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Evolution from Decompressive Craniectomy to Early Minimally Invasive Surgical Approach for Refractory Increased Intracranial Pressure Treatment: Merit or Social Problems?

Rudin Domi[1], Filadelfo Coniglione[2], Gentian Huti[1], Mario Dauri[2], Asead Abdyli[1], Krenar Lilaj[1], Federico Bilotta[3]

[1]University of Medicine, Tirana (UMT), Department Anaesthesiology and Intensive Care, Tirana, Albania
[2]University of Rome Tor Vergata, Department of Anaesthesia and Intensive Care Medicine, Rome, Italy
[3]Sapienza University of Rome, Department of Anaesthesiology and Intensive Care, Rome, Italy

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Abstract

In conclusion, treating increased intracranial pressure is a significant challenge for physicians in intensive care units and emergency departments. If not managed properly, elevated intracranial pressure can lead to brain edema, reduced oxygenation, and, ultimately, death. Intracranial hypertension can be caused by various conditions, including traumatic brain injury, massive intracranial bleeding, and large ischemic stroke, such as middle cerebral artery thrombosis. Treatment consists of both pharmacological and surgical. Surgical treatments include early surgical evacuation and decompressive craniectomy (DC). DC is a critical intervention for managing refractory intracranial hypertension when all conventional therapies fail. It is a decisive step that is intended to save lives and minimize long-term neurological deficits. The procedure must be carefully planned and executed based on the patient's specific clinical scenario and needs. The decision to proceed with DC should be based on a comprehensive assessment of the patient's condition, the effectiveness of other treatments, and the potential benefits and risks of the procedure. If all conventional pharmacological and non-pharmacological therapies fail and intracranial hypertension persists, regardless of the underlying cause, DC is indicated and can be considered a critical intervention. Currently, surgical treatment has gained popularity, and many papers have been published. This review summarizes the tendencies in the literature.

Keywords: Decompressive craniectomy, intensive care unit, intracranial pressure, ischemic stroke, traumatic brain injury

Main Points

- Surgical treatment can effectively reduce refractory malignant intracranial pressure.
- The functional outcome of decompressive craniectomy remains uncertain although it appears to be generally poor.
- The prognosis for patients is influenced by the cause and severity of increased intracranial pressure.

Introduction

Decompressive craniectomy (DC) is usually performed when standard medical therapy fails to maintain intracranial pressure (ICP) below 20 mmHg. The procedure helps reduce the increased ICP, thus increasing cerebral blood flow and cerebral oxygenation. Although skull decompression has been reported both before and after the medieval period, the first documented decompressive surgery in modern times was performed by Marcotte.[1] Kocher[2] was

Corresponding author: Rudin Domi, e-mail: rdomi73@yahoo.it

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the first to report the use of DC after traumatic brain injury (TBI). After Kocher,[2] Cushing[3] expanded the indications for DC. He reported performing the procedure to address increased ICP resulting from brain tumors and penetrating brain injuries. Cushing's[4] work significantly influenced the broader acceptance and utilization of DC in neurosurgery. In the mid-1970s, there were significant reports and published papers by various authors detailing the use and outcomes of DC. These publications highlighted serious cases in which DC was employed, contributing to the growing body of evidence supporting the procedure's effectiveness in managing increased ICP due to various causes, such as TBIs and other conditions.[5,6] Nowadays, DC is a standardized procedure for managing severe, refractory increased ICP. Numerous studies and published papers support the efficacy of DC in improving outcomes in patients with conditions such as TBI, stroke, and other causes of elevated ICP. These studies have provided robust evidence demonstrating that DC can significantly reduce mortality and improve functional outcomes in appropriately selected patients.[7,8] DC is typically reserved for cases in which third-tier therapies are unsuccessful. By reducing ICP, DC can significantly decrease mortality. Several situations justify the use of DC, including TBI, subdural hematoma, and cerebrovascular diseases, such as: hemispheric ischemia and hemorrhage-induced intracranial hypertension. These conditions can lead to critically elevated ICP, where standard medical treatments fail to provide adequate relief. In such scenarios, DC becomes a crucial intervention to mitigate the risk of severe brain damage and improve patient outcomes.[9,10]

TBI is a significant public health concern and a major cause of increased ICP, contributing to global mortality rates. TBI can be caused by either blunt or penetrating trauma to the head. It is associated with a wide range of physiological and organic brain damage, leading to various degrees of brain malfunction.

The physiological consequences of TBI include disrupted blood flow, swelling, and increased ICP, which can further damage brain tissue and impair its function. Organic damage can involve bleeding (hematomas), bruising, and neuronal death. The combination of these factors can lead to a wide range of symptoms, from mild cognitive impairment to severe disability or even death.

Effective management of TBI involves prompt medical assessment, imaging studies like computed tomography or magnetic resonance imaging scans, and interventions to stabilize the patient and minimize secondary brain injury. Treatment strategies may include surgical procedures to relieve pressure, medications to control symptoms, and rehabilitation to support recovery and improve long-term outcomes.[11] Increased ICP and cerebral edema are the main complications of TBI. Due to these phenomena, further cerebral ischemia and brain herniation can occur, making DC an alternative to conventional medical therapy in patients with intracranial hypertension.

Pathophysiology of Increased ICP and Its Treatment

The Monro-Kellie doctrine explains the dynamics of the three main components within the cranial vault: brain tissue, cerebral blood flow, and cerebrospinal fluid (CSF). According to this doctrine, the cranial compartment is incompressible, and the volume inside the cranium is fixed. Therefore, an increase in the volume of any one of the intracranial constituents must be compensated by a decrease in the volume of another; otherwise, ICP will increase. Brain tissues comprise most of the intracranial content. If there is an increase in brain tissue volume, such as from swelling or a mass lesion, compensatory mechanisms should be initiated. Cerebral blood flow and volume can change rapidly to compensate for ICP changes. For example, vasoconstriction or vasodilation of cerebral blood vessels can occur in ICP management. CSF can be displaced into the spinal canal, its production can be decreased, and absorption can be increased to balance the ICP. When one of these elements increases, the body attempts to maintain a normal ICP by decreasing the volume of one or both components. However, these compensatory mechanisms are limited. If compensatory mechanisms are overwhelmed, ICP can increase, causing severe neurological damage or death if not managed promptly.[12] Therefore, if brain content is increased by tumors, edema, and bleeding, the other components (cerebral blood flow and CSF) tend to be diminished to maintain a normal ICP value. When compensatory mechanisms are exhausted, ICP can increase, leading to intracranial hypertension. The normal ICP value is typically 5-15 mmHg. Intracranial hypertension is defined as an ICP>22 mmHg sustained for at least 5 minutes. Initially, the body attempts to compensate for increased intracranial volume (e.g., from edema, mass lesions, or hemorrhage) by displacing CSF into the spinal canal and reducing cerebral blood volume. However, these mechanisms have limitations. As ICP continues to rise beyond compensatory limits, the brain attempts to maintain homeostasis by directing blood (particularly venous blood) and CSF out of the skull. Increased ICP can cause brain tissue to swell (edema) and shift from a normal midline position. This shift can further impair cerebral vascularization, particularly affecting blood flow to critical brain areas. As ICP rises, blood vessels are compressed, thereby reducing cerebral blood flow. This leads to decreased oxygen and nutrient delivery to brain tissue, causing cerebral ischemia. Reduced blood flow and oxygenation exacerbate brain tissue damage, leading to a vicious cycle in which ischemia causes more swelling (edema), which in turn raises ICP further. As cerebral tissue becomes increasingly deprived of oxygen, it swells, further increasing the ICP. This condition creates a feedback loop

of worsening edema and ICP. Ultimately, if not managed, this can lead to severe consequences, including brain tissue herniation, significant neurological impairment, and potentially death. Managing elevated ICP often involves medical interventions to reduce brain swelling, optimize cerebral blood flow, and sometimes surgical procedures to remove mass lesions or CSF to lower pressure. Prompt recognition and treatment of elevated ICP are crucial to prevent irreversible brain damage.[13] Finally, increased ICP diminishes cerebral oxygenation, forces brain to "escape" in anatomic holes i.e. brain herniation. The final stage is brain death.

Many publications have focused on increased ICP treatment, particularly after TBI and intracranial hemorrhage. After the exclusion of neurosurgical emergency, medical therapy is initiated to manage the increased ICP. Standard early treatment begins after a carefully neurological examination. Glasgow Coma Scale (GCS) score of 8 points indicates the patient intubated and sedated. The recommended head position is 30 grades upright and neutral to avoid any situations that can impair venous return. The patient needs to be fully sedated, and the use of muscle relaxants is crucial to avoid any increase in ICP during coughing and spontaneous forced respiration. Osmotic therapy using mannitol and hypertonic saline. It is of great importance to avoid hypotension and to maintain blood pressure above 110 mmHg. Hyperventilation is reserved only in cases of sudden increased ICP, maintaining a $PaCO_2$ around 30-35 and taking into consideration that aggressive CO_2 reduction can lead to vasoconstriction and further ischemia. The aggressive treatment of fever and seizures is crucial to prevent secondary brain damage. Barbituric coma is used in severe TBI with refractory uncontrollable increased ICP.[14] There are no reports of the efficacy of hypothermia in patients with TBI and intracranial hypertension.[15] The three-tier therapy model includes all therapeutics in three tiers depending on severity.[16,17] Tier Zero includes early evaluation and admission (neurological evaluation, intubation, ventilation, monitoring, and sedation); Tier One is focused on cerebral perfusion pressure (CPP) 60-70 mmHg, analgesia and sedation, osmolar therapy, and antiseizures treatment; Tier Two is composed by the combination of mild hypocapnia ($PaCO_2$ 30-35 mmHg), neuromuscular blocking, and mean arterial pressure adjusting according to adequate CPP; Tier Three includes barbituric coma, mild hypothermia (32-35 grades Celsius), and DC.[18] Robba et al.[19] published data from their study SYNAPSE-ICU. The aim of this study was to provide a full picture of the increased use of ICP treatment modalities and differences among countries and institutions. This study enrolled 2,320 patients with the following inclusion criteria: patients aged ≥18 years, traumatic injury/ICP/subarachnoid hemorrhage, GCS score 7 (E1, V1, M≤5), or new neurological deterioration in intensive care unit (ICU) within 48 hours after ICU admission. They found that therapies to control increased ICP are generally used, and aggressive treatment modalities seem to have a positive effect on 6-month mortality.

If all conventional pharmacological and non-pharmacological therapies fail and intracranial hypertension persists independently as the cause of increased ICP, DC is indicated and can be considered.[20]

Decompressive Craniectomy

Prior to performing DC, patients must exclude the non-efficacy of other treatments and the indication for this procedure. DC helps increase cerebral blood flow, reduce damage size, and reduce ICP. Surgical plan and extension depend on damage location, size of damage, bilateral or unilateral ICP value, and presence of external ventricular drainage. DC may be performed as hemi-craniectomy or bilateral craniectomy.[20,21] In hemispheric craniectomy, a larger frontoparietal skull fragment (up to 15 cm) is performed. Several early and late complications have been reported.[22] These complications include wound infections, meningitis, CSF leakage, external herniation, bleeding, postoperative seizures, subdural hygroma, and hydrocephalus.[22] The indications for DC include TBI, malignant hemispheric ischemia (middle cerebral artery thrombosis), intracranial hemorrhage, intracranial infection, massive brain tumors, and cerebral venous system thrombosis.[23] DC can control increased ICP, but the prognosis and their permanent disabilities are not known. Therefore, appropriate indication, careful patient selection, a detailed surgical plan, and detailed explanations for relatives are of great importance.

Early Surgical Treatment and DC in Different Clinical Scenarios

Hutchinson et al.[24] conducted Randomized Evaluation of Surgery with Craniectomy Evacuation for Acute Subdural Hematoma-*RESCUE-ASDH* trial. The study included patients with acute traumatic subdural hematoma scheduled for craniotomy or DC.[24] The patients were divided into 2 groups: 228 patients who underwent craniotomy and 222 patients who underwent DC. The authors measured as endo-points: outcome measured by Glasgow Outcome Scale-Extended (GOSE) at 12 months after surgery. They reported that the rates of serious disability and quality of life did not statistically significantly changes in compared groups.[24,25] DCs were primarily used for high-refractory ICP treatment after TBI. Several authors reported their data when DC regained popularity, emphasizing the crucial role of DC in controlling intracranial hypertension.[26,27] The randomized evaluation of surgery with craniectomy for uncontrollable elevation of intracranial pressure (RESCUEicp) and decompressive craniectomy in patients with severe traumatic brain injury (DECRA) trials remain the main trials for DC after TBI intracranial hypertension.

The RESCUEicp trial was published in 2016, and the study aimed to evaluate the efficacy of DC in controlling ICP.[28] The authors' endpoint was the 6-month evaluation of the GOSE (8 grades from "death" to "good recovery") at 6 months after. The multicenter study included 408 patients suffering from ICP>25 mmHg for 1-12 hours. Interesting conclusions came from the study, establishing DC as an effective method to control increased ICP, but a high percentage of vegetative state in survivals. DECRA trial conclusions were recently published, arriving in the same conclusions as RESCUEicp.[29,30] Kolias et al.[31] published an interesting paper in JAMA 2022, expanding the GOSE up to 24 months after treatment. They enrolled 408 patients (206 in the surgical group and 202 in the medical group). Interesting data emerged from the study, revealing that even extended RESCUEicp produced the same findings as RESCUEicp, but the surgical group showed more improvement over months compared with the medical group.[31]

Intracranial bleeding is a major cause of ICU admission. Different papers have been published, and several data have been reported in the literature. Mendelow et al.[32] published in Lancet their first study called surgical trial in intracerebral hemorrhage (STICH). They enrolled 1033 patients from 87 centers, and the endpoint was the GOSE at 6-month follow-up. Mendelow et al.[33] found no difference between early surgery and medical treatment between groups. The STICH II trial results were published in 2013.[33] The authors compared early surgery with medical treatment in patients with superficial lobar intracerebral bleeding without intraventricular hemorrhage. The results found no significance in rate deaths and slight clinical improvement in patients who underwent early surgical treatment. The minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation phase III (MISTIE III) study was a randomized and controlled trial.[34] The authors included 506 patients divided into the MISTIE and standard medical groups. The MISTIE III group concluded that reduction in the size of bleeding was associated with improved prognosis. Pradilla et al.,[35] in their published paper in the New England Journal of Medicine, reported data on early minimally invasive removal of intracerebral hemorrhage. This multicenter randomized trial enrolled 300 patients with basal ganglia bleeding and lobar hemorrhage. The 30-day mortality rates were 9.3% in the surgery group and 18.0% in the control group. The 180-day functional outcomes were significantly better in the group with early invasive evacuation of hematoma.

Conclusion

DC and other early surgical approaches decrease ICP and improve patients outcome. The long-term effects of functional outcomes are prone of controversies and not yet clear. The surgical approach must be strongly considered as an effective option to treat increased ICP, even when associated with unclear benefits for functional outcomes.

Footnotes

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Original Article
Geriatric Anaesthesia

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A Comparative Study on Minimal Flow Anaesthesia in Geriatric and Middle-aged Patients

Sinan Ünsal[1], Gülay Erdoğan Kayhan[2], Meryem Onay[2], Mehmet Sacit Güleç[2]

[1]University of Health Sciences Türkiye, Gaziantep City Hospital, Clinic of Anaesthesiology and Reanimation, Gaziantep, Türkiye
[2]Eskişehir Osmangazi University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Eskişehir, Türkiye

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Abstract

Objective: Minimal flow anaesthesia reduces costs and environmental pollution, and has a protective effect on the respiratory tract. This study aimed to compare the ease and tolerability of minimal flow anaesthesia in the geriatric and middle-aged patient populations.

Methods: In this prospective study, we enrolled 40 patients between 18 and 50 years (Group Y) and 40 patients 65 years or older (Group E), scheduled for abdominal surgery under general anaesthesia. Following a period of high flow with desflurane in O_2/air, the fresh gas flow was reduced to 350 mL min^{-1}. Desflurane concentration was adjusted to maintain a bispectral index between 40 and 50. The oxygen concentration in fresh gas flow was titrated by ±10%. Throughout the surgery, gas concentrations, oxygenation parameters, hemodynamic data, and the depth of anaesthesia were monitored. The number of alterations in fresh gas oxygen and desflurane concentrations was recorded.

Results: The depth of anaesthesia and oxygenation parameters were adequately sustained within safe limits among all patients, while the number of changes in the fresh gas flow oxygen levels was found to be significantly lower in geriatric patients. The increase in the number of oxygen level was 1.1±0.8 in Group E and 1.8±1.2 in Group Y (P=0.006). Total alteration in oxygen was 1.2±1 in Group E and 1.9±1.3 in Group Y (P=0.01). Oxygenation parameters consistently remained within clinically acceptable ranges in both groups, and the amount of change in desflurane concentration showed no intergroup difference.

Conclusion: Administering minimal flow anaesthesia at a rate of 350 mL min^{-1} in the geriatric population, compared to the younger population, can be performed requiring less manipulation, without inducing hypoxia or inadvertent awareness.

Keywords: Anaesthesia, geriatrics, intraoperative awareness, oxygen consumption, rebreathing

Main Points

- Minimal flow anaesthesia (MFA) reduces costs and environmental pollution and has a protective effect on the respiratory tract.
- The incorporation of MFA as an anaesthesia modality should be promoted.
- To the best of our knowledge, this is the first study of comparing the impacts of MFA across various age demographics.
- MFA can be performed without inducing hypoxia or inadvertent awareness in suitable elderly patients.

