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Clinical Considerations and Outcomes of Robotic Urologic Surgery in Obese Patients

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Abstract

Obesity is associated with many significant physiological changes. These considerations are important to surgery, especially in urological procedures. Obese patients often undergo surgical procedures and are at higher risk of complications. This investigation reviews physiological and anaesthesia considerations for obese and morbidly obese patients. In addition, urological surgeries and procedures should be considered for these higher risk patients. Clinical anaesthesiologists must use detailed assessment and, when appropriate, consultation in developing safe anaesthesia plans for these patients. Newer technologies have improved safety related to airway management, advanced airway devices, and regional anaesthesia with ultrasound-guided nerve blocks, which can reduce the need for opioids postoperatively. Recent developments in drug and monitoring technologies have also been developed and can be effective for obese and morbidly obese patients undergoing urological procedures and perioperative surgery, thus improving the likelihood of safety in this higher risk population.

Keywords: Anaesthesia, airway, complications, obese, urology surgery

Main Points

- Robotic pelvic surgery in obese patients presents with unique challenges.
- Specific ventilator settings and adjusting inspiration to expiration ratio, respiratory rate, and tidal volume, and utilizing pressure control ventilation can all help optimize respiratory function and prevent complications.
- Regarding cardiovascular Intraoperative strategies focus on maintaining adequate volume status and ensuring adequate mean arterial pressure (MAP).
- With respect to cardiovascular changes, intraoperative strategies focus on maintaining adequate volume status and ensuring adequate MAP

Introduction

Robotic surgery is currently the most commonly adopted approach in minimally invasive urologic conditions. Obese patients are at a higher risk during surgical procedures, and robotic surgery may add more risk. Over the past 20 years, obesity in the United States (US) has increased tremendously. Based on the current available Centers for Disease Control and Prevention data, the prevalence of obesity in the US was 42.4% in 2017-2018. It appears that from 1999-2000 through 2017-2018, the prevalence increased from 30.5% to 42.4%. Concomitantly, the prevalence of severe obesity increased from 4.7% to 9.2%.[1] The World Health Organization describes obesity based on body mass index (BMI) and includes 3 grades: Grade I (BMI between 30 and 34.9 kg m^{2-1}), Grade II (BMI between 35 kg m^{2-1} and 39.9 kg m^{2-1}), and Grade III (BMI of 40 kg m^{2-1} and higher). Grade III represents "morbid" obesity.[2] Robotic surgery in obese patients represents a real challenge to the urologic surgeon and anaesthesiologist.

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Robotic pelvic surgery (prostate cancer, bladder cancer) puts the patient at risk for potential deep venous thrombosis (DVT), pulmonary embolus (PE), and increased intracranial pressure (ICP). Obesity adds more complexity to the surgical procedure, resulting in prolonged operative time related to challenges in patient positioning, excessive intra-abdominal fat, delicate surgical planes, and sometimes pelvic lipomatosis that may narrow the robotic surgical field of view.[3,4] Morbid obesity may prolong the operative time due to difficulty reaching the pelvis with the robotic arms, in addition to special considerations with trocar selection.[5] Prolonged operative time would expose the patient to more hemodynamic changes and anaesthetic considerations. Robotic kidney surgery (for kidney cancer and other benign renal conditions) has also been studied by Kott et al.[6] where an increased BMI above 30 kg m^{2-1} has been shown to contribute to post-operative complications (POC) in patients undergoing robotic assisted partial nephrectomy. Therefore, the present investigation aimed to analyze the most current anaesthetic and surgical considerations of robotic urologic surgery in morbidly obese patients. We analyzed a recent literature to attempt to recognize any common findings regarding patient BMI and surgical outcomes and/or complications.

Methodology

A literature review was performed on previously published manuscripts on robotic urologic surgery in obese patients. This included evaluation, anaesthetic considerations, and expected hemodynamic changes that may occur. The databases searched in this investigation included PubMed and Google Scholar, and 53 published manuscripts were reviewed.

Clinical and Research Consequences

Current available robotic surgeries in urology

Robotic surgery in urology was introduced in the early 2000s. Robotic prostatectomy, more commonly known as robotic-assisted laparoscopic prostatectomy (RALP), was performed in the US in 2000. Since then, almost every open urologic surgery has been performed robotically. Robotic surgery platforms have also evolved from the multi-port DaVinci S, Si, and Xi to the most recent single-port SP platform. Robotic surgery is currently available for prostate, kidney, bladder, and other urologic pathologies (Table 1).

Hemodynamic changes that occur during robotic surgery in obese individuals compared with non-obese individuals

Robotic assisted surgery offers many potential benefits for obese patients, including reduced fasciotomy size, decreased postoperative pain, and reduced postoperative wound complications, which are more prevalent in obese patients than in non-obese patients.[7] However, this type of surgery also causes physiological stresses on the body that can be even more dramatic in obese patients. Obesity significantly alters the physiology of different organ systems, including the cardiovascular and pulmonary systems. These complex changes are especially relevant considerations when planning and performing robotic surgery because the physiologic burden caused by the surgery can cause further decompensation in this patient population.[8] At baseline, obese patients have increased cardiac work because of increases in stroke volume and cardiac output (CO) and decreases in vascular resistance. These changes lead to hypertension and ventricular hypertrophy, which can eventually lead to congestive heart failure. These changes

Table 1. Most Performed Robotic Urologic Procedures (Using the Multi-port DaVinci Xi Platform)

Robotic procedures	Urologic pathology	Patient positioning
RALP	Prostate cancer	Trendelenburg
Robotic simple prostatectomy	BPH	Trendelenburg
Robotic radical cystectomy	Bladder cancer	Trendelenburg
Robotic radical nephrectomy	Kidney cancer	Lateral decubitus
Robotic partial nephrectomy	Kidney cancer	Lateral decubitus
Robotic pyeloplasty	UPJO	Lateral decubitus
Robotic nephro-ureterectomy	Kidney Cancer (for UCC urothelial cell carcinoma)	Lateral decubitus then Trendelenburg for the distal ureteral part and bladder cuff excision
Robotic distal ureterectomy	Distal ureteral cancer	Trendelenburg
Robotic radical cystectomy	Invasive bladder cancer	Trendelenburg
Robotic RPLND	Testicular cancer, etc	
Robotic ureteral re-implant	Ureteral stricture, etc	Trendelenburg

Robotic assisted laparoscopic prostatectomy is indicated in the table above as RALP. Benign prostate hypertrophy is abbreviated BPH in the table above. Urothelial cell carcinoma is abbreviated UCC in the table above

also cause increased pulmonary artery pressure and worsen cardiac dysfunction. Obesity causes changes in pulmonary physiology that follow a restrictive pattern. Elevated intra-abdominal pressure due to excess weight can reduce lung and chest wall compliance. It also causes lower functional residual capacity (FRC) and expiratory reserve volumes (ERVs), which can cause rapid oxygen desaturation and increase the likelihood of atelectasis.[9]

Abdominal insufflation is required to facilitate the movement of surgical instruments; however, the resultant pneumoperitoneum significantly alters hemodynamic properties.[7] Pneumoperitoneum increases heart rate, systemic vascular resistance, and mean arterial pressure (MAP). This is likely due to compression of the major abdominal vessels, and smaller mesenteric vessels may also show changes in flow. Compression of vessels can also increase the likelihood of venous stasis and thromboembolism, for which obesity is also an independent risk factor. Increased baseline intra-abdominal pressure in the obese population can exacerbate these changes. Pneumoperitoneum also decreases respiratory function due to cranial displacement of the diaphragm, decreased FRC and ERV, and increased atelectasis and airway resistance, all of which are already present in obese individuals.[10,11] Other complications can arise because the carbon dioxide used to insufflate the abdomen can be absorbed, leading to increased partial pressure of carbon dioxide. In non-obese patients without comorbid lung disease, this increase can be normalized by increasing minute ventilation and decreasing intraperitoneal CO_2 pressure to prevent hypercapnia. However, lung pathology caused by obesity can prevent these compensatory mechanisms, leading to respiratory acidosis and hypercapnia.[7,12] Hypercapnia can cause cardiac arrhythmias, pulmonary vasoconstriction, and autonomic nervous system stimulation, resulting in tachycardia and increased cardiac contractility. However, concomitant acidosis can depress myocardial contractility.[13]

Steep Trendelenburg positioning (STP) provides favorable surgical exposure in lower abdominal and pelvic robotic surgeries and is therefore strongly recommended. However, this position causes significant haemodynamic changes and is especially unfavorable for obese patients.[9] This position further increases the compression of the diaphragm already present at baseline in obese individuals and is increased by intra-abdominal insufflation. Therefore, this position further increases the volume of atelectasis and the risk of hypoxemia.[7] Additionally, due to the 30-40 degree angle at which patients are at during this positioning, significant decreases in both stroke volume and CO can be expected.[14] Additional risks for STP include nerve injury, especially in the brachial plexus due to stretch injury, excess pressure on the head may lead to cervical spine injury, and prolonged lithotomy positioning increases patients' risk for compartment syndrome, rhabdomyolysis, and increased intraocular and/or ICP[9,15].

Risks of Robotic Pelvic Surgery in Obese Patients

Risks for obese patients undergoing robotic pelvic surgery

An individual is defined as obese when the BMI is >30 kg m^{2-1} and morbidly obese when BMI is >35 kg m^{2-1}. [5] For obese patients, robotic pelvic surgery poses several risks that involve physiological aspects of the cardiovascular and pulmonary systems, central nervous system, and special positioning of the patient.

Risks related to the cardiovascular system include decreased mesenteric blood flow, elevated MAP, elevated central venous pressure (CVP), decreased CO, and greater blood loss[11]. RAL procedures require STP, a method in which the patient's head is slightly angled down, and abdominal insufflation with carbon dioxide to adequately visualize the abdominal contents adequately[9]. These two techniques increase intrabdominal pressure and compress abdominal arteries, leading to decreased mesenteric flow, increased systemic vascular resistance, and increased MAP, which can result in small decreases in CO.[9] When combined with pneumoperitoneum, which adds cephalad pressure by abdominal contents pressing on the diaphragm, STP increases intrathoracic pressure, leading to increased CVP.[9] Lindner et al.[16] observed greater blood loss in obese patients than in non-obese patients during open radical retropubic prostatectomy.

Risks related to the pulmonary system include hypercapnia, atelectasis, hypoxia, hypoxemia, hypoventilation, apnea, respiratory distress, decreased lung compliance (LC), and reduced FRC and ERV.[9] Hypercapnia can develop from the use of pneumoperitoneum with carbon dioxide via the absorption of gas from the insufflated abdomen,[9] especially in the presence of a ventilation/perfusion (V/Q) mismatch or underlying lung pathology, such as chronic obstructive pulmonary disease, which would inhibit adequate compensatory changes.[9] Additionally, because increasing evidence supports lower tidal volumes for ventilation in obese patients, a higher fraction of inspired air may be needed to maintain oxygenation, therefore increasing the risk of atelectasis leading to hypoxia and further exacerbating hypercapnia.[9] pneumoperitoneum can cause atelectasis, which increases the volume of atelectasis in dependent lung regions.[11] Obese patients are at increased risk for hypoxemia and may demonstrate arterial oxygen insufficiency compared with non-obese patients, which can be due to increased venous admixture and pulmonary shunt, as seen by the increased alveolar to arterial oxygen gradient of partial pressure of oxygen.[17] Trendelenburg positioning may exacerbate this effect.[18]

In addition, obese patients commonly suffer from obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS), which greatly increase the risk of pulmonary complications in the postoperative period. Even mild cases of OSA threaten serious complications when combined with narcotics and general anaesthesia.[4,19] Grieco et al.[18] warn that intraoperative pressure control ventilation (PCV) could lead to severe alveolar hypoventilation in patients with airway opening pressures greater than 15 cm H_2O. Wiltz et al.[3] reported a significantly higher incidence of aborted procedures in obese patients due to respiratory distress. A risk of decreased LC may be observed with pneumoperitoneum and prolonged Trendelenburg positioning at a 40-degree to 45-degree angle in extremely obese patients.[10,20] Decreased FRC and ERV can have both intraoperative and postoperative consequences. If the FRC is depressed below the closing capacity, patients can experience airway closure and subsequent hypoxemia, leading to rapid desaturation with hypoventilation, apnea, or respiratory failure. These effects are amplified by STP, pneumoperitoneum, and general anaesthesia.[9,10] Risks involving the airway include subcutaneous emphysema from pneumoperitoneum, airway edema from fluid administration and prolonged Trendelenburg positioning, respiratory depression, airway closure, desaturation events, need for reintubation, and aspiration.[4,9,20] Patients with a history of OSA or OHS are at increased risk of respiratory depression both intraoperatively and postoperatively related to commonly used intraoperative agents, including sedatives, neuromuscular blockade agents, analgesics, and residual anaesthesia.[9] The risk of airway closure is increased in patients with STP.[17] Grieco et al.[18] reported severe expiratory flow limitation and airway closure in 22% of patients after Trendelenburg positioning. Postoperatively, obese patients are at increased risk of reintubation and desaturation events, especially those with OSA.[9] An increased risk of aspiration may occur due to increased respiratory workload, higher gastric residual volumes, and increased difficulty of intubation in obese patients.[4,21]

