguinal hernia surgery.
- Low-dose intravenous ketamine bolus followed by infusion reduces perioperative and chronic pain at 3 months after laparoscopic hernia surgery, with minimal delay in recovery and no side effects.

Corresponding author: Renu Sinha, e-mail: renusinhaagarwal@gmail.com

Received: October 09, 2024 Accepted: November 21, 2024

Introduction

Systemic inflammatory response depends on the release of various hormones, cytokines, and acute phase reactants during surgery.[1,2] An optimum inflammatory response would enhance the patient's recovery, but an excessive inflammatory response may adversely affect the recovery and postoperative outcome due to immune depression and increased susceptibility to sepsis.

The inflammatory response is assessed by immune mediators like interleukins (IL), C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and procalcitonin; which require specific tests and are time-consuming. Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are easy to assess inflammatory response after surgery through complete blood counts.[1,3] Studies have shown that NLR and PLR can correlate with IL-6, CRP, and TNF- levels and can predict postoperative surgical complications and cancer prognosis.[4-9]

Anaesthesia techniques and anaesthetic agents also affect the inflammatory process perioperatively.[1] Ketamine reduces inflammation after surgery by acting at various levels in the inflammatory process.[10] Low-dose ketamine also provides good analgesia during and after surgery by antagonizing N- methyl D- aspartate (NMDA) receptors and by centrally desensitizing pain without significant side effects, such as emergence delirium and sedation.[11-14] The incidence of chronic post hernia pain syndrome after laparoscopic inguinal hernia surgery ranges from 6-20% and has adverse implications on morbidity, healthcare costs, and quality of life.[15,16] Previous studies have suggested that low-dose ketamine decreases the incidence of chronic pain after various surgeries.[17,18]

Therefore, we hypothesized that low-dose ketamine infusion would result in decreased inflammatory response and chronic pain after laparoscopic inguinal hernia surgery. The primary objective of the study was to evaluate the effect of low-dose ketamine on the inflammatory response in terms of NLR and PLR. The secondary objectives were to evaluate the effect of low-dose ketamine on perioperative pain, opioid consumption, emergence delirium, awakening, postoperative nausea and vomiting, shivering, nystagmus, and chronic pain at 3 months.

Methods

This prospective, randomized, double-blind study was approved by the Institutional Ethics Committee for Post Graduate Research All India Institute of Medical Sciences, Ansari Nagal, New Delhi for this study (approval no.: IECPG-268/28.06.2018, date: 26.07.2018) and registered with the Clinical Trials Registry, India, (CTRI/2018/08/015320). Written informed consent was obtained from the patients before recruitment.

Sixty patients aged 18-60 years with American Society of Anesthesiologists I and II who were scheduled for laparoscopic inguinal hernia surgery were randomized using computer-generated random numbers into groups K and S. Patients with a history of epilepsy, recurrent hernia, complicated hernia, conversion from laparoscopic to open surgery, inability to understand the scoring system, and refusal to participate were excluded from the study. Allocation was enceallled by the closed envelop method, which was opened in the operating room. The study drugs and infusions were prepared by the anesthesiologist; who was not involved in the study.

Pre-anaesthesia examination was performed one day before surgery, and a blood sample was drawn to obtain a complete blood count at baseline. The verbal analog scale (VAS) was explained to all patients to measure postoperative pain. On the day of surgery, baseline vitals [heart rate (HR), non-invasive blood pressure, SpO_2] were noted before induction of anaesthesia. Anaesthesia induction was performed with fentanyl 2 μg kg^{-1}, propofol 2 mg kg^{-1} followed by atracurium 0.5 mg kg^{-1} . In group K, ketamine bolus 0.5 mg kg^{-1} followed by ketamine infusion 0.2 mg kg^{-1} h^{-1} was administered until the end of surgery. In group S, patients received a saline bolus and infusion until the end of the surgery. The airway was secured with an appropriately sized cuffed endotracheal tube. Anaesthesia was maintained with O_2, air (FiO_2 0.5), and isoflurane (MAC 0.8-1.2). Vital signs were noted every 5 minutes.

If HR or mean arterial pressure increased by more than 20% from baseline, 1.0 μg kg^{-1} fentanyl was administered. Paracetamol (1 g) and ondansetron (4 mg) were administered 10 minutes before the end of surgery. At the end of the surgery, after regaining spontaneous breathing, neuromuscular blockade was reversed with a combination of 50 μg kg^{-1} neostigmine and 10 μg kg^{-1} glycopyrrolate. The trachea was extubated after regular respiration with adequate tidal volume. The time from stoppage of isoflurane to extubation and time from stoppage of isoflurane to following verbal commands were noted, and the patient was shifted to the post anaesthesia care unit. Postoperative hemodynamic monitoring, time to reach modified Aldrete score of ≥9, VAS score, emergence of delirium by Richmond agitation sedation scoring system (RASS), shivering, nystagmus, and postoperative nausea or vomiting (PONV) were noted at regular intervals.

If the RASS was +2 or +3, no interventions were performed. If the RASS was 3 or 4, midazolam 0.4 μg kg^{-1} was administered. If the PONV score was 3, ondansetron 4 mg was administered. If still PONV was not controlled then metoclopramide 150 μg kg^{-1} was given. If VAS was 4-6 then fentanyl 0.5 μg kg^{-1} and if VAS was ≥7 then fentanyl 1 mg kg^{-1} was administered.

Patients were shifted to the ward after achieving a modified Aldrete score of ≥9 tramadol 50 mg and paracetamol 1 g twice daily were administered as and when required. On POD1, the patient was followed-up in the ward, and the requirement for analgesics was noted. The patients were discharged with instructions for oral paracetamol 500 mg.

Blood samples (two mL venous blood) were collected in EDTA vials at pre-anaesthetic check-up (T0), 2 hours postoperatively (T1), and on POD1 (T2).

The neutrophil count (NC), lymphocyte count (LC), and platelet count (PC) were noted. The NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count (ALC); PLR was calculated by dividing the absolute platelet count by the ALC.

Three months later, patients were interviewed telephonically for chronic pain. Their VAS, analgesic intake, radiating pain on exertion, pain at rest, throbbing pain, discomfort, wound site infection, and any need for a doctor consultation for a condition related to hernia surgery during the last three months were asked and noted.

Statistical Analysis

There is no previous study on the reference of changes in NLR and PLR after laparoscopic surgery with low-dose ketamine administration, so we included 60 cases as a pilot study.

Categorical data were summarized according to frequency (percentage). Continuous variables were summarized by mean ± standard deviation, 95% confidence interval (CI), and median [interquartile range (IQR)/minimum and maximum] as appropriate. Qualitative data is compared using the chi-square test between the groups. Quantitative data is compared by Student's t-test, Kruskal-Wallis test, and Mann-Whitney U test between the groups. STATA 14.0 (2015) statistical software was used for analysis. *P* value <0.05 is considered to be significant.

Results

Data of 60 patients were included until POD1. At 3 months, telecommunication was not possible in two patients in group K and one patient in group S. Twenty-eight patients in group K and 29 patients in group S were followed up until the end of the study (Figure 1).

Demographic data, type and duration of surgery, and hemodynamic parameters were comparable between both groups (Table 1). The mean intraoperative fentanyl requirement was significantly lower in group K (7±15.2 µg) [95% CI (1.35-12.64 µg)] than in group S (26.6±28.3 µg) [95% CI (16.07-37.2 µg)] (*P*=0.01) (Table 2). The time taken for extubation was comparable between both groups. The time to follow verbal commands (13.7±5.9 vs 10.3±4.0 min) and time taken to reach modified Aldrete's score >9 (18.6±5.8 vs 16±4.2) were significantly longer in group K than in group S (*P*=0.01 and 0.05 respectively) (Table 2).