Introduction

The re-breathing of ≥50% of exhaled air within the semi-closed re-breathing circuits present in contemporary anaesthesia workstations is commonly denoted as low flow anaesthesia (LFA). According to the sub-classification of flow rates of gases into anaesthetic circuits proposed by Baker[1] and Simionescu, very high flow is defined as >4 L min^{-1}, high flow as 2-4 L min^{-1}, medium flow as 1-2 L min^{-1}, low flow as 0.5-1.0 L min^{-1}, minimal flow as 0.25-0.5 L min^{-1},

Corresponding author: Gülay Erdoğan Kayhan, e-mail: drgulayer@yahoo.com

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and metabolic flow as <0.25 L min^{-1}.[1] LFA offers several pivotal advantages, including cost reduction, decreased environmental pollution, respiratory tract protection, and the preservation of body temperature. Therefore, it is recommended to reduce the fresh gas flow (FGF) in the anaesthesia machines.[2]

The safe administration of LFA requires close monitoring by an anaesthesiologist and the use of technical equipment available in all modern anaesthesia machines. This enables monitoring of inspiratory and expiratory gas concentrations (oxygen, carbon dioxide, inhalation anaesthetics), as well as minute volume (MV) measurements. When necessary precautions are not taken, potential risks associated with LFA applications include hypoxia and inadequate depth of anaesthesia. Preventing hypoxia and ensuring an adequate level of anaesthesia necessitate the establishment of alarm thresholds aligned with predetermined targets. In instances where these thresholds are exceeded, adjustments to oxygen and inhalation anaesthetic levels become imperative. Such adjustments, accompanied by meticulous monitoring, play a pivotal role in maintaining patient safety during LFA administration.

Anaesthetic oxygen consumption during anaesthesia is estimated using the Brody formula [10 x bodyweight $kg^{3/4}$], with the outcome varying according to weight. However, it is suggested that due to decreased muscle mass and slowed metabolism in elderly patients, their oxygen requirement during surgery might be lower. A recent study conducted on geriatric patients undergoing major abdominal surgery suggested that their oxygen requirement decreased to one-third.[3] Additionally, the minimum alveolar concentration (MAC) determining the requirement for inhalation anaesthetics decreases by 6% per decade, and it is well-known that MAC values are lower in elderly patients.[4]

We hypothesized that minimal flow anaesthesia (MFA) at 350 mL min^{-1} would be manageable and tolerated in older adult patients, given the presumed decreased requirement for oxygen and inhalation anaesthetics. To investigate this hypothesis, we compared young, middle-aged, and older adult patients undergoing elective open abdominal surgery under general anaesthesia with MFA. The primary comparison focused on the number of interventions in oxygen and inhalation anaesthetic levels, alongside evaluations of oxygenation parameters and depth of anaesthesia.

Methods

This prospective study was conducted following approval from the Eskişehir Osmangazi University, Clinical Trials Ethics Committee of Studies (approval no.: 21, dated: December 22, 2022), and informed consent from all patients was obtained. The study included patients undergoing elective open abdominal surgery lasting more than 2 hours under general anaesthesia, in the supine position, and classified as American Society of Anesthesiologists physical status I-III. A total of 80 patients, comprising 40 elderly patients aged 65 and above (Group E), and 40 younger patients aged between 18-50 (Group Y), were planned to be enrolled in the study. Patients were excluded from the study if they had severe cardiovascular and respiratory diseases, cerebrovascular diseases, uncontrolled diabetes, profound anaemia (hemoglobin <7 g dL^{-1}), a body mass index (BMI) of <20 or >35, were heavy smokers (>1 pack/day), had alcohol or drug addiction disorder, had expected increases in O_2 consumption (such as in sepsis or hyperthermia), or did not agree to participate in the study.

Patients admitted to the operating room without premedication underwent monitoring procedures, including electrocardiography, peripheral oxygen saturation (SpO_2), non-invasive blood pressure measurements, bispectral index (BIS) monitoring using Datex-Ohmeda equipment, and near-infrared spectroscopy (NIRS) (COVIDIEN Invos 5100C Somanetics, Massachusetts, USA) for regional cerebral oxygen saturation on the right (rSO_2-R) and left (rSO_2-L) hemispheres. Additionally, neuromuscular monitoring was conducted using the ulnar nerve and adductor pollicis muscle. Baseline values were recorded prior to induction.

The Dräger Perseus® A500 anaesthesia machine (Dräger Medical, Lubeck, Germany) was employed in this study. Prior to anaesthesia induction, the soda lime was replaced for all patients, and the anaesthesia apparatus and breathing circuit underwent an automated test. The anaesthesia machine's alarms were set as follows: a lower limit of 30% for inspiratory oxygen concentration (fiO_2), an upper limit of 5 mmHg for inspiratory carbon dioxide concentration ($fiCO_2$), 30-45 mmHg for end-tidal carbon dioxide pressure ($etCO_2$), 5-30 cmH_2O for peak pressure (P_{peak}), and an expiration gas volume lower limit set 500 mL below the desired MV. If $FiCO_2$ exceeded by 5 mmHg, the CO_2 absorber (Drägersorb) was to be replaced.

All patients were pre-oxygenated with 100% O_2 for 3 minutes. For induction of anaesthesia, 4-7 mg kg^{-1} thiopental, 1 µg kg^{-1} fentanyl, and 0.6 mg kg^{-1} rocuronium bromide were administered. After induction, radial artery cannulation was performed in all patients, followed by invasive artery monitoring. After achieving adequate muscle relaxation [train of four (TOF): 0], endotracheal intubation was performed. Ventilation was maintained with volume auto-flow (AF) mode with 30-45 mmHg $EtCO_2$ (tidal volume, 6-8 mL kg^{-1}; positive end expiratory pressure, 5 cmH_2O; and respiratory frequency 10-14 min). Anaesthesia maintenance started in both groups with a FGF of 4 L min^{-1}, consisting of a mixture of 50% oxygen and 50% air and 6-8% desflurane. When the BIS value reached a value between 40 and 50 (approximately 10 minutes later), the total gas flow was set

to 350 mL min^{-1}, with an oxygen concentration (fgO_2) of 70% and a desflurane concentration (fgDes) of 12% within the FGF. Throughout the maintenance of anaesthesia, the desflurane concentration was titrated, and reduced to maintain the BIS value within the range of 40 to 50. Concurrent with surgical incision, all patients received a remifentanil infusion (20 µg mL^{-1}) at a rate of 0.08-0.1 µg kg^{-1} min^{-1}.

Throughout the surgical procedure, it was planned to increase the fgO_2 by 10% (80%, 90%, 100%) under specific conditions: if the fiO_2 dropped below 30%, if SpO_2 decreased to <95%, or in the event of a 20% reduction in cerebral oximetry values (rSO_2-L or rSO_2-R) compared to baseline. If any of these parameters fell below the specified targets despite the fgO_2 being set at 100%, the anaesthesiologist planned to increase the FGF to 500 mL min^{-1}. If necessary, they intend to further increase fgO_2 by 10% until reaching the target values.

Throughout the operation, FGF rate, and gas components (fgO_2, fgDes), inspiratory and expiratory gas concentrations [desflurane (fiDes and etDes), O_2, and CO_2 values], rSO_2-L and rSO_2-R, hemodynamic data, TOF, and BIS levels were recorded. After induction, recordings were taken every 5 minutes for the initial 30 minutes and subsequently every 10 minutes for the following 90 minutes.

Total interventions (reductions and increases) in fgO_2 and fgDes levels were noted at the end of two hours. Arterial blood gas samples were obtained from all patients at 10 and 70 minutes, and the results (pH, pO_2, pCO_2, lactate, and HCO_3) were recorded. Data recording terminated at the end of the second hour, and gas consumption was noted. Patients were visited 24 hours postoperative and queried regarding intraoperative awareness using the modified Brice scale ("What is the last thing you remember before going to sleep?"; "What is the first thing you remember after waking up?"; "Did you have any dreams or other experiences while sleeping?").[5]

When mean arterial pressure (MAP) increased by 20% or more from baseline for 1 minute or longer, the remifentanil infusion was increased. In the absence of a satisfactory response, intravenous nitroglycerin was planned, in pulse or infusion form. If the MAP dropped below 65 mmHg for a duration of 1 minute or longer, the primary intervention involved intravenous crystalloid fluid replacement, with subsequent administration of 5-10 mg of ephedrine in case of persistent hypotension. Atropine administration was scheduled at a heart rate (HR) below 45 beats per minute (bpm). If the HR exceeded 100 bpm, an initial 20 µg bolus of remifentanil was planned, followed by potential treatment with esmolol if the elevated HR persisted.

Statistical Analysis

The sample size of the study was calculated using G*Power 3.1.9 (G*Power, Universität Düsseldorf, Germany). The primary outcome of the study was the number of interventions (reductions and increases) in fgO_2 and fgDes levels during the first two hours of operation. From an earlier study,[6] power analysis showed that 37 patients were necessary to detect a difference of 0.20 between the number of interventions (effect size 0.66, 5% type I error rate, 80% power, two tailed t-test). Considering study withdrawals or protocol violation, we set a sample size of 40 in each arm.

All analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) software package. Normality of continuous variables across groups was assessed using the Shapiro-Wilk normality test. The Independent Samples t-test and the Mann-Whitney U test were employed for between-group comparisons of continuous variables. Repeated measures analysis of variance (ANOVA) was utilized for continuous variables involving repeated measurements, with multiple comparisons assessed using the Sidak test. Group comparisons of categorical variables were conducted using the chi-square test. Various test methods such as Pearson's chi-square, Yates' correction, Fisher's exact test, and Monte Carlo simulation were employed in chi-square analyses. Pearson correlation analysis was employed to determine relationships between variables. A significance level of $P < 0.05$ was set.

Results

The study included a total of 80 patients (40 in Group E and 40 in Group Y). The demographic data of the patients are presented in Table 1.

The number of interventions (changes in intraoperative fgO_2 and fgDes levels) is demonstrated in Table 2. Statistical analysis of the groups revealed a higher frequency of fgO_2 increases and overall changes in Group Y compared to Group E ($P < 0.05$). The fgO_2 was higher in the young patient group recorded at the 40th minute and from the 60th minute onward (Figure 1). Three patients in Group Y did not achieve oxygenation targets, necessitating an increase in FGF, whereas in all geriatric patients, maintaining a 350 mL min^{-1} FGF demonstrated the ability to sustain oxygenation targets with fewer interventions and lower fgO_2 levels.

No statistically significant difference was found between the two groups regarding interventions at desflurane levels. The fgDes, fiDes, and etDes concentrations are shown in Figure 2. A significant intergroup difference was found in terms of fgDes at all times except for the 10th and 15th minutes ($P < 0.05$). Group E exhibited lower desflurane concentrations overall. A statistically significant difference between groups was observed in terms of fiDes and etDes across all time

Table 1. Patients' Demographic Data [Mean ± Standard Deviation, Min.-Max. (Median), Count]			
	Group Y (n = 40)	**Group E (n = 40)**	***P* value**
Age	43.9 [25-50 (46)]	70.3 [65-82 (70)]	
Weight (kg)	77.9±17	74.5±11.5	0.47
BSA (m^2)	1.9±0.24	1.8±0.16	0.26
BMI (kg m^{2-1})	26.4±4.7	26.1±3.74	0.93
Gender (F/M)	18/22	14/26	0.49
ASA (1/2/3)	3/36/1	2/34/4	0.48
Min.-Max., minimum-maximum; BSA, body surface area; BMI, body mass index; F/M, female/male; ASA, American Society of Anesthesiologists			

Table 2. The Number of Interventions in Intraoperative fgO_2 and fgDes Concentrations (Mean ± SD)			
	Group Y	**Group E**	***P* value**
Number of increases in oxygen	1.8±1.2	1.1±0.8	0.006*
Min.-Max. (median)	0-4 (2)	0-3 (1)	
Number of decreases in oxygen	0.07±0.26	0.10±0.3	0.9
Min.-Max. (median)	0-1 (0)	0-2 (0)	
Total alteration in oxygen	1.9±1.3	1.2±1	0.01*
Min.-Max. (median)	0-5 (2)	0-4 (1)	
Number of increases in desflurane	0.12±0.3	0.07±0.2	0.46
Min.-Max. (median)	0-1 (0)	0-1 (0)	
Number of decreases in desflurane	4.2±1.7	4.1±1.3	0.47
Min.-Max. (median)	0-7 (4)	2-7 (4)	
Total alteration in desflurane	4.3±1.8	4.2±1.3	0.46
Min.-Max. (median)	0-8 (5)	2-7 (4)	
*There is a significant difference between groups ($P < 0.05$) Min.-Max., minimum-maximum; SD, standard deviation; fgDes, fresh gas desflurane concentration; fgO_2, fresh gas oxygen concentration			

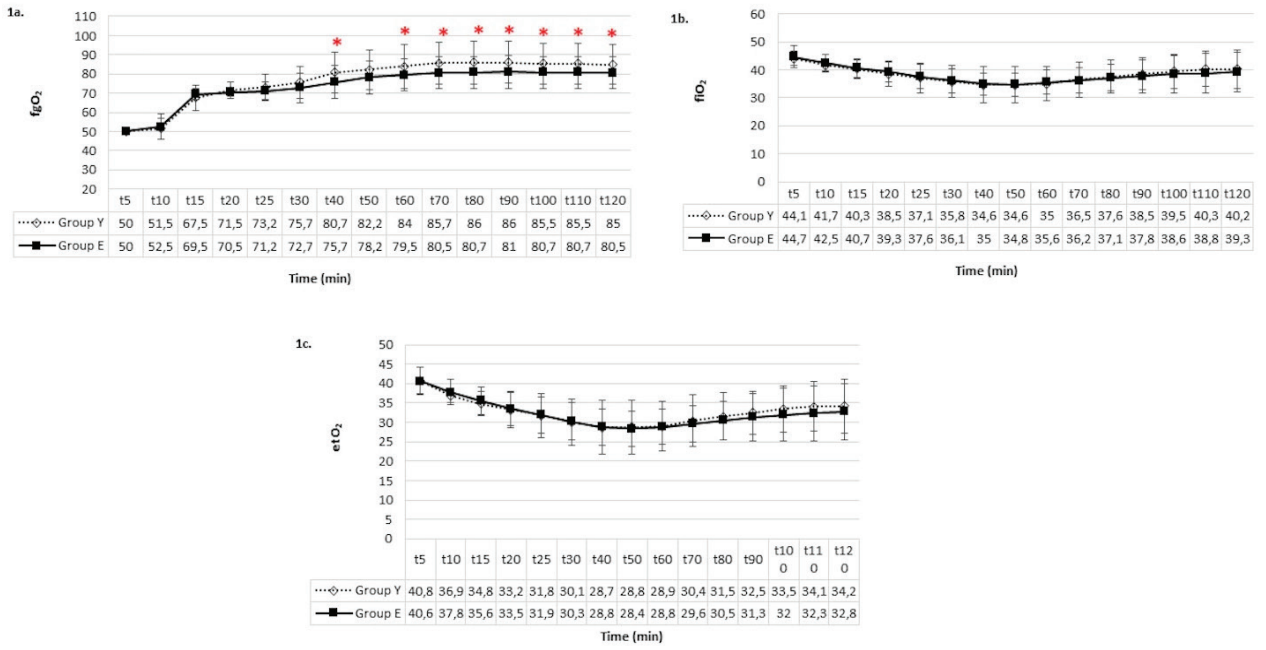
points ($P < 0.05$). Group E consistently demonstrated lower fiDes and etDes levels. Throughout the operation, BIS values were maintained within the range of 40-50 (Figure 3). In the intergroup comparison of intraoperative BIS values, no significant difference was observed except minutes 70, 90, and 120, though considered clinically insignificant. Postoperative evaluation at the 24th hour, did not reveal any instances of intraoperative awareness under anaesthesia in any of the patients based on the interrogation conducted.

In the intergroup comparison of intraoperative SpO_2 values, no significant difference was observed except for minutes 0 and 5, and the difference was considered clinically insignificant.

The rSO_2 values obtained by cerebral oximetry in both groups were analysed. In the intergroup evaluation, a significant difference was observed in the rSO_2-R and rSO_2-L values at 60, 80, 90, 100, 110, and 120 minutes ($P < 0.05$) (Table 3). rSO_2-R and rSO_2-L were higher in Group Y; however, no patient experienced a reduction of more than 20% from the baseline levels in intragroup comparisons. There were no statistically significant differences in MAP in intragroup comparison after transitioning to MFA. In intergroup comparison, MAP was higher in Group E at the 20th minute while it was lower at the 40th, 50th, 60th and 100th minutes (Figure 4).

Intraoperative arterial blood gas results obtained from all patients at 10 and 70 minutes are presented in Table 4. No statistically significant differences were observed between groups concerning pH, PO_2, PCO_2, lactate, and HCO_3 ($P > 0.05$).