Risks related to the central nervous system include decreased cerebral and ocular perfusion pressure, increased intracerebral and intraocular pressure (IOP), and ischemic optic neuropathy leading to vision changes or vision loss.[9] Cerebral perfusion pressure initially increases with STP; however, it may decrease throughout the procedure due to head-down positioning and rising CVP. In contrast, intracerebral pressure (ICP) increases because of hypercarbia, causing cerebral vasodilation, increased intraperitoneal pressure, and increased intrathoracic pressure. As a result, CSF drainage is decreased and ICP subsequently increases. STP can lead to ischemic optic neuropathy due to elevated IOP and decreased ocular perfusion pressure. Obesity can further exacerbate CVP and end-tidal carbon dioxide elevations and lead to longer surgical duration, causing further increases in IOP[9]. Risks related to special positioning include worsening of obesity-related respiratory disorders, brachial plexus nerve injury, rhabdomyolysis, compartment syndrome, eye injury, cervical spine injury, dermal injury, and robotic trocar site-related injuries.[1,2,18]

Obese patients may be more sensitive to special positioning commonly used in robotic pelvic surgery, namely STP and pneumoperitoneum.[4] Grieco et al.[18] reports that in bariatric laparoscopic surgery, pneumoperitoneum and Trendelenburg positioning worsen obesity-related respiratory disorders and increase the anaesthetic risk. STP may cause a brachial plexus injury due to stretching between the shoulder and neck. Obese patients are especially at risk for mechanical cephalad slippage on the table due to STP and therefore require the use of various braces and pads, which can further injure the brachial plexus, especially with the use of shoulder braces and beanbag positioners.[9] Because of traumatic compression of muscle tissue during extended surgical procedures, extremely obese patients are at increased risk for postoperative rhabdomyolysis because of their excessive weight, which can induce hypocalcemia.[2,5] One study found that rhabdomyolysis, compartment syndrome, peripheral nerve injuries, and eye injuries were the most frequent positioning complications in patients with robotic-assisted radical prostatectomy (RARP).[22] Prolonged lithotomy positioning similarly increases the risk of several perioperative complications, including common peroneal nerve injury, compartment syndrome, and rhabdomyolysis.[23] The risk of eye injuries includes corneal foreign bodies, visual disturbances, and vision loss in one eye.[22] Cervical spine injury risk is increased with the use of devices that place excess pressure on the head, and the risk of slippage of the patient increases with increasing weight.[9] Should supportive positional devices fail and the patient slip while the robotic system is engaged, they are at increased risk of dermal, nerve, and incisional tears at robotic trocar sites.[9] Acquisition of pressure injuries, of which obese patients are at great risk, can lead to further skin breakdown.[24] In a non-experimental study that identified risk factors for pressure injury in surgical positioning, Menezes et al.[22] found a significant association between patients with a BMI 30 kg m^{2-1} and risk of pressure injuries (Table 2).

Recent Studies

Recent studies have shown additional risks of robotic pelvic surgery in obese patients. A summary of these results is presented in Tables 3 and 4.

A 2020 retrospective cohort study by Kott et al.[6] investigated the association between obesity and the rate of POC following RALP nephrectomy (RPNx). The study revealed an association between BMI and POC in patients undergoing RPNx. The rate of POC was found to be higher in patients with a BMI above the inflection point (30 kg m^{2-1})

Table 2. Risks Associated with Obesity in Robotic Pelvic Surgery

Cardiovascular	Decreased mesenteric blood flow Increased MAP Increased CVP Possible decreased CO Increased blood loss
Pulmonary	Hypercapnia Atelectasis Hypoxia Hypoxemia Hypoventilation Apnea Respiratory distress Decreased lung compliance Decreased FRC Decreased ERV
Airway	Subcutaneous emphysema Airway edema Respiratory depression Respiratory failure Airway closure Desaturation events Need for reintubation Aspiration
Central nervous system	Decreased cerebral perfusion pressure Decreased ocular perfusion pressure Increased ICP Increased IOP Ischemic optic neuropathy causing vision changes or vision loss
Special positioning	Respiratory disorder worsening Brachial plexus injury Rhabdomyolysis Compartment syndrome Eye injury (corneal foreign bodies, visual disturbances, vision loss) Cervical spine injury Dermal injury (pressure injuries) Robotic trocar site-related injuries

CVP, central venous pressure; MAP, mean arterial pressure; CO, cardiac output; FRC, functional residual capacity; ERV, expiratory reserve volume.

and lower with increasing BMI up until the inflection point. Paradoxically, these results showed that overweight and mildly obese patients have a lower risk of POC after RPNx, and both morbidly obese and underweight patients have the most significant risk of developing POC. Overall, these data suggest that BMI may be an essential factor for clinicians and surgeons to consider in managing patients undergoing RPNx[6].

A 2019 retrospective cohort study by Knipper et al.[25] investigated the effects of obesity on perioperative and various early postoperative complications with stratification based on surgical approach, robot-assisted vs open radical (RARP vs ORP) in patients undergoing RP. The study found that for both RARP and ORP, obese patients had higher overall perioperative complications, total hospital costs, and longer length of stay compared with non-obese patients, as well as more cardiac, respiratory, and genitourinary complications following RP. In addition, although RARP was associated with higher total hospital costs, it had a more favorable complication profile than ORP. Overall, these data suggest that obesity is a significant risk factor for perioperative complications during RP and that RARP may be more beneficial than ORP in preventing adverse outcomes.[25]

A 2020 retrospective analysis by Han et al.[26] investigated the effects of obesity on perioperative outcomes, including blood transfusion rates, intraoperative and postoperative outcomes, total costs, and healthcare resource utilization following RA laparoscopic RP (RALRP).[26] The study found that patients diagnosed with class I-II obesity (BMI 35-39.99 kg m^{2-1}) and morbid obesity (BMI ≥40 kg m^{2-1}) experienced greater overall postoperative complications than non-obese patients. Additionally, morbidly obese patients experienced more adverse perioperative events, including overall, cardiac, respiratory, and genitourinary complications, increased hospital length of stay, and 12% higher costs. Overall, these data suggest that in patients undergoing RALRP, morbid obesity is associated with poor perioperative outcomes, requiring close management by physicians both in and out of the operating room.[26]

A 2020 multicenter retrospective cohort study by Nik-Ahd et al.[27] investigated the association between obesity and positive surgical margins (PSMs) in patients undergoing RALP versus retropubic RP (RRP). The study found that at all locations except the bladder neck, higher BMI was associated with increased odds of overall, peripheral, and apical PSMs among all patients. In addition, there was a significant association between obesity and peripheral PSMs in men undergoing RRP, but not RALP. Higher BMI is a risk factor for PSMs, and the association between obesity and PSMs is slightly stronger for men undergoing RRP than for those undergoing RALP.[27]

A 2018 meta-analysis by Wei et al.[28] investigated the effects of obesity on long-term urinary incontinence (UI) following robotic-assisted laparoscopic RP (RLRP). The study found a significant association between obesity and UI in patients undergoing RLRP. When the surgical methods were stratified into laparoscopic RP and RLRP, the results indicated that obesity increased UI risk in patients who underwent RLRP but not LRP at 24 months.

Table 3. Clinical Efficacy and Safety

Author (Year)	Groups studied and intervention	Results and findings	Conclusions
Kott et al.[6] (2020)	Two hundred and fifty one adult patients undergoing RPNx	Odds of POC were significantly <1 for BMIs under 30 kg m^{2-1} (P=0.005) and significantly >1 over the BMI inflection of 30 kg m^{2-1} (P=0.007). BMI was significantly associated with POC rate.	Morbidly obese and underweight patients have the greatest risk for developing POC following RPNx, while overweight and mildly obese patients are less at risk.
Knipper et al.[25] (2019)	89,383 patients from the National Inpatient Sample (NIS) database undergoing RARP (60%) and ORP (40%) separated into obese (7.9%) or non-obese patients	Obese patients had significantly greater cardiac (P < 0.001), respiratory (P < 0.001), and genitourinary (P < 0.001) complications in both RARP and ORP than non-obese patients. Obese patients having RARP experienced significantly more total costs but more favorable complication profile.	Obesity is a risk factor for unfavorable perioperative outcomes in patients having RARP or ORP, and RARP may be more beneficial than ORP in preventing adverse outcomes.
Han et al.[26] (2020)	53,301 patients from NIS database who underwent RALRP, 3572 diagnosed with obesity class I-II, and 1004 with morbid obesity	Morbid obesity was associated with higher postoperative rates of cardiac, respiratory, genitourinary adverse events, 12% higher costs, and longer length of stay.	Morbid obesity is a risk factor for poor perioperative outcomes in patients undergoing RALRP.
Nik-Ahd et al.[27] (2020)	Three thousand one hundred and forty one men undergoing RRP versus RALP	Higher BMI was associated with increased odds of positive surgical margins ($P \leq$ 0.02) in all patients, and higher BMI was associated with greater peripheral positive surgical margins in RRP alone (P < 0.001).	Higher BMI is a risk factor for positive surgical margins in patients undergoing RRP and RALP.
Wei et al.[28] (2018)	Two thousand eight hundred and ninety adult participants from four different studies with varying BMIs (normal <25, overweight 25-30, and obese >30 kg m^{2-1}) who had RLRP and LRP	There was a significant association between obesity and UI in patients who underwent RLRP (P=0.01) at 12 months. At 24 months, there was a significant association between obesity and UI patients who underwent RLRP (P < 0.001), but not LRP.	Obesity is a risk factor for urinary incontinence in patients undergoing RLRP.
Porcaro et al.[30] (2018)	Two hundred and eleven adult patients undergoing RARP with EPLND stratified by BMI into low (normal weight), intermediate (overweight), and high (obese) risk categories	Increasing BMI was an independent predictor of higher rate of Clavien-Dindo grade 3 complications, which increased by 18.4% for each unit rise in BMI in patients undergoing RARP with EPLND.	Higher BMI is a risk factor for CD grade 3 complications in patients undergoing RARP with EPLND.

RPNx, RALP nephrectomy; RALP, robotic-assisted laparoscopic prostatectomy; POC, post-operative complications; BMI, body mass index; RARP, robotic-assisted radical prostatectomy; ORP, open radical prostatectomy; RALRP, robotic-assisted laparoscopic radical prostatectomy; RRP, radical retropubic prostatectomy; UI, urinary incontinence; EPLND, extensive pelvic lymph node dissection.

Table 4. Comparative Studies

Author (Year)	Groups studied and intervention	Results and findings	Conclusions
Yu et al.[29] (2019)	Two thousand two hundred and eight adult men who underwent RALP between 2014 and 2017	Higher BMI was associated with increased risk of PPCs, higher rates of ICU admission, longer length of stay, greater hospital costs, and increased morbidity and mortality in patients undergoing RALP.	Obesity is a risk factor for postoperative pulmonary complications, worsened quality outcomes, and higher morbidity and mortality in patients undergoing RALP.
Pathak et al.[32] (2021)	49,238 patients who underwent MI-RRP during 2007-2017	Severity of obesity was negatively correlated with quality indicators. Obese patients experienced prolonged LOS, increased readmission rates, and higher morbidity after MI-RRP.	Obesity is a risk factor for higher morbidity and poorer quality outcomes following MI-RRP.

RALP, robotic-assisted laparoscopic prostatectomy; BMI, body mass index; PPC, postoperative pulmonary complication; ICU, intensive care unit; MI-RRP, minimally invasive-radical retropubic prostatectomy; LOS, length of stay.

Therefore, obesity is associated with an increased risk of UI in patients undergoing RLRP at 12 and 24 months.[28]

A 2019 retrospective observational analysis by Yu et al.[29] investigated the incidence and risk factors of postoperative pulmonary complications (PPCs) in patients who underwent RALP under specific conditions, including pneumoperitoneum and STP. The study found that in addition to other risk factors such as age >65 years, hypoalbuminemia, and inadequate positive end-expiratory pressure, higher BMI was associated with an increased risk of PPCs in patients undergoing RALP. In addition, prostate cancer patients with PPCs experienced more admissions to the intensive care unit (ICU), longer ICU length of stay, higher hospital costs, and higher overall morbidity and mortality. Overall, these data suggest that obesity could potentially lead to PPCs in patients undergoing RALP, which may increase the difficulty of care management for both the anaesthesiologist and surgeon and lead to higher rates of ICU admission, length of stay, and overall morbidity and mortality.[29] A 2018 retrospective analysis by Porcaro et al.[30] investigated the effects of clinical factors such as BMI on the risk of grade 3 Clavien-Dindo complications (CDCs) in patients having RARP with extensive pelvic lymph node dissection (EPLND). Clavien-Dindo grade 3 complications are defined as moderate-to-severe complications leading to lasting disability or organ resection and requiring surgical, endoscopic, or radiologic intervention, with or without the addition of general anaesthesia.[31] The study found that increasing BMI was an independent predictor of a higher rate of grade 3 CDCs, which increased by 18.4% for each unit increase in BMI. Specifically, possible complications after RARP included ureteral injury, anastomotic urinary leakage, and symptomatic lymphocele. Overall, these data suggest that BMI is a risk factor for grade 3 CDCs in patients undergoing RARP with EPLND.[30]

A 2021 double-blind, placebo-controlled study by Pathak et al.[32] investigated the effects of obesity on quality indicators such as length of stay and readmission after minimally invasive-radical retropubic prostatectomy (MI-RRP). The study found that obese patients experienced prolonged length of stay, increased readmission rates, and higher overall morbidity than non-obese patients, and there was a negative correlation between obesity severity and quality indicators. Overall, these data suggest that in patients undergoing MI-RRP, obesity increases the risk of poor quality outcomes; therefore, physicians should carefully consider these risks and discuss them with their at-risk patients.[32]

Discussion

Reducing Complications in Obese Patients Undergoing Robotic Surgery

Robotic pelvic surgery in obese patients presents unique challenges. From an anaesthesia standpoint, accounting for both the physiological changes associated with obesity and the impact of patient positioning is paramount.