Preoperative TLC, PC, NC, LC, NLR, and PLR values were comparable between the groups. TLC and NC increased at T1 and T2 from T0, but the increase in TLC was comparable between the groups. The increase in median (IQR) NC at T1 from T0 values was significantly more in group S [84 (80-88.75)%] in comparison to the group K [77 (67.5-80)%] (p=0.0005) (Table 3). Median (IQR) LC reduction from T0 to T1 was more in group S [29 (24-34.25)% to 11 (6.25-14.5)%] compared to group K [31.5 (25-37.95)% to 14.5

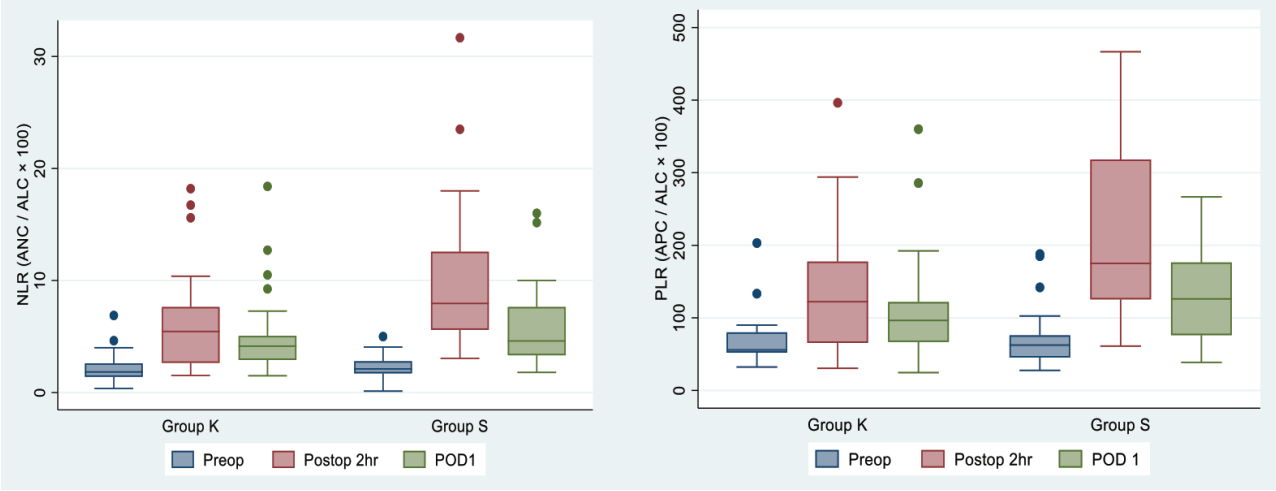

Figure 1. Consort diagram

NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte rat

Table 1. Demographic Data, Comorbidities of Patients, Type of Inguinal Hernia and Surgical Procedure					
			Group K, n = 30 (%)	Group S, n = 30	*P* value
Age, years (Mean ± SD, 95% CI)			38.9±13.1 (34.1-43.9)	38.2±13.6 (33.2-43.4)	0.84
Gender		**Male**	29 (96.7)	30 (100)	0.31
		Female	1 (3.3)	0 (0)	
Weight, kg (Mean ± SD, 95% CI)			62.3±8.7 (59.1-65.6)	65.3±10.6 (61.3-69.2)	0.25
Comorbidities		**None**	22 (73.3)	27 (90)	0.09
		Hypertension	7 (23.3)	1 (3.3)	
		Diabetes	1 (3.3)	0 (0)	
		Asthma	0 (0)	1 (3.3)	
		Hypertension and diabetes	0 (0)	1 (3.3)	
Type of inguinal hernia	**Direct**	**Bilateral**	2 (6.7)	2 (6.7)	0.9
		Right-sided	3 (10)	2 (6.7)	
		Left-sided	1 (3.3)	0 (0)	
	Indirect	**Bilateral**	6 (20)	8 (26.7)	
		Right-sided	12 (40)	13 (43.3)	
		Left sided	6 (20)	5 (16.7)	
Type of surgery		**TAPP**	16 (53.3)	12 (40)	0.3
		TEP	14 (46.7)	18 (60)	
Duration of surgery, minutes (Mean ± SD, 95% CI)			60.5±18.6 (55.8-68.5)	62.2±17 (53.5-67.5)	0.71

n, number of patients; SD, standard deviation; CI, confidence interval.

Table 2. Perioperative Fentanyl Requirement and Recovery After Anaesthesia				
		Group K, n = 30 Mean±SD (95% CI)	Group S, n = 30 Mean±SD (95% CI)	*P* value
Fentanyl (µg)	**At induction**	126.2±17.9 (119.52-132.88)	127.8±18.1 (121.08-134.59)	0.72
	Intraoperative period	7±15.2 (1.35-12.65)	26.6±28.3 (16.07-37.2)	**0.001***
	Postoperative period	40.3±13.7 (30.5-50.02)	57.7±24.4 (45.6-69.8)	**0.047***
Time taken for extubation (minutes)		9.4±4.3 (7.8-11)	8.6±3.6 (7.2-9.95)	0.42
Time taken to follow verbal commands (minutes)		13.7±5.9 (11.5-15.9)	10.3±4.0 (8.8-11.8)	**0.01***
Time taken to reach MAS >9 (minutes)		18.6±5.8 (16.5-20.8)	16±4.2 (14.4-17.6)	**0.05***

*Statistically significant.

mg, milligram; µg, microgram; MAS, modified Aldrete score; n, number of patients; SD, standard deviation; CI, confidence interval.

Table 3. Total Lymphocyte Count, Neutrophil Count, Platelet Count, Lymphocyte Count, Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio at Various Time Intervals				
		Group K, n = 30 Median (IQR)	Group S, n = 30 Median (IQR)	*P* value
TLC (Number of cells x 10^6/liter)	T0	6815 (5650-7590)	6790 (5572-7287)	0.65
	T1	9700 (7520-14635)	11450 (9375-14687)	0.32
	T2	7455 (5725-9445)	8400 (1057-11040)	0.13
NC (% of TLC)	T0	59.5 (48.25-63.5)	60 (53-65.75)	0.21
	T1	77 (67.5-80)	84 (80-88.75)	**0.0005***
	T2	72.5 (68-75.75)	75 (69.3-81.5)	0.28
LC (% of TLC)	T0	31.5 (25-37.95)	29 (24-34.25)	0.51
	T1	14.5 (10.25-21.5)	11 (6.25-14.5)	**0.01***
	T2	18.5 (15-21.98)	18 (11-20.75)	0.49

Table 3. Continued

		Group K, n = 30 Median (IQR)	Group S, n = 30 Median (IQR)	*P* value
PC (number of cells × 10^{11}/liter)	T0	1.85 (1.36-2.05)	1.71 (1.50-1.98)	0.80
	T1	1.64 (1.23-2.12)	1.66 (1.42-2.18)	0.41
	T2	1.58 (1.34-2.06)	1.81 (1.6-2)	0.21
NLR (ANC/ALC × 100)	T0	1.85 (1.4-2.61)	2.07 (1.72-2.79)	0.47
	T1	5.45 (2.89-7.61)	7.91 (5.74-14.7)	**0.007***
	T2	4.14 (2.93-5.05)	4.21 (3.39-7.55)	0.34
	Number of times rise in NLR at T1 from T0	2.53 (1.73-4.56)	4.63 (2.72-6.43)	**0.02***
	Number of times rise in NLR at T2 from T0	2.41 (1.66-3.43)	2.23 (1.66-4.37)	0.81
PLR (APC/ALC × 100)	T0	55.2 (52.03-78.91)	58.9 (45.57-76)	0.99
	T1	124.55 (66.45-174.79)	157.78 (127.42-305.89)	**0.03***
	T2	97.77 (66.67 -121.41)	126.14 (76.31-169.49)	0.19
	Number of times rise in NLR at T1 from T0	1.94 (1.38-3.21)	2.98 (2.11-4.4)	**0.02***
	Number of times rise in NLR at T2 from T0	1.73 (1.37-2.03)	2.01 (1.27-2.95)	0.41

*Statistically significant.

IQR, interquartile range; TLC, total leucocyte count; NC, neutrophil count; ANC, absolute neutrophil count (%NC/deciliter); PC, platelet count; APC, absolute platelet count (PC/deciliter); LC, lymphocyte count; ALC, absolute lymphocyte count (%LC/deciliter); n, number of patients; T0, preoperative; T1, two hours postoperatively; T2, postoperative day one.