The relationships of the number of changes in fgDes and fgO_2 with weight, body surface area (BSA), and BMI were also evaluated. A positive correlation was observed among BSA, BMI, and weight with the amount of change in O_2 value, and the total change in all patients and separately in both groups ($P < 0.05$).



	t5	t10	t15	t20	t25	t30	t40	t50	t60	t70	t80	t90	t100	t110	t120
Group Y	50	51,5	67,5	71,5	73,2	75,7	80,7	82,2	84	85,7	86	86	85,5	85,5	85
Group E	50	52,5	69,5	70,5	71,2	72,7	75,7	78,2	79,5	80,5	80,7	81	80,7	80,7	80,5

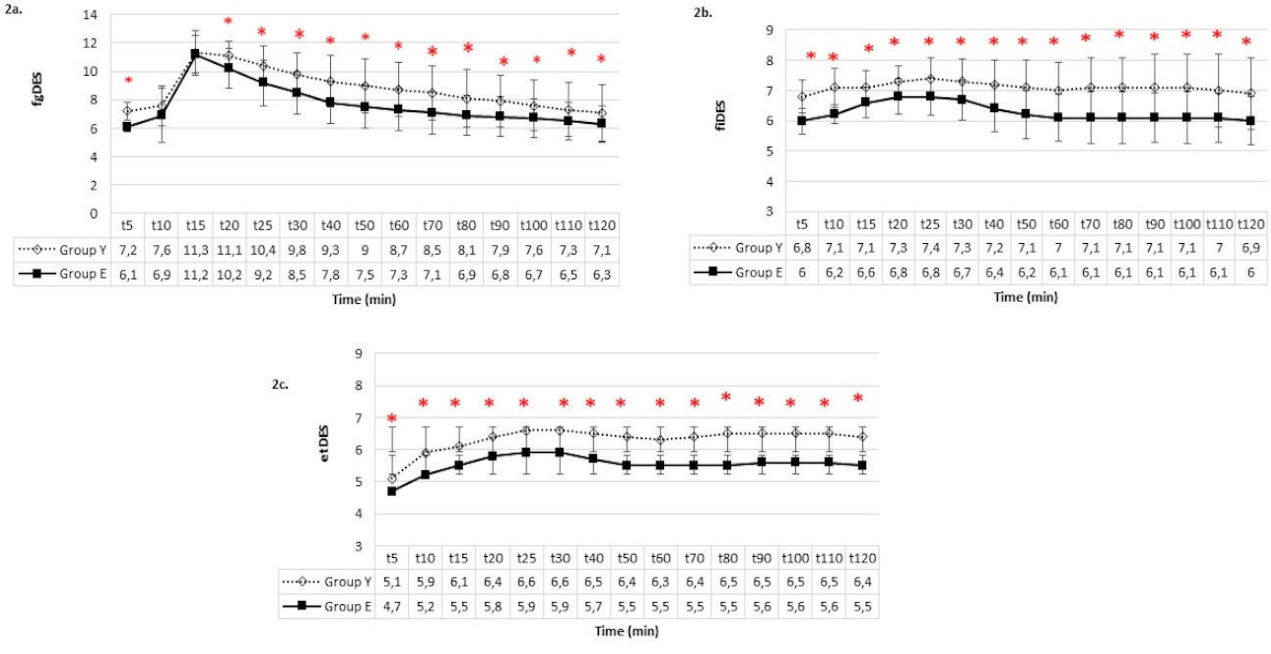
	t5	t10	t15	t20	t25	t30	t40	t50	t60	t70	t80	t90	t100	t110	t120
Group Y	44,1	41,7	40,3	38,5	37,1	35,8	34,6	34,6	35	36,5	37,6	38,5	39,5	40,3	40,2
Group E	44,7	42,5	40,7	39,3	37,6	36,1	35	34,8	35,6	36,2	37,1	37,8	38,6	38,8	39,3

	t5	t10	t15	t20	t25	t30	t40	t50	t60	t70	t80	t90	t100	t110	t120
Group Y	40,8	36,9	34,8	33,2	31,8	30,1	28,7	28,8	28,9	30,4	31,5	32,5	33,5	34,1	34,2
Group E	40,6	37,8	35,6	33,5	31,9	30,3	28,8	28,4	28,8	29,6	30,5	31,3	32	32,3	32,8

Figure 1. Oxygen concentrations a) fgO_2 b) fiO_2 c) etO_2.

***There is a significant difference between groups ($P < 0.05$).**

fgO_2, fresh gas oxygen concentration; fiO_2, inspiratory oxygen concentration; etO_2, expiratory oxygen concentration.



	t5	t10	t15	t20	t25	t30	t40	t50	t60	t70	t80	t90	t100	t110	t120
Group Y	7,2	7,6	11,3	11,1	10,4	9,8	9,3	9	8,7	8,5	8,1	7,9	7,6	7,3	7,1
Group E	6,1	6,9	11,2	10,2	9,2	8,5	7,8	7,5	7,3	7,1	6,9	6,8	6,7	6,5	6,3

	t5	t10	t15	t20	t25	t30	t40	t50	t60	t70	t80	t90	t100	t110	t120
Group Y	6,8	7,1	7,1	7,3	7,4	7,3	7,2	7,1	7	7,1	7,1	7,1	7,1	7	6,9
Group E	6	6,2	6,6	6,8	6,8	6,7	6,4	6,2	6,1	6,1	6,1	6,1	6,1	6,1	6

	t5	t10	t15	t20	t25	t30	t40	t50	t60	t70	t80	t90	t100	t110	t120
Group Y	5,1	5,9	6,1	6,4	6,6	6,6	6,5	6,4	6,3	6,4	6,5	6,5	6,5	6,5	6,4
Group E	4,7	5,2	5,5	5,8	5,9	5,9	5,7	5,5	5,5	5,5	5,5	5,6	5,6	5,6	5,5

Figure 2. Desflurane concentrations a) fgDes b) fiDes c) etDes.

***There is a significant difference between groups ($P < 0.05$).**

fgDes, fresh gas desflurane concentration; fiDes, inspiratory desflurane concentration; etDes, expiratory desflurane concentration.

The desflurane, O_2, air, and remifentanil consumption at the end of two hours were analysed. The desflurane consumption was significantly higher in Group Y ($P < 0.05$) (Table 5). In Group E, 19 patients received ephedrine and 3 patients received atropine. In Group Y, 18 patients received ephedrine and 3 patients received atropine.

Discussion

As per our hypothesis, the changes in oxygen levels, reflecting the requirement for intervention during MFA, were notably reduced among geriatric patients compared to younger and middle-aged adults. Meanwhile, oxygenation parameters were consistently maintained within safe thresholds.

Table 3. Regional Cerebral Oxygen Saturations (rSO_2-R and rSO_2-L) (Mean ± Standard Deviation)

	rSO_2-R			rSO_2-L		
	Group Y	**Group E**	***P* value**	**Group Y**	**Group E**	***P* value**
t0	65.6±9.7	67±6.1	0.45	65.2±10.6	66.3±7	0.57
t5	77.6±11.2	75.2±8.2	0.28	76.6±11.4	74.8±7	0.39
t10	76.4±11.1	72.8±9.1	0.11	74.4±11	71.9±7.4	0.25
t15	74±11.7	71±9	0.19	73.2±11.4	70±7.5	0.14
t20	73±11.5	71±8.7	0.38	71.8±10.7	69.7±8	0.32
t25	72.2±11.2	70.4±8.3	0.41	70.9±10.6	68.5±8.1	0.27
t30	72.8±10.7	69.6±8.6	0.15	70.6±10	68.8±7.9	0.37
t40	72.6±10.7	68.9±8	0.08	71.1±10.7	68.3±6.3	0.16
t50	71.8±10	68±7.7	0.05	71±10	67.3±6.8	0.06
t60	73.2±10.7	68.1±7.4	0.01*	71.6±10.2	66.7±6.5	0.01*
t70	71.7±11.4	68.1±7.4	0.09	70.8±10.3	67.3±6.4	0.07
t80	72±11.6	66.9±7.6	0.02*	71.8±11.3	66.4±6.7	0.01*
t90	72.9±10.8	66.4±7.5	0.003*	72.1±11.3	66.2±6.1	0.005*
t100	72.8±10.6	66.9±7	0.004*	72±10.4	66.5±6.2	0.006*
t110	72.6±11.2	67.3±7.3	0.01*	72.5±11.7	66.5±6.5	0.006*
t120	73.4±10.9	67.4±7.4	0.005*	73.4±11.3	66.3±7	0.001*

*There is a significant difference between groups ($P < 0.05$)
rSO_2-R, regional cerebral oxygen saturation on the right; rSO_2-L, regional cerebral oxygen saturation on the left

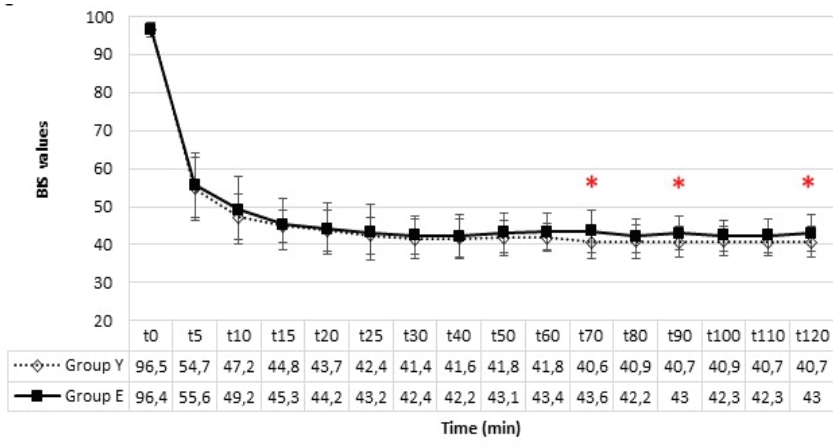


Figure 3. BIS values.

***There is a significant difference between groups ($P < 0.05$).**

BIS, bispectral index.

Table 4. Intraoperative Arterial Blood Gas Measurements (Mean ± Standard Deviation)

		Group Y	Group E	*P* values
pH	t10	7.38±0.4	7.40±0.4	0.76
	t70	7.36±0.4	7.38±0.4	0.12
PO_2	t10	183.7±74.4	183.3±88.6	0.9
	t70	117.3±31	106.3±19.6	0.06
PCO_2	t10	37.7±5.6	36.8±4	0.37
	t70	36.1±4.3	35.6±3.5	0.53
Lactate	t10	1.15±0.56	1.09±0.67	0.67
	t70	1.35±0.62	1.24±0.5	0.40
HCO_3	t10	22.5±2	22.8±2.2	0.49
	t70	20.8±2.1	21.3±2.2	0.24

There are no significant differences between the groups ($P > 0.05$)

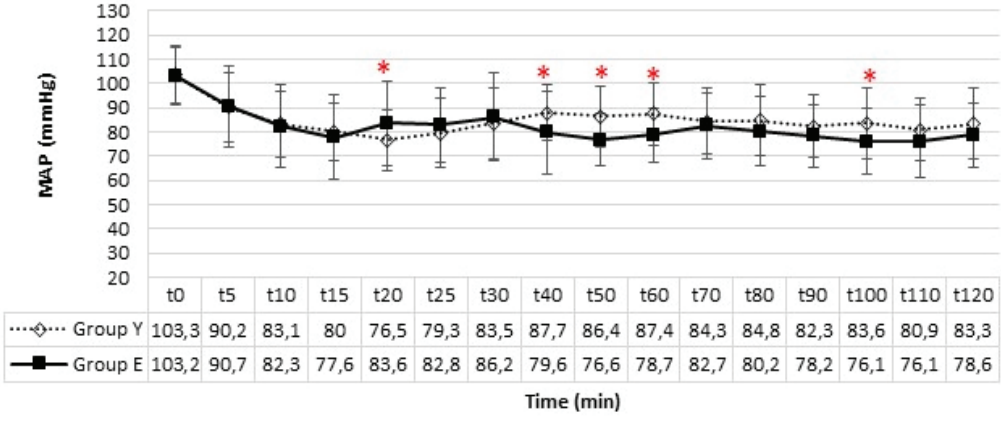


Figure 4. Intraoperative mean arterial pressure.

***There is a significant difference between groups ($P < 0.05$).**

MAP, mean arterial pressure.

Table 5. Comparison of Desflurane, O_2, Air and Remifentanil Consumption Between Groups

	Group Y	Group E	*P* value
Desflurane consumption	38.2±7.1	34.3±5.3	0.012*
O_2 consumption	125.4±27.9	127.2±30.4	0.92
Air consumption	40.2±6.3	43±10.1	0.25
Remifentanil consumption (mL)	36.4±7.8	34.9±6.4	0.4

*There is a significant difference between groups ($P < 0.05$)

The alteration in desflurane levels exhibited parallel patterns between the two groups, and none of the patients reported experiencing awareness during the procedure.

Due to the rising concerns regarding healthcare costs, environmental pollution, and global warming, MFA-as an anaesthesia technique-has become increasingly important in recent years due to its beneficial effects. These advantages encompass the reduction in consumption of inhalation anaesthetics and the promotion of environmental sustainability by reducing the carbon footprint.[7-9]

The evolution of technology integrated into anaesthesia machines enables the reduction of FGF by elevating the rate of rebreathing during general anaesthesia and allows

for closer monitoring of adverse events such as hypoxia or intraoperative awareness under anaesthesia. Furthermore, the low solubility and metabolic rate of contemporary inhalation agents have played a crucial role in the widespread adoption of this technique.

The increasing life expectancy and improvements in analysis of diseases have resulted in the increased frequency of geriatric individuals in health services. Some of the physiologic changes that occur in the geriatric population have a negative impact on life, whereas others may compensate for these changes. Furthermore, aside from reduced metabolism and HR, a more sedentary lifestyle contributes to decreased oxygen consumption in older adults.[10] Additionally, the concentrations of inhalation agents required for the maintenance of general anaesthesia decrease with advancing age.[4] The current study was designed to evaluate the manageability and tolerability of MFA in older and young-middle-aged patients using a Dräger-Perseus® A500 anaesthesia workstation with suitable conditions for the administration of MFA. Desflurane, which rapidly reaches equilibrium between alveolar and brain concentrations due to its low blood/gas solubility, was also studied.

It was suggested that a one-third reduction in oxygen consumption during general anaesthesia could be achieved in the study, involving 20 elderly patients (aged 65 and above) undergoing major abdominal surgery.[3] In an assessment evaluating the relationship between anaesthesia and oxygen, it was stated that fiO_2 levels of 30-40% or lower could be sufficient in clinical use if the lungs are kept open. They also mentioned that higher fiO_2 values might lead to atelectasis.[11] In our study, the minimum fiO_2 threshold was established at 30%. If fiO_2, SpO_2, or NIRS targets fell below the specified levels, the fgO_2 was increased by 10%, and changes in oxygen, both in terms of increments and decrements, as well as the total number of alterations, were recorded at the end of each case. When comparing the two groups, there was a statistically significant difference, with a higher number of oxygen increases and alterations in the younger patient group. The lower fgO_2 levels in the geriatric patient group support our hypothesis, indicating the necessity for lower fgO_2 levels during MFA to prevent hypoxia. This finding substantiates that MFA can be more readily applied in the geriatric population.

During the intraoperative period, monitoring fiO_2, SpO_2, NIRS, or arterial blood gas for PO_2 and lactate levels is frequently used to ensure adequate oxygenation and avoid hypoxia. Park et al.[12] conducted a study on 50 patients undergoing laparoscopic robotic surgery lasting more than 6 hours, comparing minimal flow (0.5 L min^{-1},) to the high flow anaesthesia. Although PaO_2 values were slightly lower in MFA, they remained within reliable limits, demonstrating the safe and effective application of MFA in prolonged laparoscopic surgeries.[12] The effects of LFA on hemodynamic parameters, recovery time, and arterial blood gas results in morbidly obese patients undergoing laparoscopic sleeve gastrectomy were investigated. The authors found that SpO_2, arterial blood gas, and recovery times were similar when compared between high-flow anaesthesia and another condition. They suggested that LFA is safe in achieving adequate tissue perfusion, anaesthesia depth, and postoperative recovery in morbidly obese patients.[13] In our study, although PaO_2 values were lower in the elderly, they remained within safe limits. Despite a significant decrease in PO_2 in both groups, the ideal PO_2 value considered in arterial blood gas measurements, remaining above 100 mmHg, was maintained during the study. SaO_2 values were maintained above 95% in all patients. Additionally, there was no statistically significant difference in lactate levels. This indicates that MFA can provide adequate tissue oxygenation across different age groups.

The brain is highly susceptible to hypoxia, which may occur during MFA. NIRS is frequently utilized for intraoperative demonstration of cerebral oxygenation and perfusion, and its monitoring has been reported to mitigate postoperative cognitive dysfunction.[14] The impact of MFA on rSO_2 and hemodynamics was investigated in the prone position. The study revealed that MFA was associated with higher MAP and left-sided rSO_2 values compared with normal flow anaesthesia, whereas no significant difference was observed in other vital signs or right-sided rSO_2. Consequently, their findings suggest that MFA can be considered safe concerning rSO_2 levels and hemodynamics.[15] In our study, despite the occasional presence of an intergroup difference in the rSO_2 values, neither group showed a decrease compared with the baseline value. No significant difference was observed in intragroup comparisons in MAP after switching to MFA, indicating that this technique did not affect cerebral perfusion. This shows that MFA can be performed with close follow-up and appropriate monitoring while preserving cerebral oxygenation and perfusion, in geriatric patients as well.

Awareness under anaesthesia is one of the most undesirable complications during surgery. Monitoring the depth of anaesthesia using vital signs and clinical data can be subjective and insufficiently reliable owing to the presence of numerous factors that may influence these measurements. In the study on awareness under anaesthesia, the incidence of awareness was found to be 1%.[16] BIS monitoring is often used to prevent this and to provide objective data. The effects of BIS use on awareness in surgeries requiring muscle relaxants and intubation were examined. It was reported that BIS monitoring significantly reduced the incidence of awareness.[17] In our study, BIS values were maintained at 40-50, which is known as the safe range, in both groups. While

no significant intergroup difference was noted in the amount of change in desflurane, the BIS target was maintained within the determined safe range, indicating that MFA can be administered safely in both groups. However, etDes was lower in the older patient group at all times, indicating that adequate depth of anaesthesia was maintained using a reduced dosage of inhalation anaesthetics, in parallel the risk of inadequate depth of anaesthesia when using MFA was also lower in these patients. No patient described awareness under anaesthesia in the interviews at the 24th postoperative hour.

In normal physiological conditions during anaesthesia, the estimated O_2 requirement is around 2-3 mL kg^{-1} min^{-1}. Based on this estimation, FGF within the range of 250-500 mL can be safely employed in healthy adults weighing less than 100 kg.[2] In a study investigating the relationship between LFA and body weight, it was argued that O_2 requirement should be determined individually in patients under anaesthesia. They stated that the hemodynamic and oxygenation parameters of the patients were maintained within the safe range; thus, FGF-which is determined according to body weight-is more reliable and physiological.[18] A positive correlation was observed between body weight, BMI, and BSA, and the amount of O_2 change in all patients in our study, and in both groups. This supported the view that there is a close relationship between body size and O_2 consumption, which is in line with the previous study. Based on these data, in MFA applications, determining FGF and the O_2 percentage is thought to be an appropriate approach after determining the O_2 demand specific to each patient, including elderly patients.

Study Limitations

This study has several limitations. Firstly, owing to the study's inherent design, blinding and randomization procedures were not feasible. Secondly, our investigation utilized anaesthesia equipment capable of administering MFA, with 350 mL. This equipment was available solely in two specific operating rooms. Consequently, surgical cases conducted in these two designated rooms were included, resulting in a relatively limited intergroup variance in mean age. Despite this constraint, the outcomes from our study might indicate a more pronounced distinction between younger adults and older patients, necessitating further research for a comprehensive understanding of this topic. It should be noted that patients with severe respiratory and cardiac diseases, which are common comorbidities in the elderly, were excluded from the study. Individual anaesthesia settings for those patients should be considered.