With respect to cardiovascular changes, obese patients may present with elevated CVP and decreased mesenteric blood flow during robotic surgery, particularly in the STP[33]. Intraoperative strategies focus on maintaining adequate volume and MAP levels. Placing an arterial line can help monitor unpredictable hemodynamic responses such as hypertension or hypotension, bradycardia, and tachycardia.[34] At the conclusion of surgery, when the legs are lowered from lithotomy, blood pressure should be measured to ensure that patients can tolerate the translocation of blood volume from the central compartment back into the lower extremities.[34]

With respect to respiratory changes, increased intra-thoracic pressure, decreased lung and chest wall compliance, and pneumoperitoneum can lead to decreased FRC, decreased ERV, hypoxia, hypercapnia, and atelectasis.[35] Specific ventilator settings, including higher positive end expiratory pressure, maintaining peak inspiratory pressure (PIP) <40 mmHg, adjusting inspiration to expiration ratio, respiratory rate, and tidal volume, and using PCV, can help optimize respiratory function and prevent complications.[34,36] In addition, patients who are obese or have OSA should be extubated while awake to prevent complications during extubation.[8]

With regard to airway optimization, increased adipose tissue in the face, neck, and abdomen can complicate patient positioning, neck extension, bag-mask ventilation, and tracheal intubation.[37] The placement of the endotracheal tube helps prevent airway collapse and pulmonary aspiration via positive pressure ventilation to decrease atelectasis and V/Q mismatch. Video laryngoscopy or transnasal humidified rapid insufflation ventilation exchange can provide an early definitive airway in obese patients. Rechecking endotracheal tube positioning once in the STP or lithotomy positions to ensure that the tube does not displace into the mainstem bronchus is imperative.

Concerning the CNS, ICP and IOP due to increased cerebral blood flow and venous congestion may occur during Trendelenburg positioning and pneumoperitoneal initiation.[34] While the STP position leads to an increase in IOP comparable to patients with glaucoma who have discontinued medication, no increased incidence of ischemic optic neuropathy has been observed in this setting. Addressing CNS risks includes achieving adequate MAP to maintain cerebral oxygenation in addition to preoperative consultation with an ophthalmologist for patients at risk of increased IOP.

Regarding patient positioning, going into the STP position is difficult in obese patients because of the excessive weight and skin laxity that can risk displacement on the operating room table. Patient positioning may be optimized using egg crates,

vacuum-molded bean bags, shoulder supports, memory foam mattresses, gel pads, and OR table extenders.[8] Other pertinent measures include having extra OR personnel assist with moving obese patients at the beginning and end of surgery.[38-41] Figure 1 illustrates appropriate Trendelenburg positioning for obese patients.

Recent Studies

Recent studies have shown how conditions can be optimized for robotic or laparoscopic pelvic surgery in obese patients. These results are listed in Tables 5 and 6. A 2020 retrospective analysis by Wilson et al.[39] investigated the effects of a weight loss program before RARP in obese men with prostate cancer. The study found that after a median of 29 days on the weight loss program, patients presented with significantly reduced weight, percent body fat, and overall fat mass, all associated with less surgery-related adverse effects. These data suggest that undertaking a weight loss program in preparation for robotic pelvic surgery may benefit postoperative outcomes.[39]

A 2018 prospective non-randomized study by Blecha et al.[40] investigated the impact of obesity on pulmonary deterioration in patients undergoing RARP. The study found that BMI was a significant predictor of increased PIP, peak driving pressure (P_{drive}), and decreased LC, further exacerbated by STP and capnoperitoneum. So, BMI can be used to predict changes in PIP, P_{drive}, and LC in the pre-operative setting.[40]

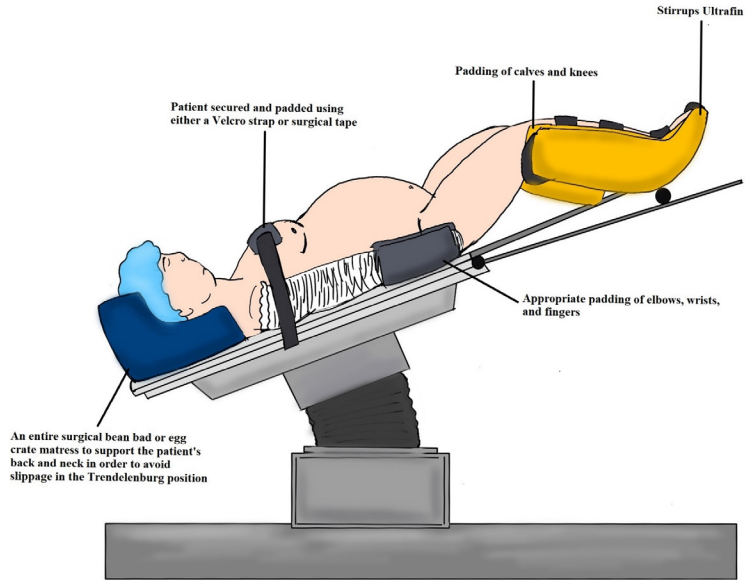

Figure 1. Trendelenburg positioning in the obese patient (drawing from Dr. Zoey Harris, MD, with permission)

Table 5. Clinical Efficacy and Safety

Author (Year)	Groups studied and intervention	Results and findings	Conclusions
Wilson et al.[39] (2020)	Forty three overweight and obese patients undergoing RARP who received a comprehensive weight loss program.	Significant reduction ($P < 0.001$) in weight, fat mass, trunk fat mass, and appendicular lean mass were associated with less surgery-related adverse effects ($P < 0.010$).	Undertaking combined low-calorie diet and exercise program in preparation for RARP may result in more beneficial surgical outcomes.
Blecha et al.[40] (2018)	Fifty one obese patients undergoing RARP evaluated for pulmonary changes in STP.	PIP and P_{drive} were significantly increased, and LC was significantly decreased after induction of capnoperitoneum ($P < 0.0001$). These changes were directly correlated with changes in BMI.	Changes in PIP, P_{drive}, and LC may be predicted by a paitent's BMI and should be considered in the preoperative setting.
Jun et al.[42] (2018)	Thirty six patients administered mannitol after pneumoperitoneum and STP with evaluation of ONSD as a surrogate for ICP.	ONSD was significantly lower in STD after initiation of mannitol compared to supine positioning.	Mannitol may provide beneficial effects on paitents undergoing RARP for prostate cancer who may be at risk of elevated ICP, including the obese.

RARP, robotic-assisted radical prostatectomy; STP, Steep Trendelenburg positioning; PIP, peak inspiratory pressure; LC, lung compliance; BMI, body mass index; ONSD, optic nerve sheath diameter; ICP, intracranial pressure.

Table 6. Comparative Studies

Author (Year)	Groups studied and intervention	Results and findings	Conclusions
Gad et al.[41] (2019)	Eighty female obese patients undergoing laparoscopic hysterectomy compared PCV-VG to VCV with ERV	PIP was significantly lower in PCV-VG group compared to VCV-ERV group while dynamic compliance was significantly greater in the PCV-VG group compared to the VCV=ERV group. No significant differences in oxygenation, hemodynamics, or ABG.	PCV-VG provided superior control for PIP and dynamic compliance in obese patients undergoing laparoscopic pelvic surgery, which may be preferable in patients susceptible to cardiopulmonary impairment.

PIP, peak inspiratory pressure; PCV-VG, pressure control ventilation with volume-guaranteed; VCV-ERV, volume-controlled ventilation with equal ratio ventilation.

A 2019 double-blind randomized study by Gad et al.[41] investigated the effects of PCV with volume-guaranteed (PVC-VG) versus volume-controlled ventilation (VCV) with equal ratio ventilation in obese patients undergoing laparoscopic hysterectomy. The study found that PCV-VG led to significantly lower PIP values and higher dynamic compliance than VCV. In summary, PCV-VG is superior to VCV in obese patients undergoing laparoscopic surgery in the Trendelenburg position.[41]

A 2018 observational study by Jun et al.[42] investigated the effects of mannitol on optic nerve sheath diameter (ONSD) as a surrogate for ICP during RARP. The study found that ONSD was decreased in STP at 3 time points up to 90 min after the initiation of mannitol Mannitol administration may provide a valuable preventive measure to patients at risk of increased ICP during RARP, including obese patients.[42]

Conclusion

Robotic urologic surgery in morbidly obese patients is very challenging but achievable. A multi-disciplinary team approach is primordial, and a dedicated anaesthesia team would lower the morbidity risk, allowing patients to undergo their planned procedure. Some pre-surgical risk factors to consider include hemodynamic changes such as hypertension and ventricular hypertrophy that can cause pulmonary hypertension and pulmonary changes such as reduced lung and chest wall compliance due to increased intra-abdominal pressure from excess weight. These factors can be exacerbated by many components, such as abdominal insufflation leading to pneumoperitoneum, STP, and use of carbon dioxide leading to complications such as DVTs due to vein compression, risk of hypoxemia or hypoxia, and hypercapnia. These potential complications lead to increased anaesthesia risks.

Studies have shown a positive correlation between patient obesity and blood loss during pelvic surgeries. Likewise, a significant increase in the number of aborted procedures related to respiratory complications has been identified in obese patients, citing expiratory flow limitation and airway closure as the chief reasons. Other correlations include increased risk of nerve damage, postoperative rhabdomyolysis, and hypocalcemia in patients with higher BMI. Other studies have identified a BMI of 30 kg m^{2-1} as significantly associated with increases in POC mentioned above, and even with increased odds of PSMs and Clavien-Dindo grade 3 complications.

While more data helps solidify this correlation, the risks of the complications listed are correlated with a BMI of 30 kg m^{2-1} and are even more significant as BMI increases. However, there are steps that physicians and surgeons can take to reduce these risks, such as placing arterial lines to monitor hemodynamic changes, adhering to specific ventilators, and extubation to minimize pulmonary risks. In addition, the use of egg crates or vacuum-molded bean bags to reduce the risks associated with STP to ensure that the patient can proceed with the procedure as planned.

Ethics

Author Contributions: Concept - N.K., A.M., D.V., A.D.K.; Design - N.K., A.M., D.V.; Supervision - N.K., A.M., A.D.K.; Data Collection or Processing - D.V., K.J.; Analysis or Interpretation - S.A., S.S., E.M.C., A.D.K.; Literature Search - N.K., A.M., D.V., K.J., S.A., S.S., E.M.C., A.D.K.; Writing - N.K., A.M., A.J.G., K.J., S.S.; Critical Review - N.K., A.M., S.A., S.S., E.M.C., A.D.K.

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Review Article
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Could MicroRNA be Neurological Prognosis Biomarkers after Cardiac Arrest?

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Abstract

For patients monitored in intensive care units in the aftermath of a cardiac arrest, one of the well-established difficulties of care after resuscitation is the ability to perform the necessary prognostic assessments as accurately and early as possible. Although current guidelines include algorithms to determine prognosis, there are still missing links and uncertainties. Biomarkers obtained from peripheral blood are generally non-invasive and easy to obtain. Although the potential to use microRNA as a prognostic biomarker after cardiac arrest has received less interest recently, its popularity has increased in the last few years. By identifying prognostic biomarkers within 24 h of cardiac arrest, clinicians in intensive care could gain valuable insights to guide patient outcomes and predict both mortality and survival rates.

Keywords: Biomarker, cardiac arrest, intensive care, microRNAs, neurological function, prognostics

Main Points

- Pinpointing a patient's prognosis after successful resuscitation remains a murky picture, largely clouded by the heavy use of medications such as sedatives, opioids, and neuromuscular blockers.
- The quest to accurately assess brain damage and forecast neurological recovery requires innovative approaches.
- MicroRNA accurately predicts good and poor neurological outcomes.
- MicroRNA is an accurate and early marker of long-term neurological outcomes following cardiac arrest.