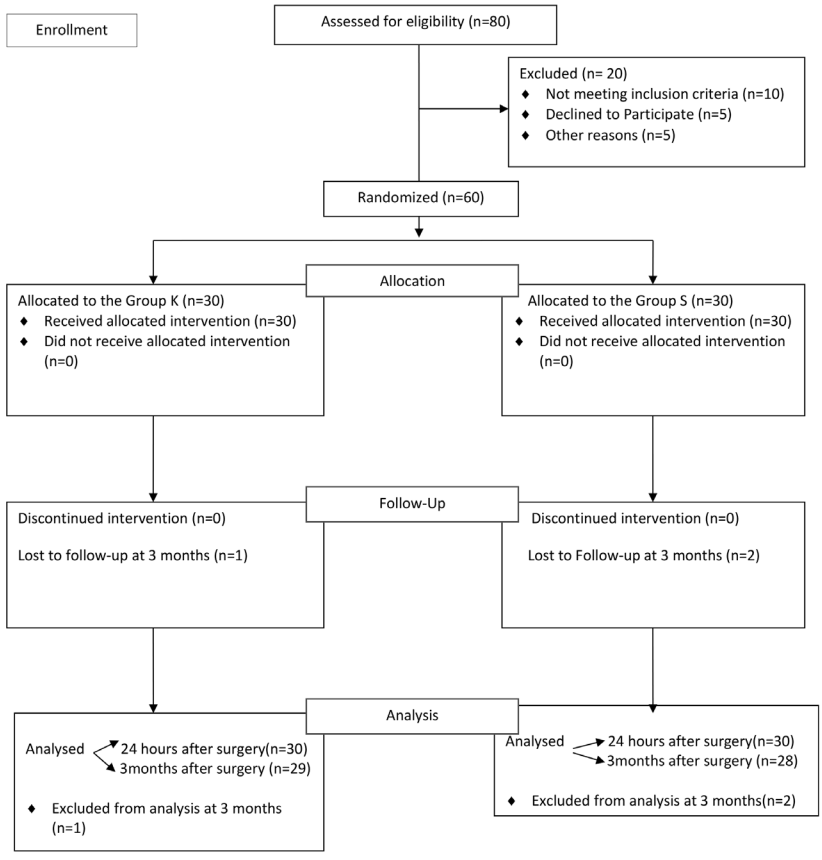

Figure 2. Neutrophil lymphocyte and platelet lymphocyte ratios at different time points

Preop, preoperative period; Postop 2hr, postoperative two hours; POD1, postoperative day one; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; APC, absolute platelet count; Mann-Whitney U test was performed, NLR and PLR showed significant rise from preoperative value after two hours of surgery

(10.5-21.5)%], which was statistically significant between the groups (*P*=0.01). At T2, NC and LC were comparable between the groups (Table 3). PC decreased at T1 and T2 from T0, but the fall was comparable in both groups.

The NLR at T0 and T2 were comparable in both groups. The NLR showed a statistically significant increase from T0 to T1 in group S compared with group K (*P*=0.007). The median (IQR) NLR in group K was 1.85 (1.4-2.61) at T0, increased to 5.45 (2.89-7.61) at T1, and decreased to 4.14 (2.93-7.61) at T2. In group S, the median (IQR) NLR was 2.07 (1.72-2.79) at T0, which increased to 7.91 (5.74-14.7) at T1 and reduced to 4.21 (3.39-7.55) at T2 (Table 3) (Figure 2).

The PLRs at T0 and T2 were comparable in both groups. The PLR showed a statistically significant increase in group S compared with group K at T1 (*P*=0.03). The median (IQR) PLR at T0 in group K was 55.2 (52.03-78.91) increased to 124.55 (66.45-174.79) at T1 and reduced to 97.77 (66.67-121.41) at T2. In group S, the PLR was 58.9 (45.57-76) at T0, which increased to 157.78 (127.42-305.89) at T1 and reduced to 126.14 (76.31-169.49) at T2 (Table 3) (Figure 2).

Postoperative pain was significantly less in the immediate postoperative phase in group K than in group S [(VAS>3)-3/30 patients vs 13/30 patients] (*P*=0.007). VAS scores at 10, 30, 60, and 120 minutes were comparable in both groups. The total postoperative fentanyl requirement was significantly lower in group K than in group S (40.3±13.7 vs 57±24.4 µg) (p=0.047) (Table 4). The postoperative RASS scores at different time intervals were comparable between both groups. The incidence of PONV, shivering, and nystagmus was minimal in both groups.

At 3 months postoperatively, six patients in group K and 12 patients in group S complained of pain during routine work. Two patients (7.1%) in group K and 11 (37.9%) in group S had a VAS score of 3. One patient (3.6%) in group K and four (13.8%) patients in group S had a VAS score of 4. Significantly more patients in group S had a greater VAS score during the three months postoperatively compared with group K (*P*=0.05) (Table 5). The incidence of discomfort and radiating pain was higher in group S than in group K. Complications like discomfort, radiating pain at 3 months were present in 13/29 (44.8%) patients in group S and in 05/28 (17.9%) patients in group K. Oral analgesics were administered to two patients in group S and one patient in group K.

Table 4. Postoperative Verbal Analogue Score

	VAS (0-3)		VAS (>3)		*P* value
Time (minutes)	**Group K n = 30 (%)**	**Group S n = 30 (%)**	**Group K n = 30 (%)**	**Group S n = 30 (%)**	
0	27 (90)	17 (56.7)	3 (10)	13 (43.3)	**0.007***
10	25 (83.3)	26 (56.7)	5 (16.7)	4 (13.3)	0.99
30	28 (93.3)	28 (93.3)	2 (6.7)	2 (6.7)	0.99
60	24 (80)	24 (80)	6 (20)	6 (20)	0.99
120	28 (93.3)	25 (83.3)	2 (6.7)	5 (16.7)	0.42

*Statistically significant.
n, number of patients; VAS, verbal analogue score.

Table 5. Incidence, Symptoms and Requirement of Medication for Chronic Pain

		Group K n = 28 (%)	Group S n = 29 (%)	*P* value
VAS after three months	**0**	20 (71.4)	16 (55.2)	**0.05***
	1	1 (3.6)	0 (0)	
	2	1 (3.6)	1 (3.4)	
	3	2 (7.1)	11 (37.9)	
	4	1 (3.6)	4 (13.8)	
Three months postoperatively	**No complaints**	23 (82.1)	16 (55.2)	0.09
	Discomfort	1 (3.6)	2 (6.9)	
	Radiating pain	4 (14.3)	11 (37.9)	
	Not on medication	27 (96.4)	27 (93.1)	0.57
	Paracetamol for pain	1 (3.6)	2 (6.9)	

*Statistically significant.
n, number of patients; VAS, verbal analogue score.

Discussion

In the present study, the NLR and PLR at 2 hours after laparoscopic inguinal hernia surgery and POD1 from preoperative values were increased in both groups. Kim et al.[1] also observed an increase in NLR until 24 hours after laparoscopic assisted vaginal hysterectomy. An increase in NLR signifies compromised immunity and activation of inflammatory response.[1] Previous studies have shown that NLR and PLR are reliable markers of inflammation and can predict disease-free survival rates, postoperative morbidity, and mortality.[4-6,8,9] Tzikos et al.[19] noted that NLP and PLR could be a good predictor for 90-day mortality and length of hospital stay in patients undergoing cardiac surgery. The mean NLRs in normal males and females were 1.63 (0.76) and 1.66 (0.82).[20] We observed comparable preoperative NLR between 1.4-2.79 in both groups. Preoperative NLR can be used as a predictor of the severity of appendicitis, with more than 8 values for severe acute appendicitis.[21] Higher preoperative NLR also helps in the diagnosis of requirement for intestinal resection for incarcerated hernia.[5] An increase in NLR of more than 2.5-5 times from baseline or normal values is considered a poor prognostic indicator in cancer surgeries.[4]

Silva et al.[3] concluded that >10 NLR on the first postoperative day may be a surrogate marker for increased complications due to significant inflammation after bariatric surgery. The authors did not note NLR before the first postoperative day. In the present study, the NLR increased to 14.7 at 2 hours postoperatively; returned to 7.55 on POD1 in the saline group, whereas in the ketamine group, the NLR remained below 7.61 postoperatively. We observed that the increase in NLR at 2 hours after surgery from baseline was significantly less i.e. 2.53 times in comparison with 4.63 times in the saline group, suggesting suppression of the inflammatory response after surgery with ketamine. Ketamine acts at various levels during the inflammatory process, including in inflammatory cell recruitment, cytokine production, and the regulation of inflammatory mediators. However, this effect was short term, as the POD1 increase in NLR in both groups was comparable.