Conclusion

To the best of our knowledge, this is the first study of comparing the impacts of MFA across various age demographics. Our findings indicate that administering MFA at a rate of 350 mL min^{-1} in the growing cohort of older adult patients can be performed without inducing hypoxia or inadvertent awareness. The use of MFA techniques has proven beneficial in diminishing gas consumption and maintaining adequate oxygen levels with reduced intervention in the elderly population. The incorporation of MFA as an anaesthesia modality should be promoted for multiple reasons: it minimizes respiratory complications when coupled with diligent monitoring and oversight by appropriately trained personnel, aligns with the goal of a sustainable future by contributing less to global warming, and contributes to reducing ambient air pollution within the operating room, benefiting healthcare professionals.

Ethics

Ethics Committee Approval: This prospective study was conducted following approval from the Eskişehir Osmangazi University, Clinical Trials Ethics Committee of Studies (approval no.: 21, dated: December 22, 2022).

Informed Consent: Informed consent from all patients was obtained.

Footnotes

Author Contributions: Concept - S.Ü., G.E.K., M.O., M.S.G.; Design - S.Ü., G.E.K., M.O., M.S.G.; Data Collection and/or/Processing - S.Ü., G.E.K., M.O., M.S.G.; Analysis and/or/Interpretation - S.Ü., G.E.K., M.O., M.S.G.; Literature Review - S.Ü., G.E.K., M.O., M.S.G.; Writing - S.Ü., G.E.K., M.O., M.S.G.

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Evaluation of ASA, SORT, and ACCI Scores in Predicting the Need for Postoperative Intensive Care Unit Admissions After Hip Surgery

Neslihan Gezer, Lütfiye Pirbudak, Elzem Şen, Ayşe Mızrak

Gaziantep University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Gaziantep, Türkiye

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Abstract

Objective: We aimed to investigate the effectiveness of the American Society of Anesthesiologists (ASA), the Surgical Outcome Risk Tool (SORT), and age-adjusted Charlson Comorbidity Index (ACCI) scores in determining the requirement for intensive care unit (ICU) admissions in patients aged 65 years and older who underwent hip surgery.

Methods: The study population consisted of 450 patients who underwent orthopedic hip surgery. The patients who were admitted to the ICU were either monitored in the postoperative ICU (Group 1) or transferred to the ward (Group 2). SORT and ACCI scores of all patients were recorded.

Results: The patients of Group 1 were significantly older than those in Group 2. SORT scores of both groups were comparable. The diagnostic sensitivity and specificity of ACCI scores were determined as 42.1% and 70.8%, respectively.

Conclusion: As a conclusion, ACCI scores can predict the need for ICU admissions in patients undergoing hip surgery. Besides, the traditionally used ASA scores are generally higher in this patient group. Determinative criteria for predicting the need for ICU admissions include older age of the patients, presence of comorbidities as hypertension and diabetes mellitus, as well as a long preoperative waiting period.

Keywords: ACCI, ASA, hip surgery, ICU admission, SORT

Main Points

- It is important to identify preoperative risk factors for unplanned admission to the intensive care unit to improve the allocation of medical resources and the quality of care.
- The Surgical Outcome Risk Tool is a simple model that predicts 30-day mortality rates before surgery using six routinely collected data elements.
- The Charlson Comorbidity Index (CCI) has been proven to predict postoperative complications and one-year mortality.
- Additionally, the age-adjusted CCI can be used to determine the need for intensive care in patients undergoing hip surgery.

Introduction

Expectedly, the number of hip fractures will reach 4.5 million by the year 2050 as a result of an increase in the aging population worldwide.[1] If not contraindicated, hip fracture cases are usually treated surgically due to the high morbidity and mortality of conservative treatment modalities. However, patients undergoing surgery may face certain challenges. Despite still significant number of patients needing to be admitted to the intensive care units

Corresponding author: Elzem Sen, e-mail: drelzemsen@gmail.com

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(ICUs) following hip surgeries, a multidisciplinary geriatric approach is employed. Due to the lack of guidelines for admissions to the postoperative ICUs, hospital organizations implement different strategies. Therefore, recognising preoperative risk factors for unplanned admissions to the ICUs is crucial to improve both allocation of medical resources and quality of care.[2]

In 1963, the American Society of Anesthesiologists (ASA) established a numerical system to assess the perioperative risk and physical health status of patients during anaesthesia and surgical procedures. Higher ASA scores were associated with increased postoperative complications, admissions to the ICU, and higher mortality rates. ASA scores are routinely determined subjectively by the anaesthesiologist before anaesthesia and can be easily found in medical records.[3] Surgical Outcome Risk Tool (SORT) is a simple model designed to preoperatively predict 30-day mortality rates, using six routinely collected data elements.[4]

The Charlson Comorbidity Index (CCI) has been shown to predict postoperative complications and one-year mortality rates in patients undergoing surgical treatment. Furthermore, since a patient's age is closely associated with prognosis, an age-adjusted CCI (ACCI) was introduced into clinical practice in 1994. A CCI score was created by adding one point for every decade of age increase for patients aged 40 years or older, resulting in the age-adjusted CCI score.[5]

In this study, we aimed to investigate the effectiveness of ASA, SORT, and ACCI scores in determining the requirement for ICU admissions in the preoperative evaluation of patients aged 65 and older who underwent hip surgery. The study's hypothesis is that SORT, a risk stratification tool comprising six preoperative variables, is superior to ACCI and ASA scores in predicting ICU admission.

Methods

This retrospective case-control study was conducted after the approval of the Gaziantep University Clinical Research Ethics Committee (date: 25.05.2022, approval no.: 2022/55) and in accordance with the ethical principles of the Declaration of Helsinki on ethical principles for medical research involving human subjects released by the World Medical Association in 2013. The study was organized after obtaining written consent from a total of 450 patients who underwent orthopedic hip surgery at Gaziantep University Şahinbey Research and Practice Hospital between April 1, 2016 and August 1, 2021. Patients aged ≥65 years with ASA scores I-IV were included in the study. Patients who underwent revision surgery, those who underwent multi-trauma surgery, those followed up in the ICU during the preoperative period, and cases with missing data were not included in the study.

Pre- and post-operative patients' data, derived from hospital records, were evaluated. The patients admitted to ICU were either monitored in the postoperative ICU (Group 1) or transferred to the ward without the need for postoperative ICU monitoring (Group 2). Information concerning the age, gender, body mass index (BMI), and ASA scores of the patients; type of surgery; smoking status; type of anaesthesia applied; preoperative period lasting from admission to the start of the surgery; duration of surgery; and comorbidities (hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease, osteoporosis, malignancy, neurological diseases) were recorded from patients' medical files.

The SORT scores of the cases were obtained from the http://www.sortsurgery.com/ website (accessed on March 15, 2022) after a detailed retrospective scan of the patients' computerized database. The ACCI index and relevant parameters were electronically entered into the https://www.mdcalc.com/charlson-comorbidity-index-cci#use-cases website (accessed on March 15, 2022), and necessary calculations were made.

Statistical Analysis

Assuming a medium effect size (Cohen's d = 0.5) with an alpha level of 0.05 and a target power of 90%, our analysis indicated a minimum of 85 patients per group, yielding a total sample size requirement of approximately 170 participants.

The normal distribution of numerical variables was tested using the Shapiro-Wilk test. For variables that followed a normal distribution, the Independent Samples t-test was used. For non-normally distributed variables, the Mann-Whitney U test was applied. The chi-square test was used to compare categorical data between groups. receiver operating characteristic (ROC) curve analysis was conducted to determine the cut-off points for ACCI, SORT, and ASA. Version 22.0 of the Windows statistical package program was used for the analyses, and $P < 0.05$ was considered statistically significant.

Results

The data on 190 patients, in Group 1, and 260 patients, in Group 2, were comparatively reviewed. Any statistically significant differences were not observed between Groups 1, and 2 in terms of distribution of male/female patients (P=0.09), mean BMIs (P=0.11), ASA physical status scores (P=0.31), the number of smokers (P=0.09), types, and duration of surgical interventions (P=0.34 vs P=0.039). However, the patients of Group 1 (mean age: 82.14±8.96 years) were significantly older compared to Group 2 (mean age: 71.61±8.06 years) (P=0.03), and time to surgery was statistically significantly longer in Group 1 patients (P

< 0.05). The groups were similar concerning the type of anaesthesia used (*P*=0.51) (Table 1).

As is seen in Table 2, statistically significant differences existed between Groups 1 and 2 in terms of the presence of hypertension (*P*=0.03) and diabetes mellitus (*P*=0.03). While mortality rates were statistically significantly higher in Group 1 (*P*=0.01) (Table 2), (complete the sentence with an independent clause).

SORT scores of both groups were similar (*P*=0.85). The ACCI scores were statistically higher in Group 1 (*P*=0.02) (Table 3).

ROC curve analysis was performed to evaluate the predictive value of three scoring systems for ICU admission. ACCI showed a statistically significant predictive ability with an AUC of 0.582 [95% confidence interval (CI): 0.535-0.628, *P*=0.003]. The optimal cut-off value was determined to be >6, with a sensitivity of 42.11% and a specificity of 70.77% (Figure 1).

The SORT score demonstrated poor predictive performance, with an AUC of 0.505 (95% CI: 0.457-0.552, *P*=0.870), indicating no significant discrimination between ICU and non-ICU patients. Despite the high sensitivity (96.32%), specificity was notably low (2.31%) at the cut-off value of >1.29 (Figure 2).

Similarly, the ASA classification yielded an AUC of 0.514 (95% CI: 0.467-0.561, *P*=0.602), also reflecting limited discriminatory power. The cut-off point >3 provided a sensitivity of 12.11% and a specificity of 90.38% (Figure 3).

Table 1. Demographic and Clinical Features of the Patients

	Group 1 n = 190	Group 2 n = 260	*P* value
Male/female n (%)	82 (43.2%)/108 (56.8%)	92 (35.4%)/168 (64.6%)	0.09
Age (years) (mean ± SD)	82.14±8.96	71.61±8.06	0.03*
BMI (kg/m$^{2-1}$) (mean ± SD)	26.04±4.03	25.41±4.03	0.11
ASA I/II/III/IV (n)	1/1/165/23	0/4/231/25	0.31
Smokers n (%)	35 (18.4%)	33 (12.7%)	0.09
Operation type n (%)			
Proximal femur nailing	54 (28.4%)	62 (23.8%)	0.34
Partial hip replacement	124 (65.3%)	186 (71.5%)	
Total hip replacement	12 (6.3%)	12 (4.6%)	
Time to operation (day) (mean ± SD)	4.23±3.55	3.46±3.05	0.006*
Operation duration (minute) (mean ± SD)	141.24±68.73	150.23±70.59	0.24
Anaesthesia type n (%)			
Spinal anaesthesia	127 (66.8%)	189 (72.6%)	0.51
Combined spinal epidural anaetshesia	29 (15.2%)	29 (10%)	
Lumbar plexus block	4 (2.1%)	6 (2.3%)	
General anaesthesia	30 (15.7%)	36 (13.8%)	

*Significant at $P < 0.05$.

Pearson's chi-square test was used for gender, smoking status, operation type, and anaesthesia type. Fisher's exact test was applied for ASA classification due to small expected cell counts. Quantitative variables (e.g., age, BMI, time to operation, operation duration) were compared using the independent samples t-test or the Mann-Whitney U test, depending on the distribution of the data (tested with the Shapiro-Wilk test).

SD, standard deviation; ASA, American Society of Anesthesiologists; BMI, body mass index.

Table 2. Comorbidities and Mortality Rates According to the Groups

	Group 1 n (%)	Group 2 n (%)	*P* value
Hypertension	123 (64.7%)	142 (54.6%)	0.03*
Diabetes mellitus	78 (41.1%)	81 (31.2%)	0.03*
Coronary artery disease	58 (30.5%)	71 (27.3%)	0.45

Table 2. Continued

	Group 1 n (%)	Group 2 n (%)	*P* value
Chronic obstructive lung disease	34 (17.9%)	34 (13.1%)	0.15
Other comorbidities			
Neurological diseases	46 (24.2%)	43 (16.5%)	
Osteoprosis	2 (1.1%)	6 (2.3%)	0.14
Chronic renal failure	13 (6.8%)	11 (4.2%)	
Malignancy	7 (3.7%)	10 (3.8%)	
Mortality	29 (15.3%)	13 (5%)	<0.01*

*Significant at $P < 0.05$.

Pearson's chi-square test was used for hypertension, diabetes mellitus, coronary artery disease, and chronic obstructive pulmonary disease. A continuity-corrected chi-square test was used for mortality. Fisher's exact test was applied for rare comorbidities with low frequencies, including neurological diseases, osteoporosis, chronic renal failure, and malignancy.

Table 3. Comparison of SORT and ACCI Scores Between Groups

	Group I (n = 190)	Group II (n = 260)	*P* value
SORT (%) (mean ± SD)	5.29±2.87	5.3±2.9	0.85
ACCI (mean ± SD)	6.4±1.41	5.98±1.17	0.02*

*Significant at $P < 0.05$, quantitative data were compared using the independent samples t-test.

SORT, Surgical Outcome Risk Tool; ACCI, age-adjusted Charlson Comorbidity Index; SD, standart deviation.

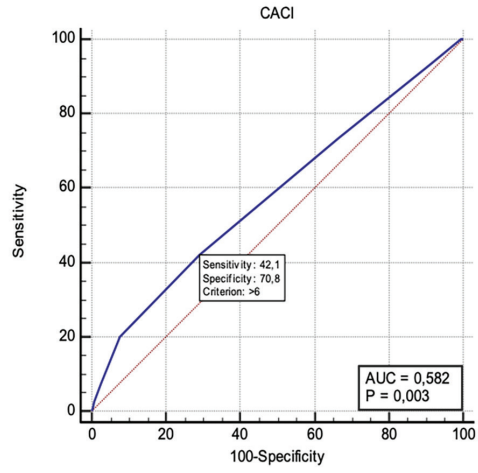

Figure 1. ROC curve analysis for ICU admission prediction based on ACCI score.

ROC, receiver operating characteristic; ICU, intensive care unit; ACCI, age-adjusted Charlson Comorbidity Index.

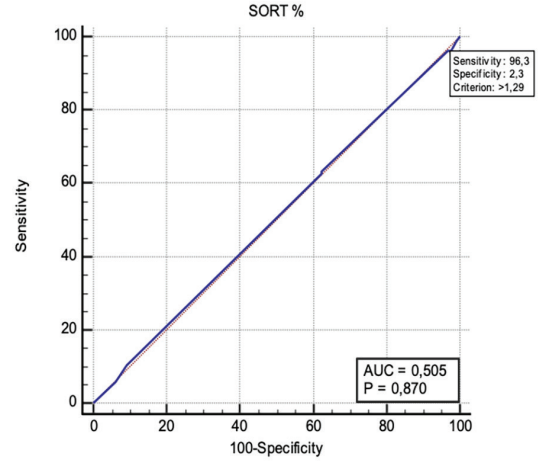

Figure 2. ROC curve analysis for ICU admission prediction based on SORT score.

ROC, receiver operating characteristic; ICU, intensive care unit; SORT, Surgical Outcome Risk Tool.

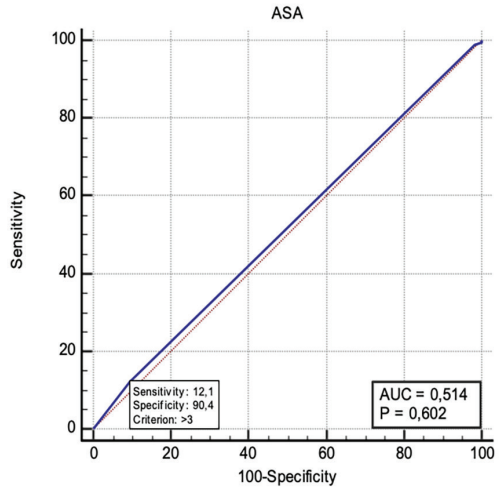

Figure 3. ROC curve analysis for ICU admission prediction based on ASA score.

ROC, receiver operating characteristic; ICU, intensive care unit; ASA: American Society of Anesthesiologists; AUC, area under the curve.

Discussion

In this study, we aimed to evaluate ASA, SORT, and ACCI scores in predicting the postoperative ICU admissions of the patients who had undergone orthopedic hip surgery. Postoperative ICU follow-up of critical patients remains an important part of the treatment process. Risk classification tools help clinicians provide more accurate information to patients, which also guide perioperative care decisions. Simple and cost-effective risk-scoring tools will become more widely used, especially with the growing availability of mobile digital devices.

Surace et al.[6] found that longer operation time was associated with a greater risk of readmissions, reoperations, surgical site infections, systemic complications, and blood transfusions. They identified that the rate of these complications increased when the duration of surgery exceeded 75-80 minutes. They also found a relationship between venous thromboembolic complications and surgeries lasting approximately 90 to 100 minutes. In this study, the duration of surgery in both groups was similar, which could be attributed to the limited number of cases in our study and the fact that postoperative complications were not investigated in the late postoperative period. Most available data point to the potential benefits of a comprehensive medical approach prioritizing regional anaesthesia for patients and the healthcare system.[7] In our study, regional anaesthesia was found to be the most commonly used type of anaesthesia for hip surgeries and was applied at similar rates in both groups.

Older age, higher ASA class, and duration of surgery longer than 4 hours have been found to be associated with a higher probability of unplanned postoperative admissions to the ICU.[8] Although there was no significant difference between the groups in our study, we observed that the mean age of the group with patients deemed appropriate for postoperative ICU admission was significantly higher. A short time interval between admission and surgery is considered ideal for geriatric hip fractures. Despite the importance of shortening the time to surgery for reducing mortality rates after hip fractures, no significant differences were found when considering 48 hours as a critical cut-off point for mortality.[9] In our study, the time to surgery was longer in the group of patients admitted to the ICU, and mortality rates were higher in these patients. Comorbidities are often cited as risk factors for mortality or morbidity assessments in ICU or ward patients.[10] Similarly, in the present study, the statistically higher number of patients with hypertension and/or diabetes mellitus was postoperatively admitted to ICUs.