Introduction

A leading contributor to both mortality and morbidity, sudden cardiac arrest claims the lives of over a million individuals worldwide each year.[1] Approximately 300,000 cardiac arrests occur in Europe annually, with 85% of these cases ending in death.[2] Early prediction of neurological outcomes following successful cardiopulmonary resuscitation using simple clinical examination is challenging. The introduction of therapeutic hypothermia as a treatment for comatose cardiac arrest patients has added another layer of complexity to the already challenging task. The pharmacokinetic profile of sedative agents is impacted by hypothermia, and effects that prolong sedation have been identified as a major factor in the decreased predictive power of clinical neurological examination in predicting unfavorable outcomes following cardiac arrest.[3,4]

Therefore, new techniques are required to quantify the extent of brain damage and forecast the results. Numerous circulatory biomarkers, including neurofilament light chain protein levels, neuron-specific enolase (NSE), and S100B, were evaluated in relation to prognosis. The effectiveness of these evaluations varied, and while resuscitation science guidelines stipulate that they should inform prognostic forecasts, the hunt for the perfect biomarker continues.[5-7] Prognostic assessment following cardiac arrest is now performed using a combination of neurological examination, biochemical and neurophysiological testing, and imaging a few days post-event.[1,6]

The primary challenge in predicting the early prognosis of individuals who are resuscitated after cardiac arrest is the absence of precise biomarkers.[8] As mentioned above the most reliable measures of neurological outcomes were, until

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recently, neurophysiological testing and clinical neurological examination performed a few days after arrest.[9,10] Guidelines and clinical practice propose using biomarkers in circulation, such as NSE, because they improve outcome prediction determination.[11,12] Nevertheless, novel biomarkers must be used for the therapy management of individual patients, and the discriminatory power of these neurophysiological tests needs to be enhanced for each patient individually.

What is the Role of microRNAs?

In Prognosis

MicroRNAs (miRNAs) discovery in 2001 sparked intense attention in the scientific community.[13-15] Their potential significance as novel disease biomarkers was highlighted by their stability and presence in blood circulation.[16,17] MicroRNAs in circulation has been used as a biomarker of cardiovascular disorders in several studies. While research has primarily focused on heart attacks and failing hearts, the potential of miRNAs as a prognostic tool during cardiac arrest has only recently begun to shine a light on its possible role.[8]

Short RNA molecules (around 21 nucleotides) known as miRNAs do not encode for proteins. These are often expressed molecules, despite being somewhat tissue specific and having been maintained by evolution. Since the MicroRBase Sequence Database's debut in December 2002,[8] the catalog of known miRNAs has been steadily blossoming. In 2578 individuals, up to 30,424 miRNAs of 206 kinds have been identified.[8] Despite being unable to code for proteins, miRNAs play crucial roles in regulating their genes and, consequently, the expression of proteins. By causing mRNA degradation, miRNA predominantly controls animal gene expression.[18] This characteristic guarantees that miRNA can control physiological, pathological and developmental processes.[19]

Numerous processes in the heart, including apoptosis, angiogenesis, contraction, and hypertrophy are regulated by miRNAs.[20] Similarly, miRNAs are highly expressed in the brain.[21] These characteristics make them essential for developing the brain and diseases.[22]

The results of PubMed screening of 624 papers suggested that miRNA might be a possible biomarker in neurological disease, according to a systematic review by Devaux et al.[8] Much of the research has focused on the usefulness of miRNA as a brain tumor diagnostic biomarker. Seven hundred twenty-four articles have discussed miRNAs as cardiovascular disease biomarkers. The majority of them were found to concentrate on heart failure (106 articles) and myocardial infarcts (125 articles).

There is a shortage of papers of research findings that solely consider cardiac arrest, and most of these studies seem to evaluate the diagnostic rather than prognostic potential of miRNA.

In one study, miRNAs levels were examined in the first 48 and 24 h following return of spontaneous circulation (ROSC) in 65 patients who had therapeutic hypothermia following cardiac arrest. Six months after cardiac arrest, miRNA levels were assessed using the cerebral performance category (CPC) score, which was divided into two categories; good neurological outcome (CPC score 1 or 2) and poor neurological outcome (CPC score 3-5). After 48 h, there were no discernible variations in the levels of miR-146a, miR-122, miR-208b, miR-21, miR-9, and miR-128 between the groups with favorable and poor neurological outcomes. On the other hand, in the 24 h and 48 h following cardiac arrest, miR-124 was sharply higher in patients who had positive outcomes than in those who had bad outcomes.[1] The researchers concluded that miR-124 was a groundbreaking new biomarker for predicting the prognosis of the nervous system in the post-cardiac arrest period based on these data. They concluded that miRNA might be a crucial factor in determining neurological outcomes and death following cardiac arrest on the basis of the data they had collected.[1]

In Cardiac Diseases

MicroRNAs has been suggested in many studies as a potential diagnostic biomarker for cardiovascular disorders, notably acute myocardial infarcts.[8] A major challenge in cardiovascular research is identifying valid biomarkers frequently measurable in readily available samples such as plasma. MicroRNAs have been studied for their potential as biomarkers for cardiovascular disorders because of their stability in circulation.[23] Currently, many models of circulating miRNAs have been discovered for heart failure, atherosclerotic disease, hypertension, type 2 diabetes, and myocardial infarctions.[23] Other studies[24-28] have examined the predictive significance of circulating miRNAs following acute myocardial infarctions.

In Brain Injury

Previous studies have examined the functions of miRNA in nervous system illnesses, including cancer, as well as in brain development and plasticity.[21,22,29,30] The brain and other peripheral organs require oxygen and nutrients after cardiac arrest because perfusion stops. Following cerebral ischemia, the brain's miRNA expression alterations[31] lead to many miRNA candidates. Following ischemia/reperfusion injury, microglial-mediated neuronal death was controlled by miR-181c in a rat global cerebral ischemia model.[32] MiRNA-181c directly targeted the area where TNF-α mRNA does not undergo 3' translation, inhibiting apoptosis triggered by TNF-α generated in active microglial cells.[32] This research illuminated the critical role of miRNAs as conductors of neurological dysfunction in the brain starved of oxygen. Consequently, miRNAs hold promise as both harbingers of

neurological outcomes and potential targets for orchestrating neuroprotective therapies after cardiac arrest.

In Terms of Neurological Protection

Scientists have identified a squad of miRNAs as potential warriors in the fight to shield the oxygen-deprived brain. Among them, valproic acid, a molecule known to unlock the cell's hidden potential, emerged as a champion.[33] In rodent stroke models, it not only mitigated neurological after effects but also revved up motor function, all while influencing the expression of miR-331 in affected brain cells.[31] Simultaneous administration of bortezomib, a drug that tackles rogue proteins in a specific cancer myeloma,[34] and tissue plasminogen activator, along with its neuroprotective effects in older rats after stroke, was linked to a surge in miR-146a levels within the brain's endothelial cells.[31,35] The million-dollar question remains can these miRNAs be individual heroes in protecting the brain, or do they require backup?

MicroRNAs as a Prognostic Biomarker after Cardiac Arrest

Studies have proposed that specific miRNAs in blood may have value as a biomarker after cerebral ischemia due to ischemic cerebrovascular accidents occurring in both animal models[36] and human patients.[37] Some of these miRNAs may also be promising diagnostic tools for ischemic stroke.[37-39]

A study on determining the power of miRNA in predicting prognosis after cardiac arrest compared plasma miRNA in patients with favorable outcomes after cardiac arrest with patients with poor outcomes.[40] They identified an outcome-linked miRNA biological signature using microsequences encompassing nearly 700 miRNAs (miRBAS version 12.0). Among miRNAs expressed differently in patients with positive and negative outcomes, miR-122 and miR-21 strongly predicted both death rates and neurological function after 6 months. Stammet et al.[40] included 28 patients who survived more than 48 h after cardiac arrest. During the post-cardiac arrest period, patients underwent therapeutic hypothermia at a target core body temperature of 33 °C for 24 h. Blood samples were collected using microarray and PCR to determine miRNA expression levels 48 h after cardiac arrest in normothermic conditions using citrate tubes. Patients underwent neurological evaluations both before discharge from the intensive care unit and at the 6-month follow-up. It was determined that miR-122 and miR-21 predicted neurological outcomes and were associated with patient mortality rates. When the miRNA expression profiles in the plasma of patients after cardiac arrest were characterized, it was understood from the study results that neurological outcomes in these patients were associated with a miRNA bio-signature. The miR-122 and miR-21 levels assessed in circulation at physiological body temperature 48 h after cardiac arrest in patients treated with hypothermia were increased in patients with poor outcomes and provided some ability to forecast outcomes. Additionally, based on evidence that miR-122 and miR-21 are produced by neuronal cells, the increase in plasma concentration. In the post-cardiac arrest period was considered to be due to injured neurons. This situation motivated the assessment of how miRNA impacts our understanding of patient recovery potential in broader cardiac arrest patient cohorts.

The hypothesis that miRNAs source in neurons dying after cardiac arrest can be measured in blood circulation was confirmed by demonstrating that miR-122 and miR-21 are consistently produced by neurons, as evidenced by other studies.[41,42] Similar to this hypothesis, another study showed that exosomes carrying miRNAs outside cells might pass the blood-brain barrier.[43] In addition, cerebral ischemia disrupted the blood-brain barrier, which may facilitate the release of neuron-derived miRNA into blood circulation easier.[44] The multicenter studies performed by Devaux et al.[45], with participation from nine countries, researched the prognostic value of miRNA levels in patients with ROSC. Of the 579 patients, 304 (52.5%) had poor neurological outcomes in the sixth month (CPC scores 3 and 4). In 50 patients, brain-enriched miR-124-3p level was defined as a predictive biomarker of neurological results with short RNA sequencing, and miR-124-3p levels were significantly elevated in patients with unfavorable outcomes compared with those with good outcomes. In univariate analysis, miR-124-3p levels were strongly correlated with neurological outcomes, whereas multivariate analysis using logistic regression independently associated miR-124-3p levels with neurological outcomes. In the advanced statistical analysis models developed in this study, higher miR-124-3p levels were proven to be remarkably associated with lower survival. This evidence-based data demonstrated that miR-124-3p levels could be used as a prognostic tool for neurological outcomes and survival after non-hospital cardiac arrest. The potential of miRNA profiling to be a valuable tool for stratifying patient care following cardiac arrest.

In another study,[46] lower miR-122-5p and higher miR-124-3p levels predicted shorter survival. The results of this new investigation showed that miR-122-5p levels measured in the 48th hour after ROSC were a unique predictor influencing both brain function and survival rates and had prognostic value.

Building on the work of Sheinerman et al.[47], researchers identified brain-specific miRNAs in the blood of patients experiencing early-stage mild cognitive decline, a hallmark of various neurodegenerative diseases. Therefore, it is understood that brain-derived miRNAs found in circulation after cardiac arrest may indicate neurological impairment. As the dimension of neurological injury

emerges as a crucial factor in determining the recovery potential after cardiac arrest, miRNAs in circulation in this environment is expected to have significant prognostic value. A new study showing that brain-enriched miR-124 was associated with neurological outcomes after cardiac arrest solidly validated this initial belief.[1] The study by Gilje et al.[1] researched the effect on mortality and neurological prognosis by assessing plasma levels of miRNA specific to selected tissues in cardiac arrest syndrome. Previous studies primarily investigated tissue samples collected after a 48-h window following cardiac arrest. As a result, Gilje et al.[1] assessed this time point first and assessed differences if present. They concluded that miR-124 levels were higher in the 24th hour, and it may show great potential as a novel marker for use in predicting outcomes after cardiac arrest. As a result that supports clinical efficacy, it provided 97% specificity and 53% sensitivity for the prognosis of CPC score 3-5 in the 24th hour. The miR-124 in plasma was previously characterized as a biomarker for brain injury in a stroke model in animal studies; however, the study by Gilje et al.[1] is the first human study to associate miR-124 with brain injury. In this study, miR-124 was compared with NSE in prognostic terms, and no increase in diagnostic accuracy was not identified by combining these two biomarkers.

In a study to assess the correlation between miRNAs in circulation and cerebral complications following resuscitation from cardiac arrest. Stefanizzi et al.[48] found strong correlations between three different brain-enriched miRNAs (miR9-3p, miR124-3p, and miR129-5p) and NSE. The authors stated that this result may indicate that miRNAs reflects the degree of brain injury. In addition, these miRNAs were associated with neurological outcomes and 6-month survival. These data support the importance of brain-enriched miRNA in predicting mortality and neurological outcomes after cardiac arrest. MicroR-124 was shown to be a promising new biomarker to predict prognosis for patients treated with hypothermia after cardiac arrest, according to receiver operating characteristic area under the curve, which was calculated as 0.87 in the 24th hour and 0.89 in the 48th hour.

Moving forward, well-designed studies are crucial to validate the potential advantages of this novel biomarker category against existing methods. In addition to the sensitivity and specificity of miRNA, their benefit for early prediction must be superior to available electrophysiological and neuroimaging tools. Finally, techniques for determining miRNA amounts are time-consuming and must be developed in terms of repeatability, speed, cost, and standardization.

Accurate assessment of prognosis shortly after cardiac arrest remains a significant hurdle. The widespread use of sedatives, pain relievers, and muscle relaxants complicates the picture. Additionally, the previously established 72-h window for neurological evaluation is no longer reliable because of the lingering effects of these medications, hindering a clear assessment of brain function. The discovery of gene expression regulators of miRNAs caused high excitement among researchers. Fueled by the potential of these molecules, numerous studies have explored their application as diagnostic tools, prognostic indicators, and therapeutic targets for cerebral and cardiovascular diseases. A critical gap exists in our knowledge regarding the use of miRNA as a biomarker for patients who have survived cardiac arrest. Future studies ideally target researching the superior value of miRNA compared with available prognostic tools and the most appropriate time to collect blood samples. While previous research has demonstrated the early release of cardiac-enriched miRNA following cardiac injury, a crucial next step lies in precisely characterizing the release pattern of brain-enriched miRNA in this context. It is essential to note the following basic technical topics related to the measurement of miRNA levels in circulation: the advantages and disadvantages of measuring miRNA in plasma compared with whole blood. Interestingly, miRNAs may be a new biomarker and potential therapeutic target after cardiac arrest.