The mean reference value of the PLR was 132.40 (46.79-218.01).[20] We observed the basal PLR value in the range of 45.57-78.91. Turkmen et al.[6] concluded that the PLR is a better inflammatory marker than NLR for predicting inflammation in end-stage renal disease and also showed its positive correlation with NLR, CRP, IL6, and TNF-α. PLR alone was also considered for predicting major surgical complications after pancreatico-duodenostomy, with an optimal cutoff of 145.3 within 30 days.[8] In the present study, the maximum PLR at two hours postoperatively with low-dose ketamine was 174.79 and with saline was 305.89; which decreased to 121.41 and 169.49 on POD1, respectively. The increase in PLR was significantly less (1.94 time) at 2 hours postoperatively with ketamine in comparison to 2.98 times with saline is due to the anti-inflammatory effect of low-dose ketamine infusion. The comparable PLRs on POD1 in both groups suggest a short-term effect of ketamine infusion. Previous studies have also shown that low-dose ketamine resulted in decreased levels of inflammation markers (IL6) during prolonged open abdominal surgeries and cardiopulmonary bypass with hemodynamic changes.[10,22]

Surgical procedures are associated with altered homeostasis, leading to the release of stress hormones, pain, and inflammatory reactions. Systemic inflammatory response includes leukocytosis, neutrophilia, lymphopenia, apoptosis of lymphocytes or inhibition of apoptosis of neutrophils.[1] Neutrophilia represents low-grade to unrestrained cellular inflammation, whereas lymphopenia is indicative of latent immune response. Platelets participate in microcirculation thrombosis at the surgical site, hampering blood supply to the surgical wound and altering the healing process, resulting in decreased platelet counts. We also observed leukocytosis, neutrophilia, lymphopenia, and decreased platelet count postoperatively in both groups until 24 hours after hernia surgery, but neutrophilia and lymphopenia were significantly less with ketamine infusion at 2 hours after surgery compared with saline infusion. Predictors of postoperative infection include significant neutrophilia and lymphopenia after surgery. Our findings suggested that the anti-inflammatory effect of intraoperative ketamine infusion as an increase in NLR and decrease in LC is present in sepsis and bacteraemia.[7]

We selected only laparoscopic inguinal hernia surgery, which had less hemodynamic changes and minimal blood loss, to avoid confounding factors like surgical procedure and duration of surgery, to evaluate the effect of low-dose ketamine on inflammatory markers. Comparable demographic data and comorbidities avoided additional confounding factors in the present study, such as diabetes, hypertension, and asthma, which may lead to change in values of NLR and PLR.[23-26] Our anaesthesia technique was also similar in both groups, except for the study drug to eliminate further bias as anaesthetic drugs can modify inflammation and pain during and after surgery.[1,2,27] Domagalska et al.[28] observed that erector spinae plane block lowers NLR and PLR ratios 12 and 24 hours after spinal surgery. Kim et al.[1] compared total intravenous anaesthesia with propofol and remifentanil with sevoflurane anaesthesia in laparoscopic assisted vaginal hysterectomy and observed a significant decrease in NLR during the immediate postoperative period and two hours after surgery with TIVA compared with sevoflurane anaesthesia. Similar to our finding, the difference in NLR values was for short term, as NLR values were comparable at 24 hours postoperatively.[1] The short term effect on NLR may be due to inclusion of minor laparoscopic surgeries.

In the present study, ketamine infusion significantly reduced fentanyl requirement during the intraoperative and postoperative periods. Our results are similar to those of previous studies in which ketamine was administered at a low-dose bolus or bolus followed by intraoperative infusion, resulting in decreased opioid requirement perioperatively.[13,14] Pain after laparoscopic inguinal hernia surgery is mainly due to peritoneal stretching caused by gas insufflation and diaphragmatic irritation. Ketamine provides preemptive analgesia by inhibiting central sensitization of pain and inflammation during and after surgery.[29]

Similar to previous findings, we found no difference in hemodynamics, extubation, side effects like emergence delirium, shivering, nystagmus, and PONV, between the low-dose intraoperative ketamine and saline groups.[11-14] Increase in time to follow verbal command and awakening was statistically significant in the ketamine group, whereas clinical delay of 2-3 minutes was not significant.

The incidence of chronic pain was significantly less in ketamine group in comparison to the saline group. Chronic post hernia pain syndrome after laparoscopic hernia surgery has somatic and neuropathic components. Somatic pain is caused by damage to the pubic tubercle during the stapling of the mesh prosthesis or deep muscle layers. Neuropathic pain is probably due to primary damage to the ilioinguinal or genitofemoral nerve. Secondary nerve damage can occur due to irritation or compression by an adjacent inflammatory process, such as granuloma.[30] Ketamine decreases the incidence of chronic pain by acting on NMDA receptors, activating descending inhibitory pathways arising from supraspinal sites, and inhibiting dorsal horn nociceptive neurons. A systematic review and meta-analysis concluded that low-dose ketamine infusion both intraoperatively and postoperatively decreased the incidence of chronic pain.[17] The timing and dosage of ketamine bolus and infusion in different studies were highly variable. We administered 0.5 mg kg^{-1} bolus ketamine at induction followed by 0.2 mg kg^{-1} h^{-1} infusion till the end of surgery. In contrast, Kwok et al.[11] did not find any difference in the incidence of chronic pain one month after laparoscopic gynecological surgeries with the pre-incision 0.15 mg kg^{-1} ketamine bolus.

Study Limitations

The limitations of the present study were the inclusion of laparoscopic surgery with less surgical trauma and the inability to assess the correlation of NLR and PLR with chronic pain due to the small sample size.

Conclusion

This study suggested that low-dose intravenous ketamine bolus followed by infusion reduced the inflammatory response, as observed by a significant decrease in the NLR and PLR values at 2 hours postoperatively from baseline after laparoscopic inguinal hernia surgery. Ketamine bolus infusion reduces perioperative and chronic pain at 3 months after laparoscopic hernia surgery, with a minimal delay in recovery without any side effects.

Ethics

Ethics Committee Approval: This prospective, randomized, double-blind study was approved by the Institutional Ethics Committee for Post Graduate Research All India Institute of Medical Sciences, Ansari Nagal, New Delhi for this study (approval no.: IECPG-268/28.06.2018, date: 26.07.2018) and registered with the Clinical Trials Registry, India, (CTRI/2018/08/015320).

Informed Consent: Written informed consent was obtained from the patients before recruitment.

Footnotes

Author Contributions: Surgical and Medical Practies - S.V.H., R.S., R.K.P., V.D., J.P., V.K.B.; Concept - S.V.H., R.S., V.D., R.Sa.; Design - S.V.H., R.S., B.R.R., V.D., J.P., V.K.B.; Data Collection and/or/ Processing - S.V.H., R.S., B.R.R., R.K.P., V.K.B., R.Sa.; Analysis and/or/ Interpretation - S.V.H., R.S., B.R.R., R.K.P., J.P., R.Sa.; Literature Search - S.V.H., R.S., V.D.; Writing - S.V.H., R.S., B.R.R., R.K.P.

Declaration of Interests: The authors declare no conflicts of interest.

Funding: No funding was received for this study.

References

1. Kim WH, Jin HS, Ko JS, et al. Effect of anesthetic techniques on neutrophil-to-lymphocyte ratios after laparoscopy-assisted vaginal hysterectomy. *Acta Anaesthesiol Taiwan.* 2011;49(3):83-877. [CrossRef]
2. Surhonne N, Hebri C, Kannan S, Duggappa DR, Rs RR, Mapari CG. Effect of anesthetic techniques on the neutrophil-to-lymphocyte ratio in patients undergoing infraumbilical surgeries. *Korean J Anesthesiol.* 2019;72(5):458-465. [CrossRef]
3. Silva MD, Cleghorn MC, Elnahas A, Jackson TD, Okrainec A, Quereshy FA. Postoperative day 1 neutrophil-to-lymphocyte ratio as a predictor of 30-day outcomes among bariatric surgery patients. *Surg Endosc.* 2016;31(6):2645-2650. [CrossRef]
4. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol.* 2005;91(3):181-184. [CrossRef]
5. Köksal H, Ateş D, Nazik EE, Küçükosmanoğlu İ, Doğan SM, Doğru O. Predictive value of preoperative neutrophil-to-lymphocyte ratio for detecting bowel resection in hernia with intestinal incarceration. *Turk J Trauma Emerg Surg TJTES.* 2018;24(3):207-210. [CrossRef]
6. Turkmen K, Erdur FM, Ozcicek F, et al. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in patients with end-stage renal disease. *Hemodial Int.* 2013;17(3):391-396. [CrossRef]
7. Westerdijk K, Simons KS, Zegers M, Wever PC, Pickkers P, de Jager CPC. The value of the neutrophil-lymphocyte count ratio in the diagnosis of sepsis in patients admitted to the intensive care unit: a retrospective cohort study. *PLoS One.* 2019;14(2):e0212861. [CrossRef]
8. Vaughan-Shaw PG, Rees JRE, King AT. Neutrophil lymphocyte ratio as a predictor of outcome after emergency abdominal surgery in the elderly. *Int J Surg Lond Engl.* 2012;10(3):157-162. [CrossRef]
9. Serban D, Stoica PL, Dascalu AM, et al. Significance of preoperative neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio

(PLR), and systemic inflammatory index (SII) in predicting severity and adverse outcomes in acute calculous cholecystitis. *J Clin Med.* 2023;12(21):6946. [CrossRef]