The positive correlation between ASA scores and postoperative mortality rates was first published in 1970 and has been recently emphasised in a large prospective study that compared more than 700,000 patients undergoing elective and emergency procedures, indicating the importance of ASA scores in predicting mortality within 48 hours after surgery.[11] In their retrospective cohort study, Park et al.[12] observed higher ICU admission rates and prolonged hospital stay in the ASA III group compared to ASA I and II groups of patients who had undergone laparoscopic colorectal surgeries. Since distribution of ASA scores between both groups was comparable in our study, we thought that ASA scoring system may not provide meaningful information in determining the need for ICU admissions.

It has been suggested that SORT scores contribute to the identification of high-risk patients, thus serving as a useful tool not only for resource planning but also for preoperative assessment, informed consent, and shared decision-making processes. Therefore, SORT is expected to have a leading role in routine clinical practice among preoperative mortality risk assessment tools in terms of evaluating and contributing to improving patient outcomes.[13] SORT has been shown to predict the risk of postoperative morbidity in major elective surgery when used preoperatively.[4] Aboosalih et al.[14] concluded that SORT can be used to identify high-risk patients and assess the need for intensive care admissions. SORT has a lower predictive value in evaluating the need for postoperative admissions to ICU, as we also investigated in our study. We also considered that there was no statistically significant difference ICU admission rates between postoperative ICU and orthopedic ward patients due to the small sample size of our study.

CCI has been used in many studies to predict postoperative mortality in patients undergoing surgery. In a study of 497 patients undergoing surgical resection for pancreatic cancer, Dias-Santos et al.[15] found that a CCI score of >4 predicted prolonged hospital stay. In another study, Zhan et al.[16] revealed a significant relationship between CCI scores and admissions to ICU in patients undergoing thoracic aortic aneurysm surgery. St-Louis et al.[17] showed that ACCI could be a reliable predictor of postoperative outcomes in emergency general surgery patients. They also found that ACCI could be a predictor of 30-day mortality. Therefore, considering the simplicity of the CCI model, it has been observed to be a good option for predicting perioperative mortality. In our study, we also found that the ACCI scores could be a valuable prognostic tool in predicting the need for postoperative admissions to the ICU with a sensitivity of 42%, and specificity of 71%.

Study Limitations

The present study was conducted at a single center. To confirm our results, we need multicenter studies with more patients.

Conclusion

In conclusion, we believe that ACCI can be a determinant in predicting the need for ICU admissions in patients undergoing hip surgery. In this patient group with generally higher ASA scores, the determinative criteria for predicting the need for ICU admissions are older age, the presence of comorbidities such as hypertension and diabetes mellitus, and a prolonged preoperative waiting period. To demonstrate the effectiveness of the SORT index, which encompasses all determinants such as the patient's age, ASA physical status, comorbidities, and surgical characteristics, in predicting the need for ICU, further clinical studies should be conducted with a higher number of patients.

Ethics

Ethics Committee Approval: This retrospective case-control study was conducted after the approval of the Gaziantep University Clinical Research Ethics Committee (date: 25.05.2022, approval no.: 2022/55).

Informed Consent: Written consent was obtained from patients.

Footnotes

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

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Original Article

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Comparison of EuroSCORE II and STS Risk Scoring Systems in Patients who Underwent Open-heart Surgery

Erkam Saka, Esin Öztürk, Aslıhan Esra Yüksel, Nüzhet Seden Kocabaş

Ege University Faculty of Medicine, Department of Anaesthesiology and Reanimation, İzmir, Türkiye

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Abstract

Objective: In the present study, European Cardiac Operative Risk Assessment System II (EuroSCORE II) and the Society of Thoracic Surgery (STS) risk scoring systems were used to predict mortality in patients who underwent various types of open-heart surgery, including coronary artery bypass grafting, aortic valve replacement, mitral valve replacement, and combined valve surgery with coronary artery bypass grafting, in the cardiovascular surgery operating room. The aim was to compare risk assessment systems regarding their clinical applicability.

Methods: A total of 469 patients, 141 (30.1%) female and 328 (69.9%) male, were included in the study. All risk factors were retrospectively recorded according to the EuroSCORE II and STS risk assessment systems. Statistical analysis was performed using the receiver operating characteristic (ROC) curve. Predicted and actual mortality rates were compared for each risk-scoring system.

Results: When the ability of the EuroSCORE and STS risk classifications to predict mortality was analyzed using the ROC curve, the area under the curve for the EuroSCORE II risk score was 78.3% ($P < 0.001$), while the area under the curve for the STS risk score was 82.3% ($P < 0.001$). In our study, the STS scoring system was found to have a greater predictive value than EuroSCORE II. When the patients' observed and expected mortality rates were examined according to the EuroSCORE II and STS risk scores, no statistically significant relationship was found between the expected and observed mortality rates for each risk group.

Conclusion: In our study, the STS risk scoring system was found to be more accurate in predicting in-hospital mortality than the EuroSCORE. However, there was no statistically significant difference between the expected and observed mortality rates in either risk-scoring system. There is no consensus in the literature regarding which scoring system is more effective. More studies from different societies are needed.

Keywords: EuroSCORE II, open-heart surgery, preoperative evaluation

Main Points

- We have found that the European Cardiac Operative Risk Assessment System II (EuroSCORE II) risk classification system's predictive ability was lower (70-80%) than that of the the Society of Thoracic Surgery (STS) system (80-90%).
- The observed mortality rate was found to be high for both the EuroSCORE II and STS risk scoring systems when compared to the expected mortality rates.

Introduction

Despite advanced surgical and anaesthetic techniques, open-heart surgery has a mortality rate of up to 4% and carries the risk of both cardiac and non-cardiac complications. Studies have shown that cardiac complications (62.1%) are the leading cause of mortality. Other complications associated with mortality include respiratory complications (11.8%), infections (7.7%), and acute neurological injury (6%).[1]

Corresponding author: Erkam Saka, e-mail: erkamsaka92@gmail.com

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Although many risk scoring systems have been developed to determine the risk of mortality and morbidity in open-heart surgery, the most widely used are the European Cardiac Operative Risk Assessment System II (EuroSCORE II) and the Society of Thoracic Surgeons (STS) scoring systems.[2]

The original version of EuroSCORE was drawn from a European database of more than 19,000 cardiac surgery patients, most of whom had undergone cardiac surgery between 1995 and 1999. Approximately one-third of the patients included in this database had undergone coronary artery and valve surgeries.[3-5] EuroSCORE has gained wide acceptance since its publication and has been used extensively in the care of cardiac surgery patients, both to assess risk and to publicize improved operations.[6] However, over time, the necessity of making improvements in practice has emerged.[6,7] New variables, including creatinine clearance and liver function, were added to the EuroSCORE II risk analysis, and the relative weighting or impact of these variables was adjusted simultaneously.[4]

EuroSCORE II evaluates risk factors related to the patient, their cardiovascular status, and the surgery performed, and it produces a risk score. When the data are evaluated, risk scores are classified as low (score: 0-2), moderate (score: 3-5), and high (score >6).

The STS risk model was created using data from its own database. The most recent update was created in 2018 by studying 579,335 cases between 2011-2014 and 670,830 cases between 2014-2016.[8,9] Patients were assessed for 65 risk factors. This scoring system provides a risk score associated with various complications: operative mortality (all deaths occurring within 30 days of surgery), stroke (acute onset focal or global neurological dysfunction occurring within 24 hours), renal risks including risk, injury, failure, loss, end-stage renal disease, prolonged ventilation or reintubation (>24 hours), mediastinitis or deep sternal wound infection, reoperation due to bleeding or tamponade, major morbidity and mortality, prolonged postoperative hospital stay (PLOS) >14 days, and short PLOS <6 days.[9]

Both scoring systems were developed in developed countries such as Europe and the United States, and there are questions about whether they reflect the true mortality and morbidity risk for each society. In addition, there is an ongoing debate about which scoring system provides more accurate statistical results and is therefore more effective.[10-12] In our study, we aimed to determine which of the EuroSCORE II and STS risk scoring systems is superior in predicting the risk of postoperative mortality and morbidity in patients undergoing open-heart surgery by comparing them using a retrospective chart review method. We also aimed to determine their suitability for Turkish society.

Methods

All patients older than 18 years who underwent open-heart surgery [coronary artery bypass grafting (CABG), aortic valve replacement, mitral valve replacement or repair, or combined valve surgery with CABG] in the cardiovascular surgery operating room of Ege University Faculty of Medicine Hospital between 2019 and 2020 were included in our study. Our study is cross-sectional, and no sample selection method was used. After approval from the Ethics Committee of Ege University Faculty of Medicine Hospital (approval no.: 20-8T/17, date: 05.08.2020), the preoperative, intraoperative, and postoperative data of the patients who gave informed consent were retrospectively retrieved from the medical records.

Patients under 18 years of age, with missing data on surgery, requiring renal dialysis due to preoperative renal failure, undergoing off-pump heart surgery, intubated before surgery, undergoing emergency surgery, or undergoing surgery with inotropic support were excluded from the study.

In addition to patient demographics, preoperative risks such as unstable angina, previous myocardial infarction, acute myocardial infarction (<3 weeks), low left ventricular ejection fraction (<35%), diabetes mellitus, hypercholesterolemia, hypertension, peripheral vascular disease, cerebrovascular disease, respiratory disease, alcohol consumption, and smoking habits were recorded. Factor-determining data were recorded. Patients' EuroSCORE II and STS Risk Scoring System scores were calculated and recorded. Postoperative cardiac complications (myocardial infarction, atrial and ventricular arrhythmias, need for more than two inotropic agents or mechanical circulatory support, respiratory complications, cerebrovascular complications, postoperative renal dysfunction, gastrointestinal complications, sepsis, multiple organ failure, sternal infection, need for reoperation) were recorded. In addition, postoperative data such as mechanical ventilation, intensive care, hospital stay, and in-hospital mortality were retrospectively collected.

Statistical Analysis

Patient data collected in the study was analyzed using IBM Statistical Package for the Social Sciences (SPSS 23.0-IBM, NY, USA). Categorical frequencies and percentages for categorical data, as well as means and standard deviations for continuous data, are provided. Receiver operating characteristic (ROC) was used to determine the predictive value of risk scores for mortality. The analysis was performed. Effect of each patient's risk score on mortality logistic regression. It was calculated using analysis. For comparison between groups, the "Independent Samples t-test", "chi-squared test", "chi-square", or Fisher's exact test" were used for comparisons between groups. Results are considered statistically significant if the *P* value is less than 0.05.

Results

The study included 469 cases, 141 female (30.1%) and 328 (69.9%) male patients. Table 1 shows the distribution of the patient's demographic and clinical findings. The distribution of preoperative comorbidities of the patients is given in Table 2. The diagnosis distribution of the patients included in the study and the mortality rates according to diagnosis are shown in Table 3. The highest mortality rate was for CABG (n = 338; 72.1%) (Table 4).

When the risk scores of the patients were examined, the mean EuroSCORE II, and STS scores were 3.1±2.2 and 7.5±5.3, respectively (Table 5). According to the EuroSCORE II and STS scoring systems, 14.3% (n = 67); and 30.3% (n = 142) of the patients were in the high-risk category, respectively. When examined using the ROC curve analysis method (Figure 1), the area under the curve (AUC) for the EuroSCORE II risk scores was 78.3% with a cut-off value of 4. The AUC for the STS risk score was found to

Table 1. Demographic, and Clinical Characteristics of the Patients

Characteristic features		
Gender	Female, n (%)	141 (30.1)
	Male, n (%)	328 (69.9)
Age, years (mean ± SD)		63±11.2
Height, cm (mean ± SD)		170±9.1
Body weight, kg		76±11.6
Tobacco use, n (%) (mean ± SD)		267 (56.9)
Left ventricular EF%	>50, n (%)	299 (63.8)
	35-50, n (%)	145 (30.9)
	<35, n (%)	25 (5.3)
Duration of anaesthesia (mean ± SD)		364±58.4
Duration of surgery (mean ± SD)		332±57.4
Arotic cross-clamp time, min. (mean ± SD)		69±31.0
Duraion of CPB, min. (mean ± SD)		99±37
Duration of mechanical ventilation, hrs (mean ± SD)		0.47±2.7
ICU stay, days (mean ± SD)		2.1±3.8
Hospital stay, days (mean ± SD)		12.3±7.6

SD, standard deviation; EF, ejection fraction; CPB, cardiopulmonary bypass; ICU, intensive care unit

Table 2. Distribution of Patients' Preoperative Comorbidities

Preoperative comorbidities	n (%)
CAD	366 (78.2)
Hypertension	310 (66.1)
DM	193 (41.2)
Unstable angina	166 (35.5)
Hyperlipidemia	144 (30.7)
COPD	52 (11.1)
Arrhytmia	35 (7.5)
Acute MI <3 weeks	34 (7.2)
History of SVO	26 (5.6)
EF% <35	25 (5.3)
PAH	15 (3.2)
Carotid artery disease	14 (3)
History of MI	9 (1.9)
CRF	3 (0.6)

CAD, coronary artery disease; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; PAH, pulmonary arterial hypertension; MI, myocardial infarction; CRF, chronic renal failure

Table 3. Distribution of Patients According to Their Diagnoses

Diagnoses	n (%)	Exitus n (%)
CAD	339 (72.3)	14 (70.0)
MI	26 (5.5)	0 (0.0)
MS	15 (3.2)	0 (0.0)
AI	10 (2.1)	1 (5.0)
AS	22 (4.7)	1 (5.0)
MI+AI	21 (4.5)	0 (0.0)
MS+MI	2 (0.4)	0 (0.0)
CAD+AS	17 (3.6)	1 (5.0)
AS+AI	2 (0.4)	0 (0.0)
CAD+MI	12 (2.6)	2 (10.0)
MI+TI	2 (0.4)	1 (5.0)
CAD+AI	1 (0.2)	0 (0.0)
Total	469 (100.0)	20 (100.0)

CAD, coronary artery disease; MI, mitral insufficiency; AI, aortic insufficiency; AS, aortic stenosis; TI, tricuspid insufficiency; MS, mitral stenosis

Table 4. Distribution of Patients by Operation Types

Type of surgery*	n (%)	Exitus n (%)
CABG	338 (72.1)	14 (70.0)
MVR	46 (9.8)	0 (0.0)
AVR	34 (7.2)	2 (10.0)
AVR+CABG	17 (3.6)	1 (5.0)
MVR+CABG	13 (2.8)	2 (10.0)
MVR+AVR	19 (4.1)	0 (0.0)
MVR+TVR	2 (0.4)	1 (5.0)
Total	469 (100.0)	20 (100.0)

*CABG, coronary artery bypass grafting; MVR, mitral valve replacement; AVR, aortic valve replacement; TVR, tricuspid valve replacement

be 82.3% with a cut-off value of 8.45 (Table 6). In other words, the STS score showed a significantly higher accuracy in predicting mortality risk compared to the EuroSCORE II, in our study (AUC: 0.823-0.783, $P < 0.05$).

When the impact of EuroSCORE II and STS risk scores on predicting mortality was examined, it was determined that a one-unit increase in EuroSCORE II risk scores increased the mortality risk (odds ratio) by 1.5 [confidence interval (CI): 1.3-1.8] times ($P < 0.05$), and one-unit increase in STS

Table 5. Distribution of Risk Scores of the Patients

Characteristic features	
EuroSCORE II (3.1±2.2)	**n (%)**
Low	199 (42.4)
Intermediate	203 (43.3)
High	67 (14.3)
STS	7.5±5.3
Low	91 (19.4)
Intermediate	236 (50.3)
High	142 (30.3)
The risk of re-operation according to STS	
Low	447 (95.3)
Intermediate	22 (4.7)
Re-operation	30 (6.4)

STS, Society of Thoracic Surgeons Score; EuroSCORE II, European Cardiac Operative Risk Assessment System II

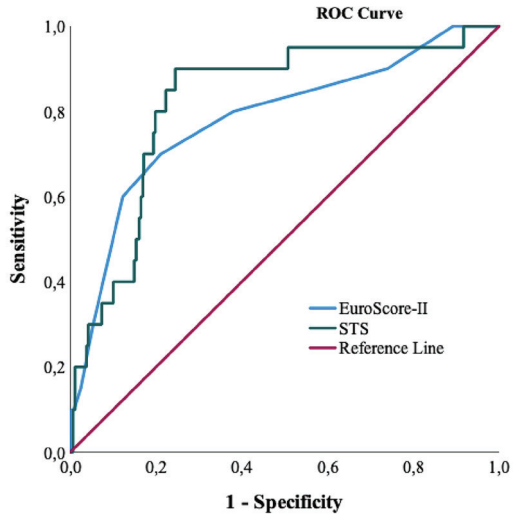

Figure 1. ROC curve sensitivity and 1 - specifity.

ROC, receiver operating characteristic; STS, Society of Thoracic Surgeons Score; EuroSCORE II, European Cardiac Operative Risk Assessment System II.

Table 6. ROC-curve Estimates of Survival Rates According to EuroSCORE II and STS Scoring Systems

Risk scoring system	AUC (CI 95%)	Cut-off value	*P* value	Sensitivity (%)	Specificity (%)	PPD (%)	NPD (%)
EuroSCORE II	0.783 (0.742-0.819)	>4.000	<0.001	70.0	78.8	12.8	98.3
STS	0.823 (0.785-0.856)	>8.450	<0.001	90.0	75.5	14.1	99.4

ROC, receiver operating characteristic; STS, Society of Thoracic Surgeons Score; AUC, area under curve; CI, confidence interval; PPD, positive predictive value; NPD, negative predictive value; EuroSCORE II, European Cardiac Operative Risk Assessment System II

Table 7. Evaluation of Observed and Expected Mortality Rates According to EuroSCORE II and STS Risk Scoring Systems

Risk scoring system	Risk group	Patients (n)	Observed mortality (n)	Observed mortality (%)	Expected mortality (%)	*P* value
EuroSCORE II	Low	199	3	1.5	1.3	1.000
	Intermediate	203	5	2.5	3.9	0.575
	High	67	12	17.9	14.2	0.635
STS	Low	91	1	1.1	2.1	1.000
	Intermediate	236	1	0.4	2.8	0.068
	High	142	18	12.7	8.1	0.170

STS, Society of Thoracic Surgeons Score; EuroSCORE II, European Cardiac Operative Risk Assessment System II

risk scores increased the mortality risk (odds ratio): by 1.12 (CI: 1.10-1.18) times ($P < 0.05$).