Ethics

Author Contributions: Surgical and Medical Practices - Ş.Ö., N.G.; Concept - Ş.Ö.; Design - Ş.Ö., N.G.; Data Collection and Processing - Ş.Ö., N.G.; Analysis and Interpretation - Ş.Ö., N.G.; Literature Review - Ş.Ö., N.G.; Writing - Ş.Ö.

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Review Article

Burnout in Anaesthesia

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Impact of Burnout on Anaesthesiologists

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Abstract

Professional burnout syndrome (PBS) is an issue affecting individuals and organizations alike, characterized by emotional exhaustion and reduced effectiveness resulting from overwhelming work demands. Root causes include excessive workload, unrealistic expectations, and blurred work-life boundaries, which are often intensified by organizational culture and inadequate support systems. The consequences range from decreased productivity and creativity to high turnover rates and financial strain on organizations. Mitigating PBS requires a comprehensive approach that addresses both individual and organizational levels. Individually, stress management techniques and self-care practices are crucial for building resilience and coping with work-related stressors. Organizations play a vital role in promoting employee well-being by fostering a supportive work environment, promoting work-life balance and providing access to support systems such as counseling and mentorship programs. Leadership is key in creating a culture that values employee health and prioritizes open communication and empathy. Policy interventions can further support efforts to combat PBS by enforcing labor laws that protect employee rights, such as setting limits on working hours and ensuring access to mental health services. Additionally, incentivise organizations to prioritize employee well-being through tax incentives or certification programs can encourage proactive measures against burnout. The aim of this review is to provide a comprehensive exploration of PBS, examining its causes, consequences, and potential mitigation strategies in individuals and organizations, with a focus on anaesthesiology.

Keywords: Anaesthesiology, occupational health physicians, professional burnout

Main Points

- Anaesthesiologists face significant burnout, which is exacerbated by the high-stress nature of their work, long hours, and critical decision-making responsibilities, which can lead to exhaustion, depersonalization, and reduced personal accomplishment.
- Burnout among anaesthesiologists not only impacts their own mental and physical well-being but also poses risks to patient safety and quality of care, including increased medical errors, reduced empathy, and diminished patient satisfaction.
- Psychological treatments such as cognitive behavioral therapy and acceptance and commitment therapy show promise in managing burnout symptoms among anaesthesiologists, while organization-directed interventions are essential for addressing systemic factors contributing to burnout.
- Addressing burnout among anaesthesiologists requires multifaceted interventions, including promoting work-life balance, providing access to confidential mental health support, and destigmatizing help-seeking behaviors within healthcare systems.
- Despite the challenges associated with treating physician burnout, acknowledging vulnerabilities, prioritizing self-care and advocating for systemic changes within healthcare organizations are crucial steps toward cultivating a healthier, more resilient healthcare workforce.

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Introduction

While burnout syndrome received significant media coverage in the past, it has become less prominent in recent years.[1] However, its relevance has increased as more than half of healthcare professionals report experiencing symptoms of burnout.[2] The coronavirus disease-2019 pandemic appears to have further exacerbated this issue,[2,3] According to a recent survey conducted by the Association of Swiss Assistant and Senior Physicians, approximately one out of every two respondents admitted feeling overwhelmed and reaching a point where they «couldn't handle any more».[4] These participants often expressed feelings of fatigue, exhaustion, and emotional drainedness. They also shared incidents where patient safety was compromised due to work-related fatigue, an observation supported by a recently published study that found that doctors with burnout were twice as likely to be involved in patient safety incidents.[5]

Among medical specialties, anaesthesiology seems particularly susceptible to burnout.[3,6] The increasing awareness of mental health issues within the healthcare profession, specifically among anaesthesiologists, has sparked a demand for a deeper understanding and proactive measures. Anaesthesiologists, who play a critical role in patient care, often operate in high-pressure environments with long working hours and the need to make life-or-death decisions. Additionally, evidence shows that the risk of developing mental illnesses, such as depression or suicide, seems to be higher among anaesthetists.[7] This review aims to delve into the various aspects of burnout within anaesthesia, its consequences, and potential methods for mitigating it.

Occupational Hazards in Anaesthesiology

Anaesthesiologists play a multifaceted role beyond operating rooms and intensive care units. They are called upon to provide anaesthesia services in various settings, including remote locations, pre-interventional consultations, pain clinics, magnetic resonance imaging suites, and radiotherapy centers. Anaesthesiologists also play a crucial role in trauma and disaster management teams, exposing them to a range of health hazards. Even a seemingly innocuous needle prick from an unidentified source can trigger intense anxiety and fear.[8,9]

Considering these challenges, prioritizing occupational health and safety becomes imperative for anaesthesiologists. The World Health Organization (WHO) defines occupational health as emphasizing promoting and maintaining the highest physical, mental, and social well-being levels for workers across all professions (www.who.int/health-topics/occupational-health). This includes preventing work-related health issues, protecting workers from adverse health risks during employment, and creating an occupational environment that aligns with the physiological and psychological capacities of the workforce. Health hazards encountered by anaesthesiologists can be broadly categorized according to Table 1.

Understanding Professional Burnout Syndrome (PBS)

Many individuals in our performance-driven society are struggling because of the increasing demands placed upon them. Those who are unable to manage the excessive workload are endangering both their emotional and physical health as well as their social life with family and friendships.[10-12] This state of work-related stress is commonly referred to as burnout[13].

According to the WHO, burnout is a syndrome resulting from workplace stress that should be adequately addressed.[14] It should be noted that burnout is considered a work-related phenomenon and is not classified as a medical condition. However, it is a diagnosis listed in the 11th Revision of the International Classification of Diseases.[15] It is work-specific, occurs in individuals without any pre-existing psychopathology, and is commonly found in caregiving professions.[16] Burnout refers specifically to phenomena in the occupational context and should not be applied to describe experiences in other areas of life.[17]

Table 1. Occupational Health and Safety Risks in Anaesthesia Practice

Category	Details
Chemical agents in anaesthesia	- Latex allergy - Hazards associated with inhaled anaesthetics, particularly concerning reproductive health
Biological hazards	- Exposure to viruses like hepatitis B, hepatitis C, and HIV - Risks from bacteria and fungi - Other unspecified biological risks
Physical factors in the anaesthetic environment	- Exposure to ionizing (X-rays) and non-ionizing (laser) radiation - Effects of noise and vibration - Temperature extremes - Adequacy of ventilation and lighting - Risks from electric charges, including both high and low voltage - Fire hazards
Occupational stress and its consequences in anaesthesia	- Chronic stress related to the job - Psychosocial disorders - Risks of drug addiction - Ergonomic concerns
Workplace standards and organization	- Type and organization of work in anaesthesia - Work schedules and patterns - Task density and workload - Exposure to workplace violence

Although there are no specific criteria for burnout, it frequently leads to the onset or worsening of mental disorders such as depression, substance abuse issues, or adjustment disorders. Additionally, burnout is associated with conditions such as cardiometabolic disorders (e.g., obesity, diabetes), hypertension, lipid metabolism issues, coronary heart disease, and even increased mortality risk. Therefore, burnout can be considered a health-threatening risk condition.

The symptoms of burnout typically manifest across three dimensions: exhaustion (feeling drained and overwhelmed), depersonalization (developing cynicism or detachment toward others) and reduced personal accomplishment (experiencing diminished productivity or effectiveness) (Table 2).[1,3,15] Unfortunately, this phenomenon is increasingly prevalent in healthcare.

Why Anaesthesiologists?

Many studies report high levels of burnout in doctors, with psychological morbidity ranging from 19% to 47%,[18] compared with a rate of around 18% for the general employed population.[19] For primary care doctors or general practitioners, most studies report a moderate degree of burnout, especially for the emotional exhaustion dimension[20,21]. Anaesthesiologists also have moderate degrees of burnout, with high job satisfaction moderating the negative effects of stressors at work.[6,22,23] However, the literature is inconsistent in what medical speciality has the highest percentage of burnout.

Burnout does not occur only in healthcare: The occurrence of burnout syndrome in diverse occupations, e.g., social workers, advisors, teachers, nurses, laboratory workers, speech therapists, police and prison officers, stewardesses, managers, and even in housewives, students, and unemployed people.[24] In most of these occupations, the combination of caring, advising, healing, or protecting, coupled with the demands of showing that one cares, is of central importance.

Table 2. Key Components of Burnout

Key components of burnout	Details
Emotional exhaustion	Core symptom: Exhaustion (emotional, physical, cognitive, and social)
	Common signs: Social withdrawal, inability to relax, sleep disorders, bruxism (teeth grinding), tension pain
Depersonalization	Characteristic: Increasing difficulty in identifying personal feelings
	Manifestations: Rising feelings of dissatisfaction and cynicism1
Reduced personal accomplishment	Outcome: A lasting perception of decreased work performance

In anaesthesiology, PBS manifests in unique ways because of the high-stress, high-stakes nature of the work. Anaesthesiologists often experience emotional exhaustion from prolonged periods of intense concentration and decision-making under pressure. Depersonalization can occur as a coping mechanism against the constant strain of patient care, leading to a sense of detachment or indifference toward patients.[25] Reduced personal accomplishment in anaesthesiologists may stem from the invisibility of their role; despite being crucial, their work is often behind the scenes and not directly recognized by patients[26]. These manifestations of PBS in anaesthesiology not only impact the mental health of professionals but also potentially affect patient safety and care quality.[6,27]

Consequences of PBS

Burnout in healthcare has far-reaching consequences, impacting both practitioners and patient care. Burnout symptoms include cognitive challenges like poor concentration and memory lapses.[28] Personality changes, such as reduced motivation, cynicism, and aggressiveness, are also common.[13] Physical symptoms include headaches, gastrointestinal issues, and cardiovascular problems like tachycardia and arrhythmia. Socially, burnout results in workplace withdrawal, relationship difficulties, and isolation. In severe cases, it can lead to anxiety, depression, and, tragically, suicide. Healthcare professionals, particularly anaesthesiologists, often develop substance abuse tendencies, turning to alcohol, drugs, and medications. Nearly 10% of them may develop substance-related disorders.[29] This is because they have access to pharmaceuticals and are usually self-medicating for pain, which can increase the risk of addiction.[30]

However, the consequences of burnout extend beyond the well-being of practitioners. They affect patient care by reducing empathy, increasing medical errors, and diminishing patient satisfaction.[24]

Burnout Amongst Turkish Anaesthesiologists

Burnout is an issue that Turkish anaesthesiologists are concerned about, as indicated by two studies conducted in the country.[31,32] The first study aimed to assess the levels of burnout among healthcare workers specializing in Anaesthesiology and Algology in a large Turkish region.[31] The results were concerning, showing high burnout scores among the participants. Healthcare workers expressed dissatisfaction with working conditions such as environment, working hours and salaries, suggesting that these factors may worsen burnout. The second study focused on trainee anaesthesiologists and shed light on how inexperienced professionals are vulnerable to stress and

burnout.[32] It revealed that perceived stress was significantly high during the years of training, which correlated with increased exhaustion and depersonalization while decreasing personal accomplishment. Additionally, gender and family factors played a role; female anaesthesiologists reported accomplishment and lower depersonalization than their male counterparts.[32] Trainees with two or more children demonstrated accomplishment while having lower depersonalization and emotional exhaustion scores. These findings emphasize the need to address burnout among anaesthesiologists. The findings from these studies highlight the pressing need to alleviate burnout and promote the physical well-being of anaesthesiologists in Turkey throughout their professional journeys.

Psychotherapy for Managing Burnout

Psychological treatments play a role in addressing burnout. One effective option is cognitive behavioral therapy (CBT).[33] CBT is a goal-oriented approach that helps individuals recognize and tackle burnout symptoms. It involves understanding the causes of stress and burnout, adjusting thoughts, enhancing work-related skills, and engaging in leisure activities for recovery.[34]

Studies examining individuals who underwent CBT sessions found reductions in cortisol levels, improvement in well-being, and diminished burnout symptoms.[35] Another study reported a 64% decrease in burnout and emotional exhaustion following CBT.[36] Mindfulness, another approach, effectively reduced burnout symptoms.[36]

Acceptance and commitment therapy (ACT) is an intervention that uses acceptance and mindfulness strategies along with commitment and behavior change strategies to increase psychological flexibility. ACT has been shown to lead to a reduction in burnout and its individual subscales.[37,38] Eye Movement Desensitization and Reprocessing also shows potential for reducing exhaustion among individuals experiencing burnout;[39] however, additional research is needed for confirmation.

Other forms of therapy, such as music therapy, stress management techniques, spa treatments, and art therapy, have shown potential in reducing the symptoms associated with burnout.[40-42] However, more research is needed to validate these findings.

Use of Medications to Combat Burnout

Medications, such as antidepressants and sleep aids, are commonly prescribed for individuals experiencing burnout. However, their effectiveness in reducing burnout symptoms remains uncertain. Currently, there is no medication specifically designed for treating burnout. Although psychotropic drugs are used in over half of the cases involving leave due to burnout-related issues,[43] limited evidence supports their efficacy in treating burnout.