10. De Kock M, Loix S, Lavand'homme P. Ketamine and peripheral inflammation. *CNS Neurosci Ther.* 2013;19(6):403-410. [CrossRef]
11. Kwok RFK, Lim J, Chan MTV, Gin T, Chiu WKY. Preoperative ketamine administration improves postoperative analgesia after gynecologic laparoscopic surgery. *Anesth Analg.* 2004;98(4):1044-1049. [CrossRef]
12. Gorlin AW, Rosenfeld DM, Ramakrishna H. Intravenous subanesthetic ketamine for perioperative analgesia. *J Anaesthesiol Clin Pharmacol.* 2016;32(2):160-167. [CrossRef]
13. Kaur S, Saroa R, Aggarwal S. Effect of intraoperative low-dose ketamine on management of postoperative analgesia. *J Nat Sci Biol Med.* 2015;6(2):378-382. [CrossRef]
14. Singh H, Kundra S, Singh RM, Grewal A, Kaul TK, Sood D. Preemptive ketamine analgesia for laparoscopic cholecystectomy. *J Anaesthesiol Clin Pharmacol.* 2013;29(4):478-484. [CrossRef]
15. Bansal VK, Misra MC, Babu D, et al. A prospective, randomized comparison of long-term outcomes: chronic groin pain and quality of life following totally extraperitoneal (TEP) and transabdominal preperitoneal (TAPP) laparoscopic inguinal hernia repair. *Surg Endosc.* 2013;27(7):2373-2382. [CrossRef]
16. Reinpold W. Risk factors for chronic pain after inguinal hernia repair: a systematic review. *Innov Surg Sci.* 2017;2(2):61-68. [CrossRef]
17. McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. *Acta Anaesthesiol Scand.* 2014;58(10):1199-1213. [CrossRef]
18. Suzuki M, Haraguti S, Sugimoto K, Kikutani T, Shimada Y, Sakamoto A. Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology.* 2006;105(1):111-119. [CrossRef]
19. Tzikos G, Alexiou I, Tsagkaropoulos S, et al. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as predictive factors for mortality and length of hospital stay after cardiac surgery. *J Pers Med.* 2023;13(3):473. [CrossRef]
20. Lee JS, Kim NY, Na SH, Youn YH, Shin CS. Reference values of neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, platelet-lymphocyte ratio, and mean platelet volume in healthy adults in South Korea. *Medicine (Baltimore).* 2018;97(26):e11138. [CrossRef]
21. Ishizuka M, Shimizu T, Kubota K. Neutrophil-to-lymphocyte ratio has a close association with gangrenous appendicitis in patients undergoing appendectom. *Int Surg.* 2013;97(4):299-304. [CrossRef]
22. Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate postoperative inflammatory reactivity? A systematic review and meta-analysis. *Anesth Analg.* 2012;115(4):934-943. [CrossRef]
23. Mertoglu C, Gunay M. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as useful predictive markers of prediabetes and diabetes mellitus. *Diabetes Metab Syndr.* 2017;11 Suppl 1:S127-S131. [CrossRef]
24. Yildirim OT, Aydin F, Aydin AH, Dagtekin E, Aksit E, Hasirci SH. The neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are independent predictors of blood pressure variability. *J Hypertens.* 2018;36:e12. [CrossRef]
25. Beyhan Sagmen S, Kıral N. Evaluation of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in asthma control. *Rev Fr Allergol.* 2020;60(1):20-23. [CrossRef]
26. Gumus F, Solak I, Eryilmaz MA. The effects of smoking on neutrophil/lymphocyte, platelet/ /lymphocyte ratios. *Bratisl Lek Listy.* 2018;119(2):116-119. [CrossRef]
27. Ní Eochagáin A, Burns D, Riedel B, Sessler DI, Buggy DJ. Effect of anesthesia technique during primary breast cancer surgery on neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and return to intended oncological therapy. *Anesthesia.* 2018;73(5):603-611. [CrossRef]
28. Domagalska M, Ciftsi B, Janusz P, et al. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) following erector spinae plane block (ESPB) in posterior lumbar decompression: a randomized, controlled trial. *Eur Spine J.* 2023;32(12):4192-4199. [CrossRef]
29. Kissin I. Preemptive analgesia. *Anesthesiology.* 2000;93(4):1138-1143. [CrossRef]
30. Wantz GE. Testicular atrophy and chronic residual neuralgia as risks of inguinal hernioplasty. *Surg Clin North Am.* 1993;73(3):571-581. [CrossRef]

DOI: 10.4274/TJAR.2024.241720

Original Article
Airway Management

Turkish Journal of Anaesthesiology & Reanimation

Turk J Anaesthesiol Reanim 2024;52(6):240-246

Focus on POCUS: Identification of Early Successful Intubation by Point-of-Care Ultrasound Versus End-Tidal Carbon Dioxide: A Prospective Comparative Study

Soma Ganesh Raja Neethirajan, Ganeshamoorthy Baskar, Aruna Parameswari

Sri Ramachandra Institute of Higher Education and Research, Department of Anaesthesiology and Pain Medicine, Chennai, Tamilnadu, India

Cite this article as: Neethirajan SGR, Baskar G, Parameswari A. Focus on POCUS: Identification of Early Successful Intubation by Point-of-Care Ultrasound Versus End-Tidal Carbon Dioxide: A Prospective Comparative Study. *Turk J Anaesthesiol Reanim.* 2024;52(6):240-246.

Abstract

Objective: Successful endotracheal intubation is a key step in advanced airway management. The gold standard confirmation for successful endotracheal intubation is end-tidal carbon dioxide ($etCO_2$) monitoring, although recent studies suggest that ultrasound can also be used. In this study, we explored the time-sensitive early recognition of successful endotracheal intubation by comparing ultrasound and $etCO_2$ monitoring.

Methods: The study included 104 patients who were posted for elective surgery under general anaesthesia requiring endotracheal intubation. The time from removal of the face mask to ultrasound visualization of flutter in the trachea was compared with that of the appearance of six consecutive capnography waveforms following endotracheal intubation.

Results: Ultrasound was a faster tool for recognizing successful endotracheal intubation [(21.63±7.38) seconds] compared with capnography [(40.62±7.93) seconds].

Conclusion: eCO_2 requires more time for 6 continuous waveforms to confirm successful intubation and has a false positive rate. Supplementing the gold standard $etCO_2$ with ultrasound is faster and reliable in patients with low pulmonary blood flow without needing positive pressure ventilation, such as during cardiopulmonary resuscitation, in high-risk emergency intubations, such as in trauma, or in difficult airways where intubation can be confirmed in real time. Ultrasound is a reliable and faster tool for the early identification of successful endotracheal intubation than end-tidal carbon dioxide.

Keywords: Airway management, end-tidal carbon-di-oxide, endotracheal intubation, intubation, POCUS

Main Points

- End-tidal carbon dioxide (etCO2) requires more time for 6 continuous waveforms to confirm successful intubation and has a false positive rate.
- Supplementing $etCO_2$ with ultrasound is faster and more reliable, especially in patients with low pulmonary blood flow who do not need positive pressure ventilation, such as during cardiopulmonary resuscitation, in high-risk emergency intubation, such as in trauma, or in difficult airway situations where intubation can be confirmed in real time.
- Ultrasound is a reliable, rapid, and valuable tool for the early identification of successful endotracheal intubation.

Introduction

The key step in advanced airway management is endotracheal intubation, which is performed to maintain ventilation and to deliver anaesthetic gases under general anaesthesia. Unintentional esophageal intubation (which is around 2.7 to 25%[1,2]) dislodgement, and misplacement of the tube are potential catastrophic complications

Corresponding author: Soma Ganesh Raja Neethirajan, e-mail: drsoms@gmail.com

Received: September 12, 2024 Accepted: December 03, 2024

during intubation that result in rapid clinical deterioration of the patient causing hypoxemia, hemodynamic instability, and death.[3]

The confirmation of successful endotracheal intubation is usually performed by direct visualization of the tube entering the glottic opening, chest auscultation, bilateral chest movement, fogging of the endotracheal tube (ETT), capnography waveform, and radiological means (such as ultrasound and X-ray). End tidal carbon dioxide ($etCO_2$) is the gold standard for identifying successful endotracheal intubation with 100% sensitivity and 100% specificity.[4,5] Recent studies suggest that ultrasound can be used to confirm endotracheal intubation and has equal validity as $etCO_2$ for confirming successful endotracheal intubation.[6-9]

In this prospective observational study, we compared ultrasound and end-tidal carbon dioxide for the early recognition of successful endotracheal intubation.

Methods

After Sri Ramachandra Institute of Higher Education and Research, Institutional Research Ethics Committee approval (approval no.: EC/NEW/INST/2023/TN/0320, date: March 12, 2024), a prospective, single center, observational study was conducted at our tertiary care hospital. The study included 104 patients aged 18-75 years who underwent general anaesthesia requiring endotracheal intubation. Patients with expected difficult laryngoscopy, indication for awake fiber-optic intubation, parturient, and refusal to participate in the study were excluded from the study.