Observed and expected mortality rates according to the EuroSCORE II and STS risk scores of the patients are given in Table 7. A statistically significant relationship does not exist between the expected and observed mortality rates for each risk group ($P > 0.05$).

Discussion

The use of risk assessment methods before cardiovascular surgery makes it possible to predict postoperative mortality and complications, to better inform patients and their families about possible problems after surgery, and to take the necessary precautions.

The EuroSCORE II and STS scoring systems are two of the most widely used validated risk assessment methods.[13,14] EuroSCORE was originally developed in Europe and is widely used throughout the world.[15] The STS risk scoring system is more widely used in North America. Both risk scores are robust predictors of postoperative mortality. However, each society has a different socio-economic and cultural structure. Both scoring systems were developed in countries such as North America and Europe. There is ongoing debate about their suitability in developing societies and about which is more effective.

Mandel et al.,[16] reported in 2003 that both the EuroSCORE and STS scoring systems needed improvement, but they were indispensable to surgeons at the time of the study. Considering 9,248 patients evaluated with EuroSCORE in 35 cardiac centers in the People's Republic of China, the authors argued that this scoring system could not be used to predict outcomes after CABG surgery and that another scoring system was needed for their race.[17]

In a large-scale study conducted by Shales et al.[11] in India in 2021, it was concluded that EuroSCORE was pessimistic in predicting mortality, while the STS risk score underestimated mortality. When the discrimination power was examined, it was determined that both risk-scoring systems had equal and sufficient power.

In another study published in 2024 on 438 patients in Brazil, Wolf and Amato[18] determined the AUC value for the discrimination power of the STS risk scoring system as 0.646 and for EuroSCORE as 0.697, emphasizing that it did not provide optimum results. In a different study conducted in China by Gao et al.[12], it was determined that both the EuroSCORE and STS risk scoring systems had sufficient discrimination power. In this study, EuroSCORE II was found to be superior to the STS risk scoring system in terms of predicting mortality.[12]

Studies conducted in different centers in Türkiye have shown that the EuroSCORE II risk classification is reliable in predicting the risk of mortality associated with cardiovascular surgery.[19] Kandemir et al.[20] found the AUC-ROC curve to be 0.83 for the EuroSCORE II risk assessment system and 0.82 for the STS risk assessment system in cases of patients undergoing isolated CABG.[20] The sample size of the study by Kandemir et al.[20] was limited to 148 patients, which is smaller than that of our study.

In studies evaluating the mortality risk of transcatheter aortic valve replacement, Sedaghat et al.[21] demonstrated the predictive superiority of EuroSCORE II over the STS scoring system in a cohort of 206 patients, and similarly, Stähli et al.[22] demonstrated this in a cohort of 350 patients. However, Hemmann et al.,[23] reported superiority of STS in their study of 426 patients. A study comparing STS and EuroSCORE II scoring systems in Pakistan showed that EuroSCORE II was superior in isolated valve surgery cases, while STS provided better predictive data for coronary artery bypass and valve surgery.[24]

In our study, when we examined the EuroSCORE II and STS risk scoring systems using the ROC curve, the AUC value for the STS risk scoring system was 0.823 and the AUC value for the EuroSCORE was 0.783. While the EuroSCORE risk scoring system showed a moderate level of discrimination (70-80%), the STS system showed better discrimination (80-90%). The STS score was a better predictor than the EuroSCORE II.

When the observed and expected mortality rates of the patients in our study were examined according to the EuroSCORE II and STS risk scoring systems, the expected and observed mortality rates for the high-risk patient group were 14% and 17.9%, respectively, according to EuroSCORE II. In contrast, the respective percentages according to the STS scoring system were 8.1% and 12.7%. We attribute the different results of these two risk scoring systems, which were developed using large databases, to the fact that the countries where they were developed are ahead of Türkiye in terms of socioeconomic and medical facilities, although the differences were not statistically significant ($P > 0.05$). When Kandemir et al.[20] compared the two scoring systems in 148 patients undergoing CABG surgery, they found no statistically significant difference between the expected and actual mortality rates for both systems. More comprehensive and multicentre studies are needed for the Turkish community and other developing societies.

The adoption of a single system to assess mortality risk worldwide will be of great convenience to physicians. However, scoring systems differ in the way they assess some risks. Each system has its own shortcomings and limitations. Given that access to health care and medical facilities is not homogeneous worldwide, along with the genetic and

geographical differences of patients, more multicentre studies are needed to determine which risk scoring system is more useful and applicable in Turkish society. Furthermore, since EuroSCORE II was developed in 2012 and the STS risk scoring system in 2018, an updated evaluation is still needed regarding the applicability of these two risk scoring systems in light of the developing technology in cardiovascular surgery and anaesthesia. In conclusion, in our study, the STS score showed a better predictive performance than the EuroSCORE II.

Therefore, it is recommended to consider STS more in clinical use. Although there is no statistically significant difference between the observed and expected mortality rates, the STS risk scoring system and the EuroSCORE II scoring system still represent the best results in this field worldwide and should continue to be used until a more optimal risk scoring system is developed.

Study Limitations

Our study was conducted retrospectively and as a single-center study. Due to the retrospective nature of our study, patients had to be excluded from the study because of insufficient patient file data. Since our study was single-center, it may not reflect the situation nationwide. Our study focused on in-hospital mortality and did not evaluate either risk scoring system regarding 5-year survival. Additional studies are needed on this subject.

Conclusion

In our study, the STS risk scoring system showed a better predictive performance than EuroSCORE II. Therefore, it is recommended to consider the use of STS more frequently in clinical practice. In cardiac surgery, patients should be approached with a multidimensional strategy from the preoperative period. Additional precautions should be taken in the high-risk patient group using risk scores in collaboration with the surgical team.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Ege University Faculty of Medicine Hospital (approval no.: 20-8T/17, date: 05.08.2020).

Informed Consent: The preoperative, intraoperative, and postoperative data of the patients who gave informed consent were retrospectively retrieved from the medical records.

Footnotes

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

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

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Should I Change Anticoagulane in Veno-Venous ECMO?

Rabia Yılmaz, Murat Arslan, Deniz Özel Bilgi, Zafer Çukurova

University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Anaesthesiology and Reanimation Critical Care, İstanbul, Türkiye

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Abstract

Objective: Due to a lack of high-quality data to guide anticoagulation therapy in extracorporeal membrane oxygenation (ECMO) patients, there is significant variation in practice among centers. We aimed to investigate the safety, anticoagulation efficacy, and cost-effectiveness of using bivaluridine as a primary anticoagulant without unfractionated heparin (UFH) in ECMO patients.

Methods: The study population included patients undergoing Veno-Venous ECMO for acute respiratory distress syndrome. A total of 56 patients were evaluated, 25 were on UFH and 31 were on bivalirudin.

Results: There was no significant difference between the time to reach the target activated partial thromboplastin time (aPTT) interval [6 (3.5-11) UFH, 9 (4-19) bivalirudin, P=0.287]. There was no significant difference between the percentage of time spent in the target aPTT interval (61.48±14.72 UFH, 62.65±11.99 bivaluridine, P=0.745). The median amount of erythrocyte suspension replacement (12.04±8.01; 7.9±4.71; P=0.028) and the median amount of fresh frozen plasma replacement [4 (2-6); 1 (0-4); P=0.001] were higher in the UFH group than in the bivaluridine group. The cost was lower in the UFH group compared to the bivalirudin group [$38.1 (13.5-48.7); $463.7 (194.3-819.8); $P < 0.001$].

Conclusion: The use of bivaluridine as a primary anticoagulant does not lead to any decrease in anticoagulant efficacy.

Keywords: Anticoagulant, bivaluridin, bleeding, ECMO, thrombosis

Main Points

- The primary result of our study is that the use of bivaluridine as a primary anticoagulant in extracorporeal membrane oxygenation (ECMO) does not cause any decrease in anticoagulant effectiveness.
- In our study, evaluating the number of patients with thrombus and bleeding alongside the total amount of replaced blood products suggests that the use of bivaluridine is more suitable than the use of unfractionated heparin (UFH) in patients undergoing Veno-Venous ECMO. In the bivaluridine group, where all patients had coronavirus disease-2019 (COVID-19), no difference occurred in thrombotic events despite the prothrombotic effect of COVID-19.
- The total amount of replaced erythrocyte solution and total amount of fresh frozen plasma solution was statistically significantly higher in the UFH group than in the bivalirudin group.
- The cost of providing 15-day anticoagulation in the UFH group is considerably lower than in the bivalirudin group, which is an advantage for the use of UFH.

Introduction

Extracorporeal membrane oxygenation (ECMO) is an invasive and last-resort treatment for circulatory and respiratory failure. Lack of high-quality data to guide anticoagulation management in ECMO patients results in marked practice variability among centers. Systemic anticoagulation is still a necessity in ECMO patients to prevent the development of ECMO circuit thrombosis and deep vein thrombosis. Unfortunately, the ideal pharmacologic anticoagulant agent remains unclear. While the risk of thrombosis is reduced with all anticoagulant therapies, the risk of bleeding increases. Intermittent blood product replacement is required to replace the loss of blood cells and clotting factors due to both bleeding and extracorporeal circulation.

Corresponding author: Rabia Yılmaz, e-mail: drrabiayilmaz@gmail.com

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The widely used anticoagulant in ECMO patients is heparin, which contributes significantly to the development of ECMO with its discovery.[1-3] Unfractionated heparin (UFH) is a glycosaminoglycan that binds to antithrombin (AT) to produce a 1000-fold increase in AT inhibition of thrombin, factor Xa, factor XIIa, and factor IXa.[4] The half-life of UFH in adult patients is 60-90 minutes.[1] UFH has the advantages of being cheap, accessible, and having an antidote (protamine). In addition to binding to AT, UFH binds to circulating plasma proteins, endothelial cells, and macrophages, which changes the pharmacokinetics of the drug and makes dose adjustment difficult. Although heparin is the most commonly used in clinical applications, heparin resistance is a major concern in ECMO. It is defined as a situation where the ability of heparin to inhibit thrombin (factor IIa) and fibrin formation is reduced such that the correlation between dose and response is lost and increasing the heparin dosage will not result in the desired anticoagulation efect.[5] It may also cause heparin-induced thrombocytopenia (HIT). The development of HIT is more common in adults, and it is a potentially life-threatening immune-mediated prothrombotic disorder, especially in patients exposed to UFH multiple times.[6,7]

While UFH requires a sufficient level of AT in the blood to be effective, bivalirudin, a direct thrombin inhibitor, does not require AT to be effective. Bivalirudin has a shorter duration of action (25 minutes) than UFH. Bivalirudin is metabolized mainly by proteolytic enzymes, and 20% is renally excreted. Bivalirudin can be rapidly removed by continuous renal replacement therapy and therapeutic plasma exchange.[8] Bivalirudin has disadvantages such as the lack of specific antidote, higher cost, and limited ECMO experience.[1] When using bivalirudin, low-flow areas in the circuit (e.g., laboratory access lines or reperfusion cannulas) may clot and require frequent changes.[9] Bivalirudin binds directly to thrombin, independent of AT, making it safer in patients with low or fluctuating AT activity.

It also does not bind to other plasma proteins or cells and, as a result, does not cause day-to-day changes in serum chemistry or cell counts. This allows for a more predictable dosing regimen with less bleeding and a consistent anticoagulant effect compared to UNFH.

Finally, it does not cause immune-mediated thrombocytopenia, such as HIT.[10]

Based on the intense working conditions during the coronavirus disease-2019 (COVID-19) period and the need to reduce patient contact, we deemed it appropriate to switch to bivalirudin, which has been shown to have fewer complications and more consistent aPTT monitoring in studies.

The aim of this study was to evaluate the safety, efficacy, and cost-effectiveness of using bivalirudin instead of UFH as the primary anticoagulant in Veno-Venous (V-V) ECMO patients.

Methods

Study Design

This study was performed retrospectively on patients hospitalized in the adult intensive care unit of the University of Health Sciences Türkiye, İstanbul Training and Research Hospital between March 31, 2013 and April 31, 2022. This study is a before-after study. Anticoagulant changes were needed due to the increase in patient density, and ECMO-related complications in the COVID-19 pandemic.

The study was conducted in full accordance with local Good Clinical Practice (GCP) guidelines and current legislation. Ethical approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no.: 2022-07-09, date: 09.05.2022). Informed consent for the study was obtained from patients or their relatives.

Study Population and Data Collection

Patients aged >18 years who underwent V-V ECMO for acute respiratory distress syndrome (ARDS) were included in the study population.

Exclusion criteria were as follows: age <18 years, pregnant women, patients who died within the first 48 hours, patients who underwent ECMO for respiratory failure secondary to trauma, patients who were referred after ECMO support was started, patients who underwent ECMO for bridging purposes for lung transplantation, patients who used anticoagulants other than heparin or bivalirudin, patients who used both heparin and bivalirudin at different times (Table 1).

Table 1. The Study Flowchart

Therapeutic respiratory failure (n = 5)
Ex in 48 hours (n = 4)
<18 years old (n = 1)
Those transferred from external center bt ECMO (n = 1)
ECMO for bridging lung transplantation (n = 3)
Who use partly UFH and bivalurudin (n = 1)
Those using anticoagulants other than UFH or bivaluridin (n = 1)
Pregnancy (n = 1)

UFH, unfractionated heparin; ECMO, extracorporeal membrane oxygenation

Study data were obtained retrospectively from the "ImdSoft-Metavision/QlinICU Clinical Decision Support Software" system. Demographic data (gender, age, weight, height, BMI), comorbidity, history of antiaggregant drug use, clinical findings, complications, laboratory, and other data of patients, before and during ECMO, were obtained from the decision support system and recorded. Before ECMO procedure, Sequential Organ Failure Score (SOFA) and Charlson Comorbidity Index (CCI) of the patients were calculated using the available data (Supplementary File 1).

Study Protocol

The decision for ECMO supportive therapy was made by the ICU ECMO physician team [It was created according to the Extracorporeal Life Support Organization (ELSO) criteria in which our clinic is located].

Routinely, 50-100 IU kg UFH was administered for thrombosis prophylaxis 5 minutes before ECMO vascular cannulation. Routine therapeutic anticoagulant infusion was started after ECMO initiation. For monitoring, only activated partial thromboplastin clotting time (aPTT), which ELSO recommended, was used in all patients. We followed our patients with aPTT because activated clotting time is not licensed for monitoring DTIs, and the results vary depending on many factors, including platelet count and function, fibrinogen level, clotting factor deficiencies, temperature, hemodilution, and technical factors. The therapeutic range for the aPTT was set at 1.5 to 2.5 times the patient's pretherapy baseline aPTT. To achieve the target aPTT level, measurements were performed every 4-6 hours; the first measurement was calculated within 1 hour after the start of anticoagulant infusion. When the target aPTT range was exceeded, measurements were performed every 2 hours until the normal aPTT target range was achieved after dose adjustment. UFH infusion dose was started as 10-15 units kg^{-1} hr^{-1}. The UFH infusion dose was increased by 2-3 units kg^{-1} hr^{-1}. In cases where adequate aPTT response could not be obtained despite increasing the UFH infusion dose and 10-15 units kg^{-1} IV bolus administration, FFP (fresh frozen plasma) replacement was performed considering AT deficiency. Bivalirudin infusion dose was increased by 0.01 mg kg^{-1} hr^{-1}. In uncontrolled bleeding or bleeding requiring blood replacement, anticoagulant infusion was interrupted until the bleeding was controlled or until the target aPTT level was achieved, until the aPTT was >120 s. The control aPTT was checked every 2 hours. ECMO blood flow was adjusted according to extracorporeal circuit pressures and pre- and post-oxygenation O_2 content.

Doppler ultrasonography was used to diagnose vascular thrombosis events. Visible thrombi in the oxygenator, pump head, cannulas, or other extracorporeal areas were considered circuit thrombosis. Bleeding from pericanular, pulmonary (intratracheal), urinary tract, gastrointestinal tract, and other areas (mouth, nose, etc.) requiring blood replacement was recorded separately.

Hemogram, biochemistry, arterial blood gas, INR and fibrinogen laboratory tests were checked daily during ECMO. After the start of ECMO, appropriate blood product replacement was performed to regulate hemoglobin concentration (target >7-9 g dL^{-1}), platelet count (target >50 10^9 L, target >100 10^9 L if active bleeding), fibrinogen level (target >100 mg dL^{-1}, active bleeding, target >150 mg dL^{-1}) and INR (target <1.5, bleeding <3) levels. Random, pooled random, or apheresis platelet solutions were used to increase platelet levels (target >50x10^9 L if no active bleeding, target >100x10^9 L if active bleeding). However, for statistical evaluation, one apheresis platelet solution was considered as 8 random platelet solutions, and one pooled platelet solution was considered as 4 random platelet solutions. When calculating the cost, the total drug doses (daily average) given to the patient during the study period were calculated, including the costs of the blood products given. The cost of laboratory test results was not added. The costs of the study were calculated on the date the data were collected.

Endpoint

The primary outcome was the statistical difference between the groups receiving UFH and bivalirudin in the effectiveness of anticoagulation. The secondary outcome was the statistical difference in blood product replacement, cost-effectiveness between both groups, and 15-day thrombosis (vascular, ECMO circuit) development and bleeding development.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to determine if the data were normally distributed. Categorical variables are given as frequency (n) and percentage (%), while numerical variables are presented as mean ± standard deviation or median with interquartile range. The Independent Samples t-test was used to compare the quantitative variables with normal distribution between the two groups. The Mann-Whitney U test was used for comparisons between two groups of quantitative variables that did not show normal distribution. Pearson chi-square, continuity correction, or Fisher's exact test was used to compare categorical variables. Statistical significance was accepted as $P < 0.05$.

Results

A total of 56 patients, 25 receiving UFH and 31 receiving bivaluridine, were enrolled in our study. The demographic data, comorbidities, history of antiaggregant drug use, and SOFA organ failure score of all patients before ECMO are shown in Table 2. Demographic data and SOFA scores

indicating disease severity were similar. CCI was higher in the UFH group, which consisted of mixed ECMO patients, whereas all patients in the bivaluridine group had received ECMO for COVID-19 pneumonia.