Strategies for Burnout Prevention

Addressing burnout among anaesthesiologists is a complex challenge, given the demanding nature of their work. Solutions should focus on efficient time management, prioritizing self-care and providing flexible mental health support. Two recent systematic reviews[44,45] evaluated the effectiveness of interventions in mitigating burnout among physicians. The first review[44] found that while existing interventions led to small but significant reductions in burnout, organization-directed approaches showed the most promising results. In the second review,[45] results showed that both individual-focused and structural or organizational strategies could lead to meaningful reductions in burnout levels. However, there was a notable scarcity of organization-directed interventions despite their demonstrated effectiveness. The review emphasized the need for more effective intervention models to combat physician burnout, advocating for approaches that foster healthy relationships between physicians and their work environments.

Both reviews highlight the urgency of addressing physician burnout through multifaceted interventions. While individual-focused strategies can yield positive outcomes, organization-directed approaches offer promising avenues for mitigating burnout and promoting physician well-being on a broader scale. Improving the work environment by incorporating facilities like sports complexes and health-focused cafeterias can promote well-being,[46] Encouraging outdoor breaks and optimizing workspaces for natural light are also beneficial. Healthcare organizations must offer flexible mental health services, including counseling during non-traditional hours and virtual options.[47] Destigmatizing mental health is key to ensure anaesthesiologists feel comfortable seeking support[48]. Finally, efficient scheduling practices, such as adequate rest periods and minimizing on-call duties, can help achieve work-life balance.[49]

Challenges in Treating Physician Burnout

Understanding the challenges in treating physician burnout is crucial for developing effective interventions. A recent study[50] delved into this issue and revealed two main obstacles:

First, physicians often hesitate to seek help until they reach severe stages of exhaustion. This delay in seeking assistance prolongs their suffering and intensifies burnout symptoms. Additionally, physicians struggle with the role reversal of becoming a patient, making it challenging to accept treatment.

Psychologists attribute these challenges to several factors. Many physicians lack a designated general practitioner, hindering their access to primary care. Moreover, guilt about reducing their workload and difficulty separating their professional and personal lives contribute to their reluctance to seek help.

The study[50] underscores that these challenges stem from physicians' perceptions of their professional identity. They view themselves as enduring and selfless, making it difficult to acknowledge their vulnerabilities and prioritize self-care.

Conclusion

Effectively addressing physician burnout requires a comprehensive strategy that targets both entrenched attitudes and systemic issues within healthcare systems. This necessitates providing accessible and confidential mental health support, advocating for work-life balance, and destigmatizing help-seeking behaviors. We can cultivate a healthier and more resilient healthcare workforce by tackling these challenges head-on.

Ethics

Author Contributions: Concept - J.B-E.; Design - J.B-E., D.S., E.K.; Analysis and Interpretation - J.B-E., D.S., S.H., E.K.; Literature Review - J.B-E., D.S., E.K., B.C.M.; Writing - J.B-E., D.S., S.H., E.K.

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Sedation for Colonoscopy Procedures Using Dexmedetomidine Versus Propofol-Fentanyl Infusions: A Prospective Randomized Controlled Trial

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Abstract

Objective: Different anaesthetists for sedation or monitored anaesthesia care have been used for colonoscopy. The target of this research was the ability to perform colonoscopy under a painless degree of sedation and the prevalence of undesired proceedings.

Methods: A total of 60 patients were randomly divided into two groups: Group D received dexmedetomidine and Group PF received propofol-fentanyl. Patients in both groups received the same infusion ratio. The minimum infusion amount of dexmetatomidine is (0.1 to 0.4 μg kg^{-1} h^{-1}) in Group D, whereas fentanyl is administered at a rate of 0.01 to 0.05 μg kg^{-1} min^{-1} in the PF group during the approximately 45-min colonoscopy.

Results: Group D exhibited significantly lower modified Observer's Assessment of Alertness/Sedation (OAA/S) scores at intraoperative time points T1-T12. Group D also exhibited significantly lower visual analog scale scores for pain at intraoperative time points T4 and T7. The mean arterial pressure was significantly lower in Group D at intraoperative times T6-T8 and T11-T12, as well as upon admission to the post-anaesthesia care unit (PACU) and 30 min after admission to the PACU. The results of the ANOVA tests revealed a significantly lower heart rate in Group D. The respiratory rate exhibited a notable decrease during time intervals T8 and T10 in the PF group.

Conclusion: The administration of dexmetatomidine and propofol-fentanyl during colonoscopy was found to be safe. In addition, dexmetatomidine may present significant benefits in this context because of its lower occurrence of adverse respiratory events.

Keywords: Colonoscopy, dexmedetomidine, outpatient sedation, perioperative care, propofol, sedation

Main Points

- Evaluate and contrast the use of dexmetatomidine versus propofol-fentanyl for painless sedation in patients undergoing colonoscopy.
- To check the effectiveness and safety of both sedation modalities.

Introduction

Sedation is used during colonoscopy procedures for patients who experience difficulty remaining calm due to issues such as anxiety, pain, or physical discomfort.[1] Various anaesthetic techniques have been employed for colonoscopy. These techniques encompass both awake and asleep periods, with or without mechanical ventilation, as well as the management of patients who remain fully conscious throughout the procedure.[2] The level of sedation required can vary from patient to patient, but the patient must remain adequately sedated and pain-free during the process.[2] Anaesthesiologists have employed various intravenous sedative drugs to induce conscious sedation or provide

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monitored anaesthesia care during colonoscopies, with many using a combination of short-acting opioids such as remifentanil and propofol.[3]

Dexmetatomidine is a highly selective and potent α2-adrenoceptor agonist that has sedative, pain killer, anxiolytic, opioid-sparing, and sympatholytic effects.[4] In contrast to alternative sedatives, α2 adrenergic receptor agonists do not induce respiratory depression.[4] The expected pharmacokinetics and brief half-life within 5-6 min following loading dose injection enable the implementation of titration to achieve a favorable effect.[4] The sedative characteristics of dexmetatomidine are expressed through the hyperpolarization of noradrenergic neurons in the locus coeruleus.[5] Dexmetatomidine exerts its sedative effects by inducing hyperpolarization of noradrenergic neurons in the locus coeruleus.[5] This particular form of sedation, known as "combining sedation", may be beneficial for colonoscopy procedures requiring a deep level of sedation, ensuring adequate patient cooperation.[5]

This research aims to evaluate and compare the use of dexmetatomidine versus propofol-fentanyl for painless sedation in patients undergoing colonoscopy for various indications. We hypothesized that dexmedetomidine can be used as a solo agent for conscious sedation in colonoscopy procedures without or with minimal affection of hemodynamics or the need for airway intervention to replace the routine practice with propofol and fentanyl.

Methods

The current study participants were recruited from different hospitals of Al-Azhar University from December 2021 to May 2023. A total of 60 eligible patients of both sexes, aged between 21 and 60 years, with an American Society of Anesthesiologists (ASA) I and II, were randomized into two groups.

This study was approved by the Ethical Committee of the Department of Anaesthesiology, Intensive Care and Pain Management at Al-Azhar University (Registration number: 00385/2023). The study was registered in ClinicalTrials.gov under the number NCT06148103.

All patients provided informed written consent. The research was conducted under the revised Helsinki Declaration of the World Medical Association and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines for rigorous clinical study practice.

Group D received dexmedetomidine, whereas Group PF received propofol-fentanyl infusions in equal ratios. The initial dose of dexmedetomidine was 1 μg kg^{-1} over 10 min, and then a maintenance infusion was titrated in a range from 0.2-1 μg kg^{-1} h^{-1}). The administration of propofol was maintained at a rate of 25 to 150 mg h, whereas fentanyl infusion was maintained at 0.01 to 0.05 μg kg^{-1} min^{-1}. The doses of all drugs were modified to achieve a target level of sedation ranging between 2 and 4 points on the modified Observer's Assessment of Alertness/Sedation (OAA/S) scale.[6]

Type of study: A prospective, randomized, double-blind trial.

Primary Outcome

The primary outcome of this study was to assess the efficacy of painless sedation during colonoscopy. The patient's ability to collaborate and perform the procedure was evaluated using a 10-point numerical rating scale (NRS).

Secondary Outcomes

- High occurrence of adverse effects such as airway obstruction, respiratory depression, and hemodynamic insecurity.
- Failure to provide adequate sedation.

Randomization

Participants were allocated to either the D or PF groups using a simple randomization procedure. The allocation sequence was generated by a single researcher who ensured blinding of the allotment process by using sequentially sealed, opaque, and numbered envelopes. Another researcher implemented the randomization process and recruited patients.

A researcher who was blinded to the study procedures was responsible for collecting all intra- and postoperative data. We blinded the patients to their group allotment. Two infusion syringe pumps were employed for each patient, and measures were taken to conceal the infusion syringes and extension lines to prevent identification.

Anaesthetic Procedure

The patients were placed in the supine position, ensuring their comfort. Vital parameters were measured using standard monitors, including electrocardiography, non-invasive blood pressure monitoring, and pulse oximetry (SpO_2). All patients exhibited spontaneous respiration and were administered oxygen at a flow rate of 4 l min via simple nasal prongs. The end-tidal carbon dioxide monitor was connected to the oxygen nasal prongs to monitor the patient's respiratory rate (RR).

Following the insertion of a venous peripheral line, the research infusions were initiated following both drug sedation protocols. In case of anxiety, pain, or restlessness during the procedure, the rate of infusion of dexmetatomidine (Group D) or propofol-fentanyl (Group PF) was markedly increased. Inadequate sedation in either group was addressed by increasing the infusion rates initially, with the backup of

a propofol stat dose of 20 to 30 mg intravenously given if first-plane treatment was unsuccessful. 10 min before the procedure, propofol infusion was stopped, and both dexmetatomidine and fentanyl infusions were downgraded. Minimum infusion rates of both fentanyl (0.01-0.05 μg kg^{-1} min^{-1}) in the PF group and dexmetatomidine (0.1-0.4 μg kg^{-1} h^{-1}) in the D group were extended during colonoscopy, which lasted approximately 45 min.

We observed patients in the post-anaesthesia care unit (PACU) after completion of the procedure for 2 h before being released into the ward. All basic monitoring procedures were performed during their time in the PACU. In cases where nausea and vomiting occurred during the postoperative period, patients were administered ondansetron 4 mg and/or metoclopramide 20 mg intravenously as necessary. Once discharged from the PACU, the gastroenterology team decided on pain management and hospital discharge.

Measurements

• The patient's ability to collaborate and perform the procedure was evaluated using a 10-point NRS, with a score of 8 or higher indicating a successful colonoscopy.

• During colonoscopy, we assessed the level of sedation using the modified OAA/S scale. In addition, we requested patients to evaluate their anxiety levels at 12 specific intervals using visual analog scales (VAS).

• We asked candidates to grade degrees of pain: 0 (no); 1 to 3 (mild); 4 to 6 (moderate); 7 to 10 (severe pain) and anxiety: 0 to 1 (no or mild); 2 to 3 (moderate); 4 to 5 (severe anxiety).

• This grading was repeated at 12 subsequent times during colonoscopy: T0 (baseline), T1 (starting of the procedure), T2 (5 min after T1), and then 5-min intervals from T3 to T9. T10 (finishing off the procedure); T11 (patient admittance to PACU); and T12 (after T11 by 120 min.).

• After 24 h of colonoscopy, patients were interviewed individually to inquire about any potential adverse events they might have encountered, such as nausea, vomiting, or pain.

• Patients were asked if they would be willing to undergo the same anaesthetic technique again if necessary. Telephone conversations were organized in cases where patients had been cleared from the hospital on the day of the procedure.

Sample Size Justification

A discrepancy of 25% in the ability to perform a successful colonoscopy was deemed clinically significant. To determine a significant difference of 2.5 grading on the NRS scale for colonoscopy between the D and PF categories, it was deemed appropriate to have a sample size of 30 participants per group, resulting in 60 participants. This decision was made on the basis of a dual-sided analysis with a significance level (α) of 0.05, a statistical power of 90%, a standard deviation of 1, and accounting for a 10% potential dropout rate.

Statistical Analysis

Statistical analysis was performed using the SAS analytical program, variant 9.3 (SAS establishment, Cary, NC, USA]. All investigations were performed on an altered motive-to-treat set, which included all participants with a basic parameter throughout the clinical evaluation. We used Wilcoxon rank-sum analysis to establish a correlation between steady variables and univariate differences in the D and PF groups. In addition, the χ^2 test was used for categorical variables. Consecutive data were expressed as median (25-75% interquartile range) or mean [standard deviation (SD)], and group variables were expressed as count (%).

The levels of pain, anxiety, and sedation were compared between the two groups using one-way analysis of variance (ANOVA). A revised analysis of variance (ANOVA) was performed to evaluate the fluctuations of HR, mean arterial pressure (MAP), SpO_2, and RR during the procedure. The least-squares mean discrepancies between both groups were correlated, and the corresponding 95% confidence intervals (CI) and *P* values were provided. A significance level of $P<0.05$ was examined.