After written informed consent, the patient was wheeled inside the operating room, and baseline monitors were connected and pre-oxygenated for 5 min with 100% oxygen. The patient was intravenously administered fentanyl (2 µg kg^{-1} and propofol 2 mg kg^{-1} intravenously, and paralyzed with vecuronium (0.1 mg kg^{-1}). An ultrasound probe (HFL38, 13-6 MHz Linear transducer, Edge II, Fujifilm Sonosite Inc, Bothell, USA) was placed over the anterolateral aspect of the neck on the left side, at the level just below the cricoid cartilage, to visualize both the trachea and esophagus in the same field (Figure 1). The ultrasound was performed by a senior anaesthesiologist having expertise in airway ultrasound and doing it for more than 10 years. After 3 min. of mask ventilation, laryngoscopy and endotracheal intubation were performed. The timer was switched on, and the time from the removal of the face mask to the recognition of ETT in ultrasound entering trachea was noted. Similarly, the time from removal of the face mask to six square wave capnography was noted. Successful endotracheal intubation is identified by the bullet sign on ultrasound and the flutter created by the ETT inside the trachea, obliterating the reverberation artifact created by the tracheal cartilage (Figure 2). Esophageal intubation is identified by the ETT entering the esophagus, visualized in ultrasound as a double bubble sign with ETT inside esophagus by the side of trachea (Figure 3).

Statistical Analysis

Sample size was calculated by taking the standard deviation (SD) of the time taken by ultrasonography to determine endotracheal intubation as 15.14 s according to the study by Chowdhury et al.[9]. The margin of error was estimated to be less than 3 s for the time taken by ultrasonography to determine endotracheal intubation. The other parameter considered for sample size calculation was 5% two-sided alpha error. The following formula was used to calculate the sample size:

$$\text{Sample size (N)} = ((Z_{\alpha/2})^2 \times SD^2) \div d^2$$

Where,

• SD = Standard deviation of the previous study.

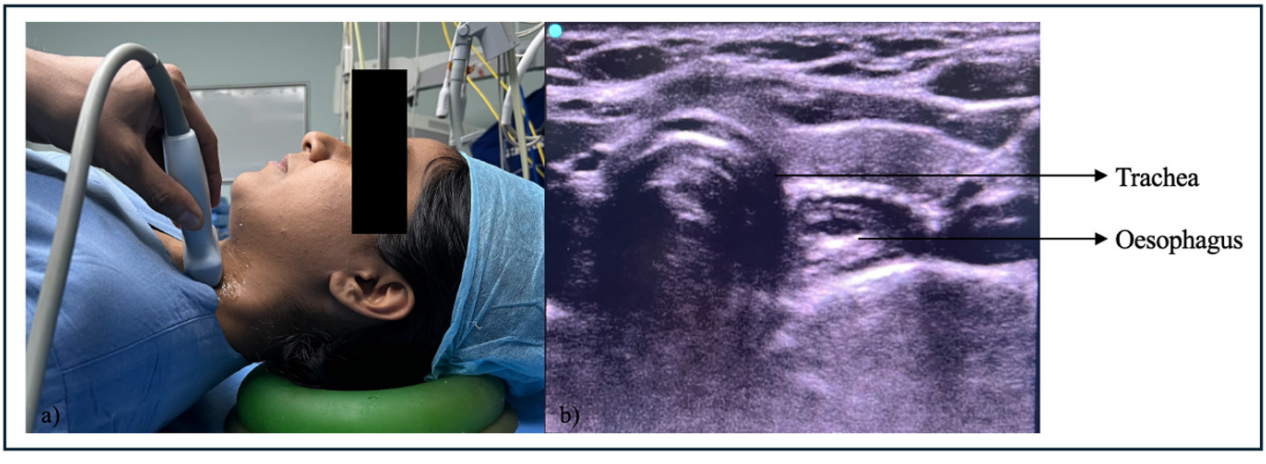

Figure 1. a) Scanning technique to visualize the trachea and esophagus. b) ultrasound image showing the trachea and esophagus in the same field

• $Z_{\alpha/2} = Z_{0.05/2} = 1.96$ (From Z table) at 5% alpha error.

• d = Estimated margin of error; and

Sample size (N) = $((1.96)^2 \times 15.14^2) \div 3^2 = 880.57 \div 9 = 97.84 \sim 98$

According to the above calculation, the required sample size is 98.

When adding 10% non-response rate:

N* = N ÷ (1-0.1) = 98 ÷ 0.9 = 103.2 ~ 103/104.

Hence, the required sample size was 104.

Pescriptive analysis was performed at frequency and proportion for categorical variables. Continuous variables are presented as mean ± SD. Spearman's rho correlation coefficient was used to check the relationship between two continuous variables. The intraclass correlation coefficient was used to check the agreement between the two methods. $P < 0.05$ was considered statistically significant. RStudio Desktop Version 2023.03.0+386 was used for statistical analysis. (Reference: RStudio Team (2023). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/).

Results

A total of 104 patients were included in the study. The demographic data of all study participants (sex, age, height, weight, and body mass index) are presented in Tables 1 and 2.

The time taken by ultrasound for confirmation of endotracheal intubation was found to be 21.63±7.38

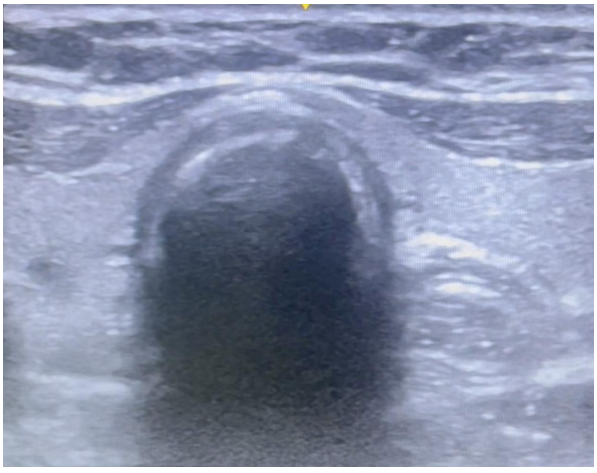

Figure 2. Ultrasound image of endotracheal intubation-bullet sign

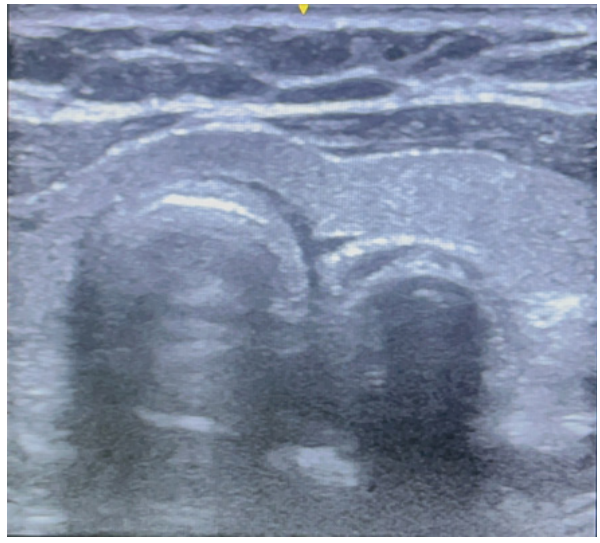

Figure 3. Ultrasound image of esophageal intubation showing the double bubble sign

Table 1. Descriptive Analysis of Gender in the Study Population (n = 104)

Gender	Frequency	Percentages
Male	59	56.73%
Female	45	43.27%

Table 2. Descriptive Analysis of Demographic Variables in the Study Population (n = 104)

Parameter	Mean ± SD	Median	Minimum	Maximum	95% CI	
					Lower	Upper
Age (years)	43.36±14.88	43.5	18	75	40.46	46.25
Weight (kg)	71.33±13.95	71	48	107	68.61	74.04
Height (cm)	163.22±9.6	162	143	190	161.35	165.09
BMI (kg/m^2)	26.79±4.82	26.5	16.9	38.83	25.85	27.73

SD, standard deviation; BMI, body mass index; CI, confidence interval

seconds, and the time taken for 6 waveform capnography was 40.62±7.93 seconds. The mean difference in recognition of successful endotracheal intubation between ultrasound and end-tidal carbon dioxide was 18.98±4.28 seconds, with ultrasound being early in recognition of successful endotracheal intubation ($P < 0.001$) (Table 3).

The correlation between the time taken for ultrasound and the end-tidal carbon dioxide was studied using Spearman's correlation coefficient. There was a strong positive correlation between Time taken for POCUS and $etCO_2$ ($P < 0.001$). Therefore, POCUS detected endotracheal intubation much earlier than end-tidal carbon dioxide in most of the study population (Table 4).