In the UFH group, the time to reach the target aPTT interval was 6 hours and the percentage of time spent in the target aPTT interval up to 15 days was 61.48%. In the bivalirudin group, the time to reach the target aPTT interval was 9 hours and the percentage of time spent in the target aPTT interval up to 16 days was 62.65% (Table 3). The median total ECMO day was 16 (6.5-24) in the UFH group and 22 (14-42) in the bivaluridine group.

The number of patients with thrombosis, the number of patients with bleeding, the amount of blood product replacement, laboratory parameters, and cost data up to the first 15 days in both patient groups are given in Table 3. In the UFH group, thrombus was observed in ECMO circuit components in a total of 5 patients (20%), but no vascular thrombus was seen. In the bivalirudin group, thrombus was seen in 2 patients with an incidence rate of 6.5% (1 patient in both vascular and ECMO circuits, and 1 patient only in the ECMO circuit). The mean erythrocyte solution replacement (12.04±8.01; 7.9±4.71) and median FFP solution replacement [4 (2-6); 1 (0-4)] were higher in the UFH group than in the bivalirudin group. The mean minimum hemoglobin was lower in the UFH group than in the bivalirudin group (6.71±1.08; 7.68±0.69). The use of UFH for anticoagulation in V-V ECMO patients was much more advantageous in terms of cost-effectiveness compared to the use of bivalirudin ($P < 0.001$).

Table 2. Thrombosis, Bleeding, Blood Replacement, and Other Features in All Patients and Patient Groups

	All patients (n=56)	UFH (n=25)	Bivaluridin (n=31)	*P*
Time to aPTT target (hour)	7.5 (4-17.5)	6 (3.5-11)	9 (4-19)	0.287
Percentage of time at aPTT target	62.13±13.16	61.48±14.72	62.65±11.99	0.745
Thrombosis	7 (12.5%)	5 (20%)	2 (6.5%)	0.223
ECMO circuit thrombosis	7 (12.5%)	5 (20%)	2 (6.5%)	0.223
Vascular thrombosis	1 (1.8%)	0 (0%)	1 (3.2%)	1.00
Bleedings	38 (67.9%)	18 (72%)	20 (64.5%)	0.758
Pericanular bleeding	24 (42.9%)	14 (56%)	10 (32%)	0.13
Pulmoner bleeding	22 (39.3%)	11 (44%)	11 (35.5%)	0.709
Hematuria	2 (3.6%)	1 (4%)	1 (3.2%)	1.00
Melena or hematemesis	3 (5.4%)	3 (12%)	0 (0%)	0.083
Other bleedings	8 (14.3%)	3 (12%)	5 (16.11%)	0.720
Erythrocyte replacement	9.75±6.66	12.04±8.01	7.9±4.71	0.028*
FFP replacement	2 (0-5)	4 (2-6)	1 (0-4)	0.001**
Platelet replacement	0 (0-3.75)	0 (0-13)	0 (0-1)	0.393
Minimum hemoglobin (g dL^{-1})	7.25±1	6.71±1.08	7.68±0.69	<0.001**
Maximum INR	1.69 (1.49-2.43)	1.67 (1.34-2.34)	1.75 (1.55-2.46)	0.204
Minimum fibrinogen (mg dL^{-1})	255±102	256±97	255,48±107	0.982
Minimum platelet (10^9 L)	60 (38.5-88.25)	60 (35-86)	60 (38-95)	0.980
Anticoagulant cost ($)	141.9 (42.3-600.7)	38.1 (13.5-48.7)	463.7 (194.3-819.8)	<0.001**
CRRT	32 (57.1%)	16 (%64)	16 (51.6%)	0.510
Therapeutic plasma exchange	17 (30.4%)	5 (20%)	12 (38.7%)	0.222
Total ECMO days	19 (10.2-33.7)	16 (6.5-24)	22 (14-42)	0.01*
In-hospital mortality	44 (78.6%)	20 (80%)	24 (77.4%)	1.00

*$P < 0.05$, **$P < 0.01$.
aPTT, activated partial thromboplastin clotting time; FFP, fresh frozen plasma; CRRT, continue renal replacement treatment; INR, international normalized ratio.

Table 3. Demographic, Comorbidity and Other Data in All Patients and Patient Groups

	All patients (n=56)	UFH (n=25)	Bivaluridin (n=31)	*P*
Male gender	32 (57.1%)	13 (52%)	19 (61.3%)	0.67
Age	39.91±11.14	41.8±13.33	38.39±8.93	0.279
Body mass index	27.54 (25.42-31.15)	26.23 (24.7-31.2)	28 (26.1-30.1)	0.242
Comorbidity				
CCVD	15 (26.8%)	11 (44%)	4 (12.9%)	0.021*
Diabetes mellitus	10 (17.9%)	6 (24%)	4 (12.9%)	0.315
CLD	6 (10.7%)	2 (8%)	4 (12.9%)	0.682
CKD	1 (1.8%)	1 (4%)	0 (0%)	0.446
Other comorbidities	12 (21.4%)	6 (24%)	6 (19.4%)	0.925
CCI	0 (0-2)	1 (0-3)	0 (0-1)	0.002**
Antiaggregant use	4 (7.1%)	2 (8%)	2 (6.5%)	1.00
SOFA score	11.39±3.19	11.2±3.43	11.55±3.04	0.689

*$P < 0.05$, **$P < 0.01$.

UFH, unfractionated heparin; CCVH, chronic cardiovascular disease; CLD, chronic lung disease; CKD, chronic kidney disease; CCI, Charlson Comorbidity Index; SOFA, Sequential Organ Failure Assessment.

Discussion

Anticoagulation in ECMO remains a challenging issue. UFH has become the anticoagulant of choice in ECMO patients due to its ease of monitoring, low cost, and abundance of data supporting its use over other parenteral anticoagulants. Bivalirudin is seen as an anticoagulation agent that can be used to limit the potential side effects of UFH.[9]

The primary outcome of our study was anticoagulation effectiveness, and no significant difference was found between the two groups. There was no statistically significant difference between the UFH and bivalirudin groups in terms of the time to reach the target aPTT level [6 (3.5-11); 9 (4-19)] and the percentage of time elapsed in the target aPTT interval (61.48±14.72; 62.65±11.99). The fact that the patient population using bivaluridine had COVID-19-related ARDS may also have made aPTT regulation difficult. In a recent study, 18% of the UFH cohort switched to the bivalirudin cohort because the therapeutic range could not be reached or maintained, and 20% of 50 patients receiving UFH never reached therapeutic targets during ECMO treatment. Among those who reached the therapeutic range, patients in the UFH cohort required significantly more dose titration and spent less time within the therapeutic range compared with patients receiving bivalirudin.[11]

There are a limited number of retrospective studies with low case volume on the use of bivalirudin as a single anticoagulant in ECMO patients.[12-16] However, in these studies, the use of bivalirudin alone was found to be safer than UFH in terms of the development of thrombus and bleeding events. In our study, when the number of patients with thrombus and bleeding and also the total amount of replaced blood products are evaluated together, it may be said that the use of bivaluridine is more suitable than the use of UFH in patients undergoing V-V ECMO. In the bivaluridine group, where all patients had COVID-19, no difference was seen in thrombotic events despite the prothrombotic effect of COVID-19.

Patients on UFH and bivaluridine were compared in terms of the number of patients who developed thrombus or bleeding, and the amount of blood product replacement up to the first 15 days of V-V ECMO initiation. There was no statistically significant difference in the number of patients who developed thrombus in the UFH group [5 (20%); 2 (6.5%); *P*=0.223] or in the number of bleeding events requiring blood product replacement, including pericanular, pulmonary, urinary tract (hematuria), gastrointestinal tract (melena or hematemesis), and other sites (mouth, nose, intracranial, etc.). The total amount of replaced erythrocyte solution was statistically significantly higher in the UFH group than in the bivalirudin group (12.04±8.01, 7.9±4.71, *P*=0.028). The total amount of FFP solution replaced was also significantly higher in the UFH group than in the bivalirudin group [4 (2-6), 1 (0-4), *P*=0.001].

A decrease in all blood cells and coagulation factors due to extracorporeal destruction is expected with ECMO support therapy. In our study, we investigated whether there was any difference in terms of this decrease, in patients using UFH and bivalirudin. Although more erythrocyte replacement was performed in the UFH group, the

minimum hemoglobin levels were statistically significantly lower than in the bivalirudin group [6.71±1.08; 7.68±0.69; $P < 0.001$]. In this respect, the data were consistent. In the UFH group, lower values of minimum platelet count could have been expected due to the potential for HIT. However, the prevalence of HIT development in ECMO patients has been found to be between 0.5-5%.[17,18] Therefore, there may not have been a statistically significant difference between the minimum platelet levels between both groups.

The fact that the cost of providing 15-day anticoagulation in the UFH group is considerably lower than in the bivaluridine group is an advantage for the use of UFH. There are also studies showing that the total cost of bivalirudin use in ECMO patients is lower, but these studies include pediatric patients, and veno-arterial ECMO patients.[12,19] It is clear that the cost of UFH is considerably lower than that of bivalirudin, but the total dose requirement of bivalirudin is fewer in pediatric patients and patients with renal impairment. The number of aPTT measurements also requires additional costs, but this was not calculated in our study.

Since the median V-V ECMO duration of the UFH group was found to be statistically significantly shorter than that of the bivaluridine group, a comparison of the ECMO durations based on the median of 15 days in the UFH group was performed [16 (6.5-24), 22 (14-42), P=0.01]. The reason for the higher V-V ECMO duration in the bivaluridine group compared to the UFH group may be because of the introduction of bivaluridine infusion into our routine use since 2020. Additionally, the patient population consists of patients in whom V-V ECMO was started due to respiratory failure caused by COVID-19. As in our study, it is seen that in studies on COVID-19 patients who received ECMO, the total ECMO duration may last longer than in non-COVID patients.[20,21]

Trigonis et al.[17] showed no statistically significant difference regarding thrombus, bleeding and in-hospital mortality between COVID and non-COVID patients on ECMO.

Study Limitations

The main limitations of our study were that it was single-center and retrospective. Although blood product replacement was statistically significant in our study, erythrocyte and FFP transfusion is a practice that varies depending on the physician. Although it was retrospective, the use of the "ImdSoft-Metavision/QlinICU Clinical Decision Support Software" system for the collection of study data was a strength of the study. In addition, since bivalirudin entered our routine use as of 2020, the ECMO etiology of the group using bivalirudin consisted entirely of COVID-19 patients. In contrast, the etiology of ECMO in the UFH group consisted of H1N1 influenza, COVID-19, bacterial pneumonia, and causes secondary to sepsis.

Conclusion

The use of bivaluridine as a primary anticoagulant does not lead to any decrease in anticoagulant efficacy. The use of bivaluridine alone as the primary anticoagulant in patients on ECMO support therapy does not lead to any increase in the development of thrombus or bleeding events, but may lead to a significant reduction in the need for erythrocyte and FFP replacement.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (approval no.: 2022-07-09, date: 09.05.2022).

Informed Consent: Informed consent for the study was obtained from patients or their relatives.

Footnotes

Author Contributions: Surgical and Medical Practices - R.Y., M.A., Z.Ç.; Concept - Z.Ç.; Design - M.A., Z.Ç.; Data Collection and/or/Processing - D.Ö.B., Z.Ç.; Analysis and/or/Interpretation - R.Y., M.A., Z.Ç.; Literature Review - R.Y., D.Ö.B., Z.Ç.; Writing - R.Y. M.A., Z.Ç.

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

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Case Report
Regional Anaesthesia

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Stereotactic Brain Biopsy with Awake Craniotomy: Our Awake Craniotomy Experience on a Complicated Case and Mini Review

Can Ozan Yazar[1], Atakan Sezgi[1], Musa Zengin[1], Caner Ünlüer[2], Seyyid Furkan Kına[1], Emine Arık[1], Elif Şule Özdemir Sezgi[1], Jülide Ergil[1]

[1]University of Health Sciences Türkiye, Ankara Etlik City Hospital, Clinic of Anaesthesiology and Reanimation, Ankara, Türkiye
[2]University of Health Sciences Türkiye, Ankara Etlik City Hospital, Clinic of Neurosurgery, Ankara, Türkiye

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Abstract

Awake craniotomy (AC) is a surgical technique where the patient stays conscious and interacts with the surgical team throughout part or all of the brain operation. In this case report, a 71-year-old ASA-3 patient with multiple comorbidities scheduled for a stereotactic brain biopsy was treated using AC. Our experience with AC, combined with a scalp block, is described in this case. AC is a safe technique that can be applied in patients with partially impaired communication abilities and may be particularly beneficial for those with multiple chronic conditions.

Keywords: Anaesthesia management, awake craniotomy, brain biopsy, pain, regional anaesthesia

Main Points

- Awake craniotomy (AC) describes a surgical approach where the patient remains conscious for a portion or the entirety of the procedure, actively engaging with the surgical team.
- Thanks to the AC performed with the scalp block, the neurological examination of the patient can be performed during surgery. Thus, the success rate of the operation increases.
- Scalp block anaesthesia is a safe approach that can be preferably applied, especially in cases where general anaesthesia poses risks of cardiorespiratory depression during induction, maintenance, and emergence.

Introduction

Awake craniotomy (AC), which was first performed in 1886 by Sir Victor Horsley to localize epileptic foci, describes a surgical approach where the patient remains conscious for a portion or the entirety of the procedure, actively engaging with the surgical team.[1] Indications for AC include tumor removal near the motor and sensory cortex, deep brain stimulation (DBS) surgery, and surgical interventions such as ventriculostomy and thalamotomy. Relative contraindications include anxiety disorders, marked dysphagia, confusion or somnolence, substance or alcohol addiction, restless leg syndrome, chronic pain conditions, low pain tolerance, obstructive sleep apnea, morbid obesity, and uncontrolled coughing.

Corresponding author: Musa Zengin, e-mail: musazengin@gmail.com

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Conscious sedation is desired in AC. During AC, the patient must respond appropriately to verbal/tactile stimuli, maintain an unobstructed airway without intervention, and exhibit adequate ventilation.[2]

AC is often preferred over general anaesthesia due to the latter's undesirable side effects. In AC, the primary goals are to optimize interventions in target areas and prevent neurological deficits to enhance survival and maintain quality of life. Communication is crucial for the success of AC, and the inability to communicate can be considered a relative contraindication. Contrary to common knowledge, we successfully performed AC in this case on a patient with limited communication abilities and a Glasgow Glasgow Coma Scale (GCS) score of 12. Our primary objective was not cortical protection but rather shielding a high-risk patient with multiple comorbidities from the hemodynamic side effects of general anaesthesia. Through this case report, in which we share our AC experience, we aim to demonstrate that AC can be a viable alternative to general anaesthesia in similar patients.

Case Report

A 71-year-old male patient was scheduled for a stereotactic brain biopsy operation due to a mass in the brain. His anamnesis included hypertension, chronic renal failure, and Stevens-Johnson Syndrome. She had undergone a mass excision operation for brain 42 years ago. On physical examination, the GCS was evaluated as 12. The patient opened their eyes in response to verbal stimuli and localized pain. However, they had limited orientation and were confused. Preoperative hemodialysis was planned because of a creatinine of 2.42 mg dL^{-1}, a glomerular filtration rate below 30 mL min^{-1} 1.73 m^2 and potassium of 6.5 mmol L^{-1}. The patient was accepted as American Society of Anaesthesiologists (ASA) physical status scale 3 risk, and a postoperative intensive care unit was prepared. A preoperative 8-hour solid and liquid diet was administered. The patient was taken to the operating room table, and routine monitoring was performed (electrocardiography, non-invasive blood pressure measurement, peripheral pulse saturation measurement). Patient compliance was not adequate, and cooperation and orientation were limited. Dexmedetomidine at a dose of 1 µg kg^{-1} was given by intravenous infusion at 15 minutes for sedation before the scalp block. During dexmedetomidine administration, consciousness level, GCS, and hemodynamic parameters were closely monitored. No additional doses of dexmedetomidine were administered. For scalp block application, 40 mL of the drug was prepared as 36 mL of 0.5% bupivacaine and 4 mL of 1:200,000 epinephrine. Then, this local anaesthetic (LA) solution was divided into supratrochlear (2.5 mL), supraorbital (2.5 mL), zygomaticotemporal (2.5 mL), auriculotemporal (2.5 mL), greater (5 mL), and lesser occipital nerve (3 mL) regions bilaterally for scalp anaesthesia. After adequate anaesthesia was achieved, the Mayfield Pins head clamp was placed, and the brain was taken to computed tomography (CT) for brain mapping (Figure 1). After the CT scan, the patient returned to the operating theater and was placed on the table and given a supine position. A nasal cannula was fixed to the patient's cheek, and oxygen support was provided. Intravenous nicardipine infusion was initiated when the noninvasive blood pressure measured 30 minutes after the start of surgery was 167/98 mmHg. Blood pressure was controlled with a nicardipine infusion (below 140/90 mmHg). The surgical team drilled a hole in the cranial bone for stereotactic brain biopsy and sent the biopsy needle to the relevant cortical region (Figure 2). The patient was awake and had limited communication throughout the operation. No deterioration in neurological status was observed. Vital signs were stable. The operation was completed without complications. The patient, with stable vital signs and a GCS of 12, was transferred to the intensive care unit postoperatively.

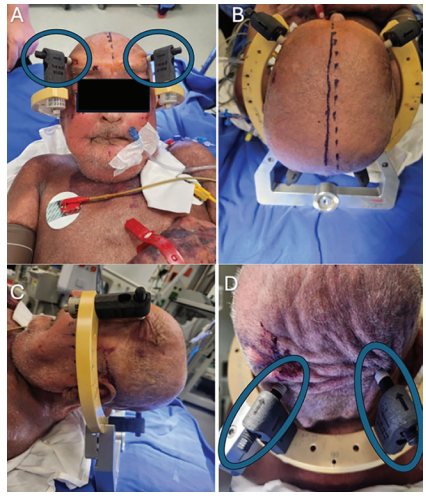

Figure 1. Mayfield Pins head clamp placement. A: Supine, B: Craniocaudal, C: Lateral, D: Posterior views. The placement of the pins is indicated by blue circles. The head was stabilized using a total of four pins.