Results

Participant Characteristics

From October 2021 to May 2023, 116 patients underwent screening to determine their eligibility for the study. Before randomization, 56 patients were excluded, resulting in 60 patients who were equally divided into two groups, as shown in the consort flow chart (Figure 1): the D group (n=30) and the PF group (n=30). Significantly, there were no participants who were lost during the study.

Table 1 presents baseline patient characteristics and clinical features. There were no significant differences between the D and PF groups regarding patient demographic data, ASA physical status, co-morbidities, and anaesthesia time.

Outcome Variables

The colonoscopy procedure, performed with effective sedation, yielded positive results in all participants, as indicated by an overall mean NRS score (SD) of 8.95 (0.51) and a range of 7-10. The study found that the ability to perform colonoscopy under sedation was comparable between the D and PF groups. The mean NRS scores (94% CI) were 9.8 (9.6-10.0) for the D group and 9.3 (9.1-10.0) for the PF group. The *P* value was 0.15. The mean OAA/S scores (94% CI) were 3.8 (3.4-5.1) and 4.8 (3.3-5.5) for the D and PF groups, respectively, with a *P* value of 0.49 (Figure 2).

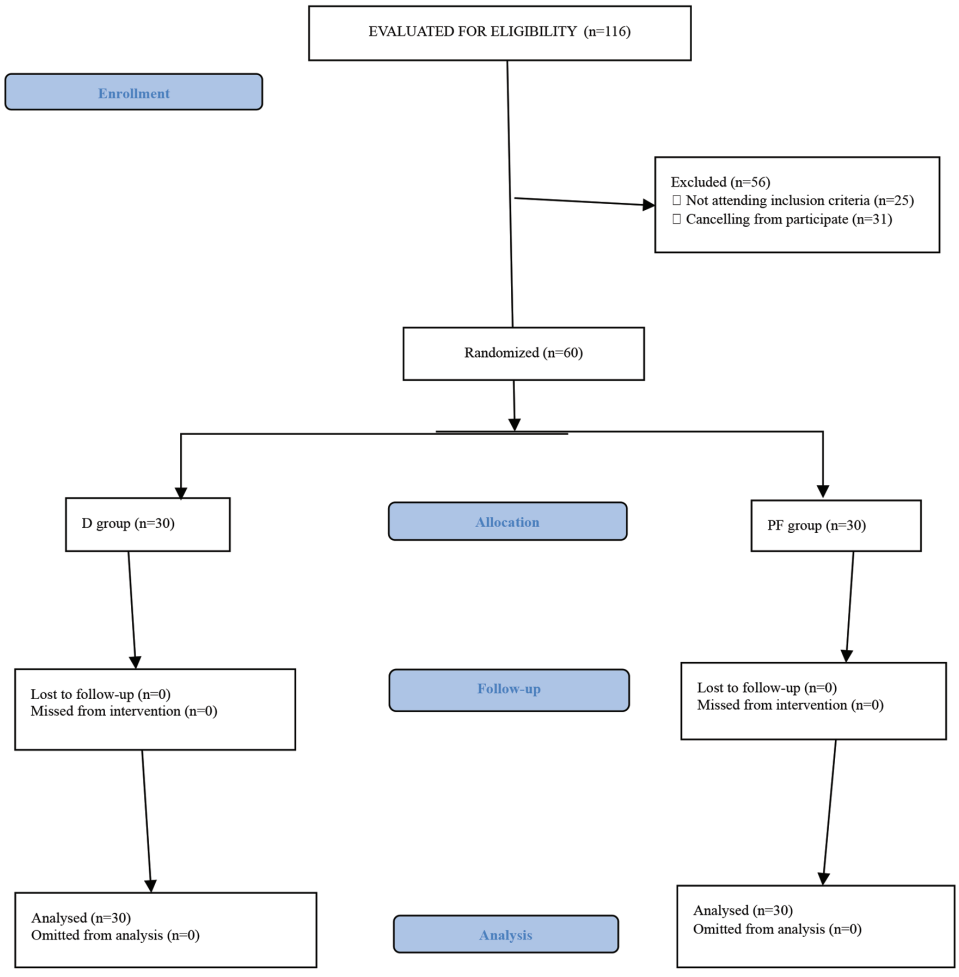

Figure 1. Consort flow graph.

Table 1. Baseline Data and Duration of Colonoscopy in All Patients

	All patients (n=60)	PF group (n=30)	D group (n=30)	*P* value
Patient baseline data				
Age [mean (range); years]	51.6 (21-66)	64.0 (2869)	57.8 (30-71)	0.12
Weight [mean (SD): kg]	77.2 (14.9)	75.7 (136)	74.5 (14.3)	0.26
Height [mean (SD): cm]	171 (15)	168 (8)	169 (18)	0.98
BMI [mean (SD): kg m/m$^{2\text{-}1}$]	29.2 (6.4)	27.7 (3.3)	26.9 (7.9)	0.05
Gender: male/female [n (%)]	31/29 (59.5/40.5)	17/13 (61/39)	13/17 (39/61)	0.83
ASA status I/II [n (%)]	10/50 (18/82)	5/25 (15/85)	6/24 (16/84)	0.89
Comorbidities [n (%)]				
Diabetes (n)	4 (8)	2 (6)	3 (10)	0.49
Hypertension (n)	8 (16)	5 (13)	5 (17)	0.73
Bronchial asthma (n)	5 (14)	5 (19)	3 (10)	0.48
Procedure duration (n)	45 (33-50)	42 (37-46)	43 (38-48)	0.51

Age is expressed as years; weight is expressed as kilograms; height is expressed as centimeters; and body mass index (BMI) is expressed as kg m$^{2\text{-}1}$. Gender, ASA category, and all comorbidities are expressed as numbers.
D group, dexmetatomidine group; PF group, propofol-fentanyl group; SD, standard deviation; ASA, American Society of Anesthesiologists.

The OAA/S scores during colonoscopy were significantly lower in the D group at time points T1-T12 (*P*=0.043) (Figure 2). The duration of awakening after the infusions ended was similar in both groups, lasting approximately 4-9 min. No notable disparity was observed in the NRS scores for anxiety between the groups throughout the procedure, as depicted in Figure 3. Group D demonstrated significantly reduced pain VAS scores during the T4 (*P*=0.030) and T7 (*P*=0.029) intraoperative time points, as shown in Figure 4.

Figures 5-7 display the measurements of hemodynamic parameters. Group D exhibited a noticeable decrease in MAP during the intraoperative period at times T6 to T8, with corresponding *P* values of 0.024, 0.006, and 0.024, respectively. The values at T11 and T12 were substantially low. It was also significantly low at T11 and T12, admittance to PACU with $P < 0.001$, and 30 min following admission to PACU (*P*=0.004). A significant interaction between time and both groups were observed for mean arterial pressure (MAP), with a *P* value of 0.044 (Figure 5). Repeated measures ANOVA analyses demonstrated a statistically significant decrease in heart rate during the procedure in Group D [mean difference (96% CI): -13.7 (-19.2, -8.6) beats min^{-1}, $P < 0.002$] over the procedure time in Group D, as demonstrated in Figure 5. In the PF group, RRs were significantly low at T8 with a *P* value of 0.030 and T10 with a *P* value of 0.002, as depicted in Figure 6. There

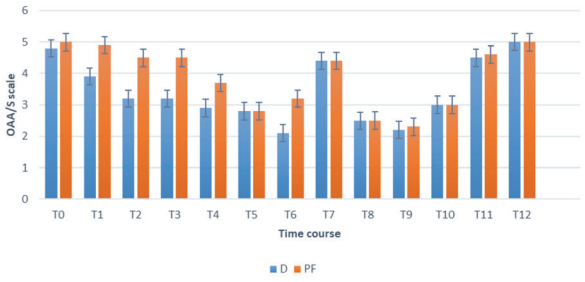

Figure 2. Modified Observer's Assessment of Alertness/ Sedation rate.

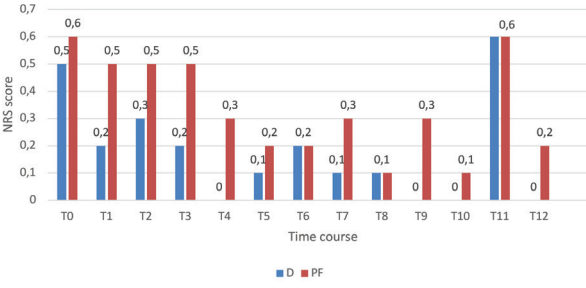

Figure 3. Numerical rating scale for anxiety.

NRS anxiety was checked at successive times (T0 to T12). Infusions of the drug were initiated at T0 and ended at T10. Outcomes are expressed as means (SD). D category is dexmedetomidine; PF category is propofol-fentanyl; T0, baseline before procedure start; T1, starting colonoscopy; T2, 5 min gap after T1; T3-T9; 5 min gaps; T10, colonoscopy finish; T11, shift to PACU; T12, after shifting to PACU by 120 min. *$P < 0.05$.

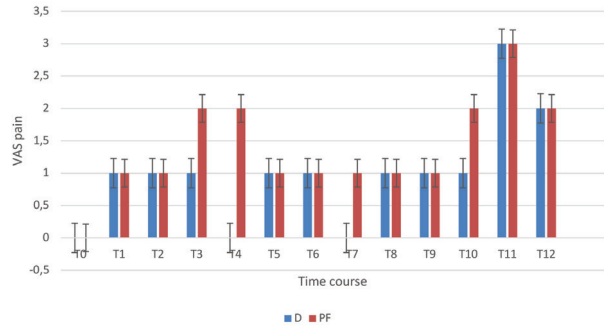

Figure 4. Visual analog scale for pain.

VAS pain was checked at successive times (T0-T12). Infusions of the drug were initiated at T0 and ended at T10. Outcomes are expressed as means (SD). D category is dexmedetomidine; PF category is propofol-fentanyl; T0, baseline before procedure start; T1, starting colonoscopy; T2, 5 min gap after T1; T3-T9; 5 min gaps; T10, colonoscopy finish; T11, shift to PACU; T12, after shifting to PACU by 120 min. *$P < 0.05$.

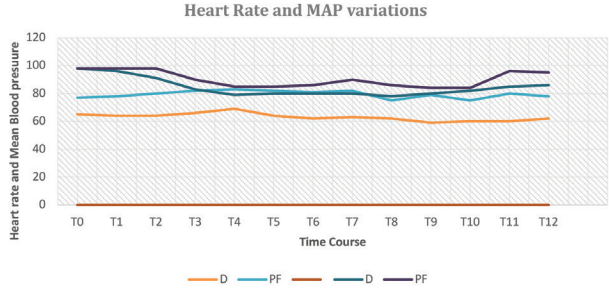

Figure 5. Heart rate and mean arterial blood pressure varieties during colonoscopy.

The spectrum of documented readings for mean arterial pressure in the D group was 60-105 mmHg; the spectrum for mean arterial pressure in the PF group was 55-100 mmHg. Infusions of the drug were initiated at T0 and ended at T10. Replicated readings ANOVA revealed that heart rate was significantly low [mean difference (94% CI): -14.3 (-18.4, -9.1) beats min^{-1}, $P < 0.001$] in the dexmedetomidine group. The dimension of documented readings for HR in the dexmedetomidine group was 38-112 beats/min; ranges for HR in the PF group were 44-148 beats min^{-1}. Infusions of the drug were initiated at T0 and ended at T10. Outcomes are expressed as means (SD). D category is dexmedetomidine; PF category is propofol-fentanyl; T0, baseline before procedure start; T1, starting colonoscopy; T2, 5 min gap after T1; T3-T9; 5 min gaps; T10, colonoscopy finish; T11, shift to PACU; T12, after shifting to PACU by 120 min. *$P < 0.05$.

was a significant difference in SpO_2 between both groups throughout the procedure (Figure 7).

Table 2 presents the prevalence of adverse events during the intraoperative period. The prevalence of pulmonary adverse effects requiring interference was low in group D compared with the PF group (0% vs. 23% respectively) (*P*=0.023).

Cardiovascular complications included transient hypotension managed with low-dose ephedrine (n=3) or phenylephrine (n=2), transient hypertension managed with labetalol (n=2) and hydralazine (n=1), a brief episode of bradycardia managed with atropine, and some agitation or emotional upset managed with a low dose of midazolam.

The assessment of patient satisfaction and memory of the colonoscopy procedure was conducted 24 h after the procedure using the Likert scale. During a structured meeting, we requested participants to assess their experience with the procedure by completing the following questionnaire: (1) overall satisfaction with comfort level, (2) intraprocedural recall, and (3) recall of the degree of intraoperative discomfort and anxiety, as indicated in Figures 8-10. All patients' inputs were significantly biased toward the D group.

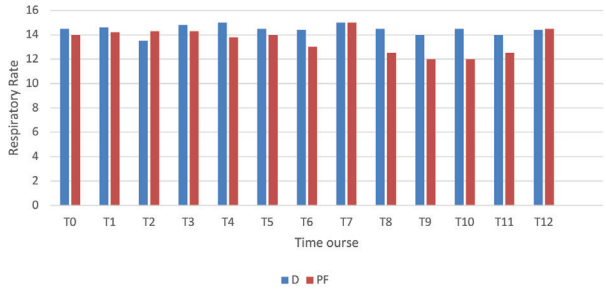

Figure 6. Respiratory rate alterations during colonoscopy.