Discussion

The present study compared two methods, ultrasonography and $etCO_2$ in early recognition of successful endotracheal intubation in 104 patients who were posted for elective surgery under general anaesthesia requiring endotracheal intubation. In our study, the mean time taken by ultrasound

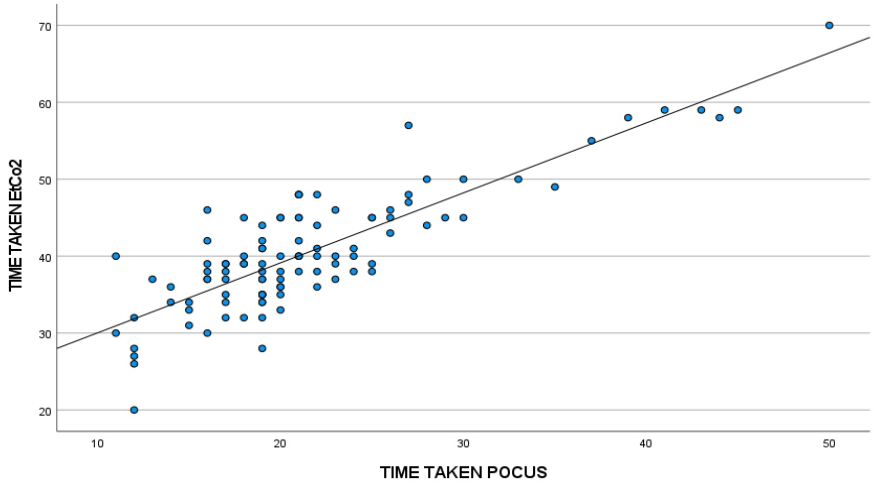

Figure 4. Scatter plot comparing time taken for POCUS vs. $etCO_2$

$etCO_2$, end-tidal carbon dioxide

Table 3. Comparison of Time Courses Between POCUS and $EtCO_2$ (n = 104)

Variable	Mean ± SD	Mean difference	Median	Minimum	Maximum	95% CI		95% confidence interval (CI) for mean difference	*P* value
						Lower	Upper		
Time taken by the POCUS (in seconds)	21.63±7.38	18.98±4.28	20	11	50	20.20	23.07	18.15-19.81	<0.001
Time taken by $etCO_2$ (in seconds)	40.62±7.93		39	20	70	39.07	42.16		

$etCO_2$, end-tidal carbon dioxide; SD, standard deviation; CI, confidence interval

Table 4. Correlation Between Time Taken for POCUS vs. $etCO_2$

Correlation between	Spearman's rho correlation (95% CI)	*P* value
Time taken to calculate POCUS vs. $etCO_2$	0.738 (0.632 to 0.816)	<0.001

$etCO_2$, end-tidal carbon dioxide; CI, confidence interval

was 21.63±7.38 seconds and time taken for getting 6 waveform capnography was 40.62±7.93 seconds to confirm endotracheal intubation. Ultrasound recognized endotracheal intubation quicker than capnography with a mean difference of 18.98±4.28 seconds ($P < 0.001$).

Endotracheal intubation and its placement inside the trachea are time-sensitive procedures. The most serious complication during ETT placement is unintentional esophageal intubation, the incidence of which ranges from 2.7% to 25%.[2,3] Several methods have been employed to confirm the ETT position like visual confirmation of tube entering the glottis, chest auscultation, chest wall movement, fogging inside the tube, capnography by $etCO_2$, esophageal detector devices, and radiologically by ultrasound and X-ray. Visualization of tube, fogging and chest auscultation are subjective and should be supplemented with a gold standard and rapid method to identify the correct placement of ETT.

Most of the above-mentioned methods have several limitations, like chest auscultation was normal in 48% of unintended esophageal intubation as described by Caplan et al.[10] which is due to the transmission of esophageal and gastric sounds to the chest wall due to its close anatomical proximity, having high false positivity rate. Visualization of the tube entering the glottic opening is operator dependent and can be difficult in cases of difficult laryngoscopy wherein the glottic view is limited or it can be difficult due to the presence of secretions or blood in larynx.[11] Fogging or condensation inside the ETT is also a not reliable predictor for successful endotracheal intubation as 83% of esophageal intubation in animal studies showed condensation inside the tube.[12]

Due to these limiting factors and low reliability, secondary adjuvant methods should be used for the proper identification of successful endotracheal intubation. Capnography by measuring $etCO_2$ from expired CO_2 remains the gold standard and is considered the most reliable indicator to confirm proper ETT placement and has been included as Class 1 recommendation by the American Heart Association since 2010.[13-16]

Asai and Shingu[17] in their observation reported a normal capnography waveform initially despite the ETT being in the esophagus. This can be explained by the pooling of expired carbon dioxide in pharynx.[17] Similarly, in cases of cardiac arrest where pulmonary blood flow is reduced, even during administration of high-quality cardiopulmonary resuscitation, the capnographic waveform has high false-positive rates due to several limitations like false positive waveform when the ETT lies at the hypopharynx, accidentally during cardiac arrest. One of the major disadvantages of etCO2 is the need for positive pressure ventilation for confirmation, which can be detrimental when ETT "is" in the esophagus, causing gastric distension, aspiration or even rupture of the esophagus. In addition, during mask ventilation, the exhaled alveolar gas containing carbon dioxide enters the stomach and causes a false-positive capnography waveform during esophageal intubation. On subsequent breaths during esophageal intubation, carbon dioxide levels decrease, resulting in a decrease in $etCO_2$. Hence, capnography requires at least 6 continuous waveform for confirmation of endotracheal intubations.[18,19]

$etCO_2$ is the gold standard for intubation detection, and it will continue to do so. There is a time lag for the detection of esophageal intubation by $etCO_2$. In fact, the presence of the first few waveforms of $etCO_2$ during esophageal intubation misguides the anaesthesiologist toward endotracheal intubation. In patients with difficult airway or low perfusion states, such as shock due to polytrauma or major obstetric hemorrhage, if the esophageal intubation is misconstrued as endotracheal intubation, the first and best intubation attempts as well as the precious time to secure the airway are lost. Moreover, in emergency situations like during cardio-pulmonary resuscitation, attempts at securing the airway can be chaotic, stressful, and time-consuming. In addition, poor circulation during cardiac arrest can cause delayed response in end-tidal carbon dioxide levels on the monitor. Moreover, the amplitude of the $etCO_2$ waveform will be reduced, and the time for it to appear will be delayed. Our argument is that the use of point-of-care-ultrasound during such situations to confirm endotracheal intubation will be more reliable, specific, and faster.

Ultrasound has several advantages over $etCO_2$ being faster and more reliable, even in conditions with low pulmonary blood flow. In addition, ultrasound does not require positive pressure ventilation.[19] Our study showed that ultrasound is a faster tool for the early recognition of successful ETT placement. The pitfalls of using ultrasound include availability of ultrasound, training of personnel, and booting time. The availability of ultrasound in every operating theater complex has become easier with the advent of POCUS. Training for airway assessment requires expertise, whereas identification of the trachea and esophagus is easier even by novice trainees. It takes less than 10 minutes to train novice trainees to identify the trachea and esophagus. The booting time of the ultrasound that we used was less than 25 seconds, unlike capnography, which can take minutes negating the time constraints associated with the use of ultrasound.

Our study involved placing a linear ultrasound probe on the anterolateral part of the neck below the level of the cricoid, and the trachea was visualized in the midline as an inverted U-shaped structure. It is characterized by a hyperechoic air-mucosal interface with a reverberation artifact that is visible posteriorly. The peristaltic movements that the patient experiences after swallowing indicate the presence of the

esophagus, which is located easily deep within the trachea on its left side. The ETT appears as a hyperechoic brilliant structure when it traverses through the trachea, which aids in its vision by causing a transient flutter and acoustic shadowing or comet-tail effects.[7,20] In case of accidental esophageal intubation, the ETT entering the esophagus shows double bubble sign.[21]

According to a study conducted by Abhishek et al.[8], both $etCO_2$ and ultrasound can be used for confirmation of ETT placement, and in their study $etCO_2$ was quicker than ultrasound. Their results were different from our study because we used six continuous waveforms in capnography for confirmation of endotracheal intubation.

Chowdhury et al.[9], in their study compared various parameters in confirmation of ETT placement on intubations done by novice anaesthesia practitioners and concluded that ultrasound was a faster tool among ultrasound and chest auscultation. This was in accordance with our study, and these results can be extrapolated to general practice.

In our study, ultrasound detected misdirected ETT entering the esophagus in two patients (who were eliminated from statistical analysis), which was corrected immediately without requiring another laryngoscopy, which is another added advantage of using ultrasound for confirmation of endotracheal intubation. This real-time ultrasound guidance for endotracheal intubation is of immense value, especially in difficult airway situations.