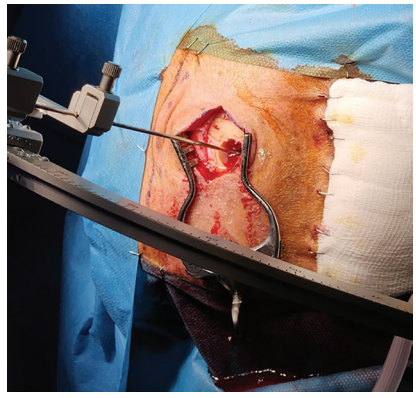

Figure 2. Stereotactic brain biopsy application.

Discussion

AC is commonly employed for procedures such as cranial mass excision, DBS, ventriculostomy, and thalamotomy. A stereotactic biopsy procedure with AC was performed on a patient with concomitant chronic diseases and limited communication skills. We tried to explain the scalp block application, the stages of AC, the points to be considered, complications, and management through this case.

Relative contraindications to AC include anxiety disorders, marked dysphagia, confusion, and somnolence. Patients with high comorbidity and poor communication skills are not preferred in the routine selection of AC cases. On the other hand, in some cases, AC may be preferred to avoid possible complications of GA for high-risk patients. In a case report by Heifets et al.,[3] it was demonstrated that a successful AC was performed in a high-risk patient diagnosed with Eisenmenger syndrome, avoiding the risks associated with GA. D'Antico et al.[4] also similarly preferred AC in a patient with cyanotic congenital heart disease who underwent emergency craniotomy due to cerebral abscess. The patient had a history of bacterial endocarditis, pulmonary hemorrhage, renal and splenic infarctions, transient ischemic attack, and recurrent supraventricular tachycardia. The cerebral abscess drainage was completed without complications under AC. Meng et al.[5] described successful anaesthetic management of AC in a patient with cardiomyopathy and low cardiac output. Sethi and Kapil[6] preferred to use AC in brain abscess surgery to maintain hemodynamic stability and prevent increased right-to-left shunting in a child with uncorrected tetralogy of Fallot. The procedure was performed without complications. The reason for choosing AC in our case was the possibility of not tolerating GA induction and even the risks of the waking period rather than conscious sedation. In our patient in the ASA 3 risk group, we completed AC surgery with a scalp block without complications.

Mapping of high-level cognitive functions is critical during AC surgery. Therefore, the depth of sedation should be at a level that does not disrupt cortical mapping. Therefore, sedative agents used in AC operations should be carefully selected. The standard protocol for sedation in AC remains the combination of propofol and remifentanil. Several studies have compared the combination of propofol and remifentanil or propofol alone with dexmedetomidine. A recent study comparing propofol-remifentanil with dexmedetomidine found that dexmedetomidine was associated with fewer intraoperative respiratory complications.[7] The primary disadvantage of the propofol-remifentanil combination is the potential for delirium during the awakening phase. A meta-analysis comparing dexmedetomidine with propofol alone demonstrated a strong association between dexmedetomidine use and surgical satisfaction.[8] Propofol has limitations, such as prolonged emergence time and interference with intraoperative brain mapping. Another study found that the dexmedetomidine group had a shorter wake-up time compared to the propofol group.[9] Although high doses of dexmedetomidine may cause bradycardia, such high doses are not required in AC. Additionally, dexmedetomidine may be beneficial for long-duration surgeries due to its suitability for prolonged sedation.[10] In epilepsy surgeries, the combination of propofol and dexmedetomidine has been compared with the combination of propofol and remifentanil during AC. No significant difference was found between the combination of propofol and dexmedetomidine and the combination of propofol and remifentanil groups in terms of patient satisfaction. However, the incidence of nausea, vomiting, and respiratory depression was statistically higher in the combination of propofol and remifentanil group.[11] The reasons for choosing dexmedetomidine for sedation in our case are that it is rapidly metabolized, has no residual effect, and does not impair the hemodynamic response in the intraoperative period.

The first stimulating parts of the procedure, such as the application of Mayfield Pins, skin incision, and bone flap removal, are painful. After sedation and before securing the head with Mayfield pins, a scalp block is typically administered bilaterally to ensure effective analgesia during AC. The primary advantage of the scalp block is that most of the nerves supplying the scalp are superficial terminal sensory branches, resulting in a lower risk of nerve damage compared to deeper motor nerves. Six nerves (supratrochlear, supraorbital, auriculotemporal, temporozygomatic, greater occipital and lesser occipital nerves) (Figure 3) are blocked bilaterally for a complete scalp block. Approximately 40 mL of LA is required. To extend the duration of action and minimize systemic absorption, the LA should be combined with 1:200,000 epinephrine. If additional dosing is necessary, one-quarter of the initial dose can be administered 2-4 hours after the first dose, half of the initial dose 4-8 hours later, and a full dose can be repeated 8 hours after the initial administration.[12] A scalp block can also include a great auricular nerve block. The great auricular nerve, the largest ascending branch of the cervical plexus, arises from the C2 and C3 spinal nerves. Its posterior branch provides sensory innervation to the mastoid process and the skin behind the auricle.

Anaesthesia during AC is primarily achieved through scalp nerve blocks with LA agents. Bupivacaine is one of these agents. Bupivacaine with epinephrine at a 0.5% concentration has an onset of action of 15-30 minutes, while the anaesthetic duration ranges from 5 to 15 hours. The metabolism of LAs varies depending on whether they are ester- or amide-based. Ester LAs are metabolized by plasma cholinesterase, whereas amide LAs are metabolized by hepatic enzymes. In the presence of hepatic diseases, the

dosage of amide LAs, such as bupivacaine, should be reduced for repeated or continuous administration. Bupivacaine is not metabolized by the kidneys; however, in conditions that reduce hepatic blood flow, such as renal or cardiac disease, the clearance of LAs may decrease, leading to a prolonged duration of action.[13] LA use should be carefully considered in similar patients. In our patient, due to the presence of renal failure, the administered dose was kept below the maximum allowable dose.

Positioning the AC patient is an important step before handing it over to the surgical team. The most commonly preferred positions are supine, semi-sitting, and lateral positions. It is important to give the sniffing position during the fixation of the head to the head clamps to facilitate access to the airway. When positioning the head, care should be taken not to over-curl the neck to reduce pressure on the neck vessels.[12] In addition to facilitating access to the surgical field, the semi-lateral position increases face-to-face interaction in the awake patient while facing the anaesthesia workstation and alleviates the respiratory workload, especially in obese patients. Especially in epilepsy surgery, patient communication facilitates the observation of the anaesthetist in terms of seizure monitoring. In our case, the patient was given a supine position due to the location of the surgical procedure, the neck was relieved, and easy airway access was provided.

Undesirable conditions such as snoring and upper airway obstruction may occur in patients undergoing AC. For this reason, continuous positive pressure can be applied with the anaesthesia circuit to reduce vibration in the surgical field. In a randomized controlled study of 65 patients undergoing AC, patients were given humidified high-flow nasal cannula (HFNC) airway management, and the safety and efficacy of this method were evaluated. Patients using HFNC with an oxygen flow rate of 40 or 60 L min showed less airway obstruction and injuries.[14] In our case, we provided oxygen support with a nasal cannula and did not observe any complications.

In cranial surgeries, urinary catheterization is generally necessary in terms of urine output and fluid balance monitoring. However, in some cases, surgery can be performed without urinary catheterization. In a study by Ozlu et al.,[15] a total of 26 patients who underwent DBS and an AC procedure did not receive a urinary catheter. Foley catheter applications are not frequently preferred because the operation time is short and the patient is awake. However, it may be considered in operations lasting longer than 4 hours and intraoperative mannitol administration.[12] Intraurethral lidocaine administration may be preferred for catheter insertion and the discomfort that may occur afterward. We did not use a urinary catheter in our case because the estimated surgical time was less than 4 hours.

During AC, potential complications include seizures, hypertension, nausea-vomiting, air embolism, and hyponatremia. Nausea has been reported in approximately 4% to 18.4% of cases and may be precipitated by surgical stimulation, particularly during manipulation of the dura or cerebral vessels, as well as by the use of opioids or the presence of anxiety.[16] Vomiting is rare and managed with antiemetics like ondansetron (4 mg); dexmedetomidine and propofol offer additional antiemetic benefits. Hypertension is treated with vasodilators or beta-blockers, with esmolol shown to provide intraoperative hemodynamic stability.[16] Airway obstruction due to hypoventilation or hypercarbia is managed by reducing sedation, encouraging deep breaths, or providing mask ventilation; uncooperative patients may require general anaesthesia. Elevating the head 30° helps prevent venous congestion, while hyperosmotic therapy and normocarbic ventilation support respiratory function. Seizures, occurring in 2-20% of cases during brain mapping, are usually brief and self-limiting. Initial treatment involves brain irrigation with cold saline; if needed, propofol (10-20 mg IV) or midazolam (1-2 mg IV) can be used, with propofol preferred for electrocorticography.[12] Levetiracetam (500 mg IV) may be given prophylactically in patients not on antiepileptic drugs. The most critical risk in the sitting position is venous

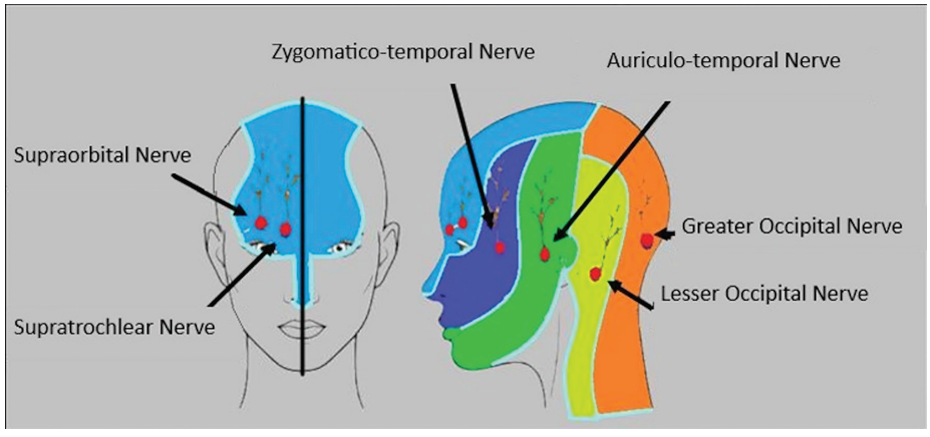

Figure 3. Sensory innervation of the skin of the head and neck.

air embolism due to negative intravascular pressure.[12] This can lead to pulmonary vasoconstriction, decreased $EtCO_2$, increased $PaCO_2$, hypoxemia, arrhythmias, and chest pain. As embolism severity increases, hypotension and tachycardia may occur due to increased right heart strain.[17] Treatment includes Trendelenburg positioning, aspiration via central venous catheter, and vasopressors such as ephedrine, dobutamine, or norepinephrine.

In AC, procedures associated with general anaesthesia, such as endotracheal intubation and mechanical ventilation, can be avoided, leading to reduced hemodynamic and physiological disturbances. Additionally, compared to craniotomy under GA, postoperative pain, nausea, and vomiting are less frequently observed. Studies have compared AC with GA for craniotomy. Both applications have their advantages and disadvantages (Table 1).[18] One study supported the superiority of AC in terms of neurological outcomes and resection quality in supratentorial mass excisions.[19] A recent meta-analysis examining AC and GA in glioblastoma surgeries found significant evidence favoring AC, with a notably longer median postoperative survival.[20] Consequently, hypotension and the need for vasopressors are less common compared to general anaesthesia. Moreover, AC is associated with a shorter hospital stay, potentially reducing the risks of hospital-acquired infections and deep vein thrombosis.

Table 1. Comparison of General Anaesthesia and Awake Craniotomy

Parameters	Awake craniotomy (AC)	General anaesthesia (GA)
Airway management	Nasal cannula	Endotracheal intubation/Laringeal mask airway
Haemodynamic effects	Comparatively more stable	There is a risk of cardiorespiratory depression
Postoperative complications (nausea, pain, hypertension, tachycardia)	Less compared to GA	More often
Advantages	- Better protection of intraoperative motor and speech functions. - Reduced hospital stay and therefore reduced risk of hospital-acquired infections. - Reduction of neurological deficits after surgery. - Less need for vasopressors.	- Intraoperative safe airway management due to endotracheal intubation/LMA. - To be able to perform the necessary interventional procedures for bleeding management, fluid volume balance monitoring, arterial blood pressure monitoring.
Disadvantages	- Difficult intraoperative airway management. - Possibility of side effects due to local anaesthetics (LAST).	- Inability to perform an intraoperative examination. - Greater risk of neurological deficits. - Adverse effects on immunity associated with general anaesthesia. - The risk of hypotension and the need for vasopressors are greater after induction.

AC, awake craniotomy; GA, general anaesthesia; LAST, local anaesthesia systemic toxicity; LMA, laryngeal mask airway.

Study Limitations

This case report has some limitations. Firstly, our report consists of a single case, and generalizations to the whole population cannot be made. Therefore, randomized controlled trials are needed in this regard. Secondly, after the scalp block, only the surgical area was checked, and no more detailed dermatomal examination was performed. Thirdly, our patient could not be monitored with a BIS monitor. Although we prefer to measure the depth of sedation with the Ramsey Sedation Scale, BIS monitoring gives more quantitative values.

Conclusion

In conclusion, it has been demonstrated that AC can be a viable method not only for functional cortical mapping but also for fragile patients with high comorbidities, limited communication, and low GCS. Scalp block anaesthesia is a safe approach, particularly in cases where GA poses a risk of cardiorespiratory depression during induction, maintenance, and recovery.

Ethics

Informed Consent: Written consent has been obtained from the patient indicating his approval for publication.

Footnotes

Author Contributions: Concept - C.O.Y., A.S., M.Z., J.E.; Design - C.O.Y., A.S., M.Z., C.Ü.; Supervision - M.Z., S.F.K., E.A., J.E.; Analysis and/or/Interpretation - A.S., M.Z., S.F.K., E.A., Literature Review - C.O.Y., A.S., M.Z., C.Ü., S.F.K., E.Ş.Ö.S.; Writing - C.O.Y., A.S., M.Z., C.Ü., S.F.K., E.Ş.Ö.S.

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Letter to the Editor

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Exploring the Hidden Therapeutic Potential of Local Anaesthetics: Antioxidant and Antimicrobial Effects

Berrin Günaydın

Gazi University Faculty of Medicine, Department of Anaesthesiology and Reanimation, Ankara, Türkiye

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Keywords: Antimicrobial, antioxidant, articaine, bupivacaine, levobupivacaine, lidocaine, local anaesthetics, pharmacology, ropivacaine

Dear editor,

Nearly two decades ago, Borgeat[1] reviewed the non-anaesthetic actions of local anaesthetics. While these drugs have been primarily known to block sodium channels for providing anaesthetic/analgesic and antiarrhythmic effects, researchers have also explored several other potential therapeutic uses, including enhanced bowel function after surgery or trauma, protection of the central nervous system, management of chronic neuropathic pain, and possibly reducing cancer recurrence.[1]

There is increasing evidence that local anaesthetics may possess antioxidant properties and interact with reactive oxygen species (ROS). ROS, including peroxyl radicals, hydroxyl radicals, hydrogen peroxide (H_2O_2), and superoxide anions (O_2-), are continuously produced in biological systems as byproducts of mitochondrial metabolism or in response to external stimuli. In healthy cells, ROS are present in low concentrations and play critical roles in defence mechanisms and cellular signalling pathways. These ROS levels are tightly regulated by antioxidant systems, which either directly scavenge the radicals or indirectly modulate their activity. When this balance is disrupted, often due to dysfunction in the antioxidant system, excessive free radical production leads to oxidative stress resulting in cellular damage that includes deoxyribonucleic acid oxidation, lipid peroxidation, protein and enzyme inactivation, and promotion of tumour growth or inflammation.[2-4]

Early studies demonstrated that some local anaesthetics could positively influence the antioxidant system, mainly through their ability to scavenge free radicals generated either by stimulated human leukocytes or by cell-free systems using luminol chemiluminescence *in vitro*. Based on lidocaine's known ability to scavenge the O_2- anion, further study results showed that prilocaine interacted with O_2-, hypochlorous acid (HOCl), and H_2O_2, while articaine reacted with O_2-, HOCl, and peroxynitrite.[2,3] More recently, it was shown that lidocaine exhibits the highest free radical scavenging activity in aqueous environments, but not in lipophilic environments, such as cellular membranes, myelin sheaths, and adipose tissue. This highlights that the scavenging activity of local anaesthetics is influenced by the lipophilicity of the surrounding environment.[4]

Another significant non-anaesthetic effect of local anaesthetics is their antimicrobial activity. Since their introduction as a cornerstone of pain management, numerous studies have explored the antimicrobial properties of local anaesthetics. For example, both bupivacaine and lidocaine have demonstrated bacteriostatic, bactericidal, fungistatic, and fungicidal activities against a wide range of microorganisms.[5] More recently, three long-acting local anaesthetics-bupivacaine, levobupivacaine, and ropivacaine-demonstrated antifungal activity at both 37 °C and 24 °C. Notably, levobupivacaine (0.75%) and ropivacaine (1%) exhibited antibacterial effects at 37 °C, but not at 24 °C.[5] These findings suggest that the antimicrobial activity of local anaesthetics may vary with temperature, which warrants further investigation.

Corresponding author: Berrin Gunaydın, MD, PhD (Pharmacology), e-mail: gunaydin@gazi.edu.tr

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Given these emerging therapeutic possibilities, local anaesthetics hold significant promise beyond their conventional use in anaesthesia. The antioxidant activity of local anaesthetics may support their potential use *in vivo*, particularly in conditions linked to free radical damage or antimicrobial effects in regional anaesthesia practice. As research continues to uncover these properties, these drugs are likely to play a larger role in the management of various conditions.

Acknowledgment

I would like to express my sincere gratitude to the late Prof. Kadir Kaya for his invaluable contributions to the design and development of the research on the antimicrobial effects of local anaesthetics (lidocaine and articaine) published in Turk J Med Sci by him (available at https://journals.tubitak.gov.tr/medical/vol37/iss1/3/). It was his visionary project that has continued to inspire and guide my efforts. His dedication and expertise in the field will always be remembered.

Footnotes

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