We conducted this study to identify early successful endotracheal intubation. Our study did not statistically address the early identification of esophageal intubation, although it is possible in a study with a large sample size. We believe that $etCO_2$ is the gold standard for confirming endotracheal intubation, and ultrasound should be used as an adjunct for identifying endotracheal intubation much earlier.

Conclusion

Ultrasound can be used as a reliable and faster tool for confirming successful endotracheal intubation than capnography using $etCO_2$. Ultrasound can be a more useful supplement to $etCO_2$, especially in high-stake environments, such as during anticipated or unanticipated difficult airway, emergency intubations during cardiopulmonary resuscitation, and poly trauma where pulmonary blood flow is reduced leading to poor $etCO_2$ waveforms.

Ethics

Ethics Committee Approval: The study was obtained from Sri Ramachandra Institute of Higher Education and Research, Institutional Research Ethics Committee approval (approval no.: EC/NEW/INST/2023/TN/0320, date: March 12, 2024).

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Author Contributions: Surgical and Medical Practices - S.G.R.N.; Concept - S.G.R.N., G.B., A.P.; Design - S.G.R.N., A.P.; Data Collection and/or Processing - S.G.R.N., G.B.; Analysis and/or/Interpretation - S.G.R.N., G.B.; Literature Review - S.G.R.N., G.B.; Writing - S.G.R.N., G.B., A.P.

Declaration of Interests: The authors declare no conflicts of interest.

Funding: No funding was received for conducting this study.

References

1. Cobas MA, De la Peña MA, Manning R, Candiotti K, Varon AJ. Prehospital intubations and mortality: a level 1 trauma center perspective. *Anesth Analg*. 2009;109(2):489-493. [CrossRef]
2. Phelan MP, Glauser J, Yuen HW, Sturges-Smith E, Schrump SE. Airway registry: a performance improvement surveillance project of emergency department airway management. *Am J Med Qual*. 2010;25(5):346-350. [CrossRef]
3. Hagberg C, Georgi R, Krier C. Complications of managing the airway. *Best Pract Res Clin Anaesthesiol*. 2005;19(4):641-659. [CrossRef]
4. Grmec S. Comparison of three different methods to confirm tracheal tube placement in emergency intubation. *Intensive Care Med*. 2002;28(6):701-704. [CrossRef]
5. Bozeman WP, Hexter D, Liang HK, Kelen GD. Esophageal detector device versus detection of end-tidal carbon dioxide level in emergency intubation. *Ann Emerg Med*. 1996;27(5):595-599. [CrossRef]
6. Sustić A. Role of ultrasound in the airway management of critically ill patients. *Crit Care Med*. 2007;35(5 Suppl):173-177. [CrossRef]
7. Kundra P, Mishra S, Ramesh A. Ultrasound of the airway. *Indian J Anaesth*. 2011;55(5):456-462. [CrossRef]
8. Abhishek C, Munta K, Rao SM, Chandrasekhar CN. End-tidal capnography and upper airway ultrasonography in the rapid confirmation of endotracheal tube placement in patients requiring intubation for general anaesthesia. *Indian J Anaesth*. 2017;61(6):486-489. [CrossRef]
9. Chowdhury AR, Punj J, Pandey R, Darlong V, Sinha R, Bhoi D. Ultrasound is a reliable and faster tool for confirmation of endotracheal intubation compared to chest auscultation and capnography when performed by novice anaesthesia residents - A prospective controlled clinical trial. *Saudi J Anaesth*. 2020;14(1):15-21. [CrossRef]
10. Caplan RA, Posner KL, Ward RJ, Cheney FW. Adverse respiratory events in anesthesia: a closed claims analysis. *Anesthesiology*. 1990;72(5):828-833. [CrossRef]
11. Birmingham PK, Cheney FW, Ward RJ. Esophageal intubation: a review of detection techniques. *Anesth Analg*. 1986;65(8):886-891. [CrossRef]
12. Kelly JJ, Eynon CA, Kaplan JL, de Garavilla L, Dalsey WC. Use of tube condensation as an indicator of endotracheal tube placement. *Ann Emerg Med*. 1998;31(5):575-578. [CrossRef]
13. Morrison LJ, Deakin CD, Morley PT, et al. Part 8: Advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2010;122(16 Suppl 2):345-421. [CrossRef]
14. Deakin CD, Morrison LJ, Morley PT, et al. Part 8: Advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Resuscitation*. 2010;81(Suppl 1):93-174. [CrossRef]

15. Field JM, Hazinski MF, Sayre MR, et al. Part 1: executive summary: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010;122(18 Suppl 3):640-656. [CrossRef]
16. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010;122(18 Suppl 3):729-767. Erratum in: *Circulation*. 2011;123(6):e236. Erratum in: *Circulation*. 2013;128(25):e480. [CrossRef]
17. Asai T, Shingu K. Case report: A normal capnograph despite esophageal intubation. *Can J Anaesth*. 2001;48(10):1025-1028. [CrossRef]
18. Linko K, Paloheimo M, Tammisto T. Capnography for detection of accidental esophageal intubation. *Acta Anaesthesiol Scand.* 1983;27(3):199-202. [CrossRef]
19. Pandit JJ. 'No trace, wrong place' does not mean 'positive trace, right place'. Identifying and managing misplaced or displaced tracheal tubes in cardiopulmonary resuscitation. *Anesthesia*. 2022;77(1):16-21. [CrossRef]
20. Singh M, Chin KJ, Chan VW, Wong DT, Prasad GA, Yu E. Use of sonography for airway assessment: an observational study. *J Ultrasound Med.* 2010;29(1):79-85. [CrossRef]
21. Tsung JW, Fenster D, Kessler DO, Novik J. Dynamic anatomic relationship of the esophagus and trachea on sonography: implications for endotracheal tube confirmation in children. *J Ultrasound Med.* 2012;31(9):1365-1370. [CrossRef]

2024 Referee Index

Adnan Bayram
Ahmet Kemalettin Koltka
Ali Ahıskalıoğlu
Ali Aydın Altunkan
Alparslan Apan
Alparslan Kuş
Alper Tunga Doğan
Asiye Uğraş Dikmen
Aslı Z. Demir
Ayça Sultan Şahin
Ayça Taş Tuna
Aynur Camkıran Fırat
Ayşe Çiğdem Tütüncü
Ayşe Hande Arpacı
Aysu Salvız
Bahadır Çiftçi
Bahar Kuvaki
Başak Altıparmak
Berna Kaya Uğur
Berrin Işık
Burhan Dost
Can Aksu
Canan Balcı
Çağla Bali
Damla Yürük
Deniz Karakaya
Didem Tuba Akçalı
Dilek Erdoğan Arı
Ebru Biricik
Elif Akpek
Elvan Öçmen
Emre Erbabacan
Ender Gedik
Eren Fatma Akçıl
Esra Çalışkan
Faisal Shamim
Fatma Ezgi Can
Fatma Nur Kaya
Ferruh Ayoğlu
Filiz Alkaya Solmaz
Filiz Üzümcügil
G. Ulufer Sivrikaya
Gaye Aydın
Gönül Ölmez Kavak
Gözde İnan
Gözen Öksüz
Gülay Ok
Güldem Turan
Hakkı Ünlügenç
Hale Aksu Erdost
Halil Çetingök
Hande Gürbüz
Hasan Kutluk Pampal
Hija Yazıcıoğlu
Işıl Özkoçak Turan
İlke Dolğun
İsmail Demirel
Jean Jacques Lehot
Jülide Ergil Hallıoğlu
Kerem Erkalp
Kübra Evren Şahin
Malika Hameed
Marta Dias da Silva Mendanha Vaz
Mehmet Emin İnce
Mehmet Turan İnal
Menekşe Özçelik
Menşure Kaya
Meral Kanbak
Mete Manici
Murat Aksun
Murat Haliloğlu
Murat Şahin
Murat Sayın
Nedim Çekmen
Nermin Kelebek Girgin
Nesrin Bozdoğan Özyılkan
Nihan Yapıcı
Nurçin Gülhaş
Nüzhet Mert Şentürk
Onat Bermede
Onur Balaban
Ömer Kurtipek
Özge Köner
Özgür Canbay
Özlem Sağır
Özlem Selvi Can
Perihan Uçar
Pınar Ergenoğlu
Pınar Kendigelen
Pınar Zeyneloğlu
Pratika Bhokare
Recep Aksu
Reyhan Arslantaş
Selcan Akesen
Serkan Tulgar
Sibel Barış
Sinem Sarı
Suna Akın Takmaz
Süheyla Ünver
Şebnem Rumeli
Şule Özbilgin
Şükran Geze Saatçi
Tülün Öztürk
Ünase Büyükkoçak
Yavuz Akçaboy
Yavuz Gürkan
Zehra İpek Arslan
Zekeriyya Alanoğlu
Züleyha Kazak Bengisun