The dimensions of documented readings for RR in the dexmedetomidine group were 6-26 cycles/m; ranges for RR in the PF group were 7-27 cycles/m. Infusions of the drug were initiated at T0 and ended at T10. Outcomes are expressed as means (SD). D category is dexmedetomidine; PF category is propofol-fentanyl; T0, baseline before procedure start; T1, starting colonoscopy; T2, 5 min gap after T1; T3-T9; 5 min gaps; T10, colonoscopy finish; T11, shift to PACU; T12, after shifting to PACU by 120 min. *$P < 0.05$.

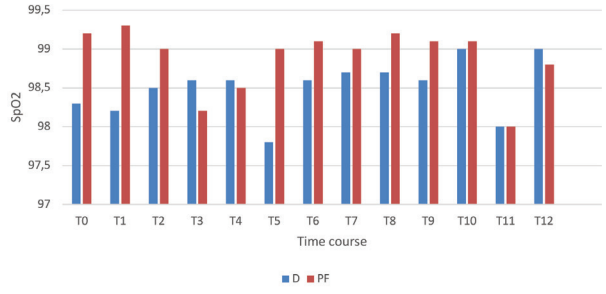

Figure 7. SpO_2 alterations during colonoscopy.

The dimension of documented readings for oxygen saturation (SpO_2) in the dexmedetomidine group was 85-99%; the dimension of documented readings for oxygen saturation (SpO_2) in the PF group was 89-100%. Infusions of the drug initiated at T0 and ended at T10. Outcomes are expressed as means (SD). D category is dexmedetomidine; PF category is propofol-fentanyl; T0, baseline before procedure start; T1, starting colonoscopy; T2, 5 min gap after T1; T3-T9; 5 min gaps; T10, colonoscopy finish; T11, shift to PACU; T12, after shifting to PACU by 120 min. *$P < 0.05$.

Table 2. Prevalence of Intraprocedural Adverse Events

	PF group (n=30)	D group (n=30)	RR	95% CI	*P* value
Pulmonary effects [n (%)]	7 (23)	0	11.12	0.61-169.03	0.025
Cardiovascular effects [n (%)]	6 (20)	4 (12)	0.89	0.31-3.78	0.89
Hypertension	3 (10)	2 (1)	1.91	0.21-18.88	0.56
Hypotension	2 (1)	1 (7)	0.51	0.03-4.66	0.54
Arrhythmias	1 (1)	1 (4)	0.90	0.05-13.91	0.90
Other events					
Psychomotor agitation	5 (13)	1 (3)	3.72	0.48-31.12	0.15
Vomiting	1 (2)	0	2.77	0.13-64.22	0.30
Participants with ≥1 adverse event [n (%)]	15 (50)	17 (56)	0.89	0.61-1.77	0.95

Inputs are presented as percentages (%).
CI, confidence interval; D group, dexmetatomidine group; PF group, propofol-fentanyl group; RR, relative risk.

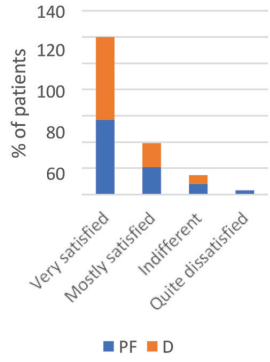

Figure 8. Patient satisfaction

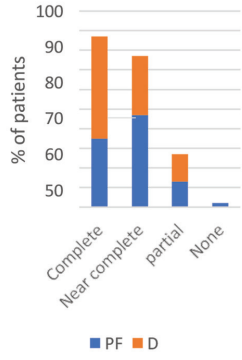

Figure 9. Experience recall

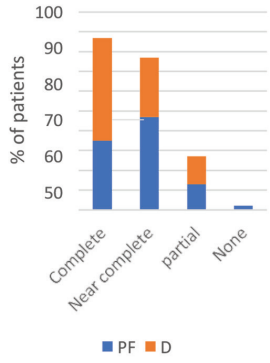

Figure 10. Anxiety recall

Discussion

In this comparative, randomized, prospective, and double-blind study, the use of either dexmedetomidine- or propofol-fentanyl-based sedation during colonoscopy yielded a similar intraprocedural efficacy. There was no difference in the occurrence of cardiovascular or other negative effects between the two groups. Furthermore, the prevalence of respiratory adverse effects was significantly higher in the propofol-fentanyl group. The levels of perioperative anxiety, pain, patient satisfaction, and recall were similar in both groups.

Compared with propofol-fentanyl, the administration of dexmetatomidine resulted in a decline in heart rate during the procedure time and a decline in mean arterial pressure throughout the minimal provocative times. However, the decline in heart rate did not exceed 20% from baseline.

Utilizing propofol for sedation, typically in conjunction with short-acting opioids, is a highly effective method for sedating patients during colonoscopy,[7] leading to a high level of patient satisfaction.[8] Nevertheless, irrespective of the selected anaesthetic method, colonoscopy remains a challenging procedure for patients who suffer from anxiety.[9] An optimal sedative medication should have extensive therapeutic evidence and anticipated pharmacodynamics to ensure adequate sedation.[10] Dexmedetomidine exhibits a synchronized sedation pattern, enabling patients to transition quickly from a state of sleepiness to wakefulness, follow instructions while conscious, and return to sleep when not stimulated.[11] The use of propofol for colonoscopy procedures was more satisfactory than dexmedetomidine infusions to patients in the Kavousi et al.[2] study, but on the other hand, there were recordings of respiratory depression in many patients who needed respiratory and airway support. This negative point will be reflected in the sedation doses needed to keep the patient well sedated, which might be increased. Our protocol is different from the Kavousi et al.[2] 2021 protocol in that we started dexmetatomidine infusion throughout the procedure, which helped to keep the patient well sedated during the procedure, but they started dexmetatomidine as a stat dose only. Consecutive research analyzing the effect of dexmetatomidine on the capability to perform intraoperative neurologic evaluation has yielded conflicting results.[12]

Recently, a comparison was performed between dexmedetomidine with midazolam and midazolam alone for procedural sedation during awake fiberoptic tracheal intubation.[13] Dexmetatomidine was determined to be as efficient when given with midazolam as midazolam alone.[13] In our study, we continued dexmetatomidine alone for the dexmetatomidine group throughout the procedure, which helped for a steady state level of sedation and a shorter awakening time after the procedure. The shorter awakening times observed in recent studies can be attributed to the comparatively lower levels of sedation administered before colonoscopy and the relatively brief duration of the procedure.

A single anaesthetic agent may not be effective for all phases of colonoscopy. The preparatory aspect of the colonoscopy procedure can be highly irritating. During this component, the patient may need further analgesia and sedation.

Ensuring that patients remain free from anxiety during this procedural period is of utmost importance.[13]

In our study, we assessed the level of sedation using the OAA/S scale. Although this scoring method is subjective and relies on analytic information, the OAA/S scale is a dependable and valid tool with minimal variability between different raters. Previous research has also demonstrated a strong correlation between bispectral index during dexmetatomidine and propofol sedation and the OAA/S scale.[14]

For our dosing of both dexmedetomidine and fentanyl-propofol, we did not find any significant variations in heart rate or mean blood pressure, which may be related to our use of glycopyrrolate prophylactically to prevent bradycardia and extrasystoles in some patients. Our findings coincide with the results of Karanth et al.[10]. They evaluated an initial dose of propofol 2-3 mg kg^{-1} over 10 min followed by a continuous infusion of 25 µg kg^{-1} min^{-1} in one group and compared it to another group where they started a bolus dose of dexmetatomidine 1 µg kg^{-1} intravenously over 10 min followed by a maintenance infusion of 0.2 µg kg^{-1} h^{-1} until the end of the procedure. They did not find any significant difference between the two groups regarding the vital parameters. However, we used fentanyl in addition to propofol to add an analgesic benefit.

Conclusion

The administration of dexmetatomidine and propofol-fentanyl during colonoscopy was found to be safe. Nevertheless, dexmetatomidine may present notable benefits in this context because of its lower occurrence of respiratory adverse events. Achieving an ideal dosage regimen of sedatives, along with maintaining a vigilant approach, are crucial factors for ensuring successful conscious sedation during colonoscopy.

Ethics

Ethics Committee Approval: This study was approved by the Ethical Committee of the Department of Anaesthesiology, Critical Care and Pain Management at Al-Azhar University (Registration number: 00385/2023). The study was registered in ClinicalTrials.gov under the number NCT06148103.

Informed Consent: All patients provided informed written consent.

Author Contributions: Surgical and Medical Practices - S.H.S; Concept - A.E.H.; Design - I.M.A.A.; Data Collection and Processing - S.H.S; Analysis and Interpretation - M.A.A.A.; Literature Review - M.A.A.A.; Writing - I.M.A.A.

Declaration of Interests: The authors have no conflict of interest to declare.

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Original Article
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Effect of Preoperative Oral Carbohydrate Intake on Perioperative Hyperglycemia in Indian Patients Undergoing Hip Fracture Fixation

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Abstract

Objective: Preoperative fasting leads to a catabolic state aggravated by surgical stress. This leads to poor patient outcomes. This study aimed to determine the effect of preoperative oral carbohydrate administration on perioperative hyperglycemia and patient comfort.

Methods: This prospective, randomized study was conducted on 60 adult American Society of Anesthesiologist I/II patients undergoing hip fracture fixation after obtaining institutional ethical committee clearance. Patients were randomly kept conventionally fasted before surgery (group F, n = 30) or were given oral carbohydrate 2 h before surgery (group C, n = 30). Under all aseptic precautions, a combined spinal epidural block was administered, and surgery was allowed. The primary outcome was blood glucose, and secondary outcomes included incidence of postoperative hyperglycemia, insulin level, blood urea, hunger, thirst, and anxiety.

Results: Blood glucose levels were not statistically different between the two groups at baseline (T0; *P*=0.400), immediately after surgery (T1; *P*=0.399) and 24h after surgery (T2; *P*=0.619). The incidence of postoperative hyperglycemia was significantly higher in group F than in group C (*P*=0.045) at T2. Insulin levels, blood urea levels, and hunger scores were also not statistically different between the groups. The thirst and anxiety scores were lower at T0 and T1 in group C.

Conclusion: Preoperative oral carbohydrate administration does not prevent perioperative increases in blood glucose levels. However, it reduces the incidence of perioperative hyperglycemia and decreases perioperative thirst and anxiety, thereby improving the quality of perioperative patient care.

Keywords: Blood glucose, carbohydrate loading, diet, enhanced postsurgical recovery, hip fractures, preoperative care/methods

Main Points

- Preoperative oral carbohydrate administration reduces the incidence of perioperative hyperglycemia.
- It improves patient comfort by decreasing thirst and anxiety.
- It enhances the quality of perioperative anaesthetic care.

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Introduction

Traumatic hip fractures are common in the geriatric demographics due to the prevalence of osteoporosis in this age group.[1] These fractures typically require surgical intervention and implant insertion. A neuraxial blockade is the preferred method of anaesthesia, barring any contraindications. However, the perioperative period can be challenging because patients often suffer from comorbid conditions and malnutrition. These factors predispose them to an increased risk of surgical site infections, wound dehiscence, and prosthetic joint infections.

Conventionally, patients scheduled for surgery are required to undergo overnight preoperative fasting to prevent the risk of pulmonary aspiration during anaesthesia. Nevertheless, the triple insult of trauma, surgery, and prolonged preoperative fasting induces a catabolic state, leading to the production of several anti-insulin hormones such as catecholamine, cortisol, growth hormones, glucagon, etc.[2] These hormonal changes contribute to the onset of stress hyperglycaemia[3] and insulin resistance, which can last for up to 3 weeks.[4,5] This state of hyperglycemia coupled with insulin resistance may be responsible for delayed wound healing, extended hospital stays, increased morbidity, and mortality.[6] Furthermore, individuals of specific Southeast Asian ethnic origins have an increased susceptibility to postoperative hyperglycemia (POH).[7] Thus, it is advisable to avoid prolonged periods of starvation in these patients.

The American Society of Anesthesiologists (ASA), the American Society for Parenteral and Enteral Nutrition, and the Enhanced Recovery after Surgery (ERAS) protocols recommend the administration of preoperative oral carbohydrate (POC)-containing fluids up to 2 h before surgery.

POC has become an integral part of the multidisciplinary approach within ERAS protocols for colorectal, cardiac, thoracic, and maxillofacial surgeries. However, the development of ERAS pathways for hip surgery is still ongoing.[8] There is limited literature concerning the role of POC in patients of Southeast Asian descent undergoing hip surgery. However, existing evidence suggests that individuals of Indian ethnicity are more prone to develop POH than those of Chinese and Malay ethnicities. Therefore, this trial was designed to include Indian patients undergoing hip fracture fixation under combined spinal-epidural (CSE) anaesthesia. Although ERAS pathways have been recently introduced in more advanced medical facilities in the country, they are not yet widely adopted in smaller or peripheral setups. The primary objective of this study was to determine postoperative blood glucose levels, with secondary objectives including the incidence of POH, postoperative insulin levels, blood urea levels, patient comfort, and the quality of perioperative care in terms of hunger, thirst, and anxiety.

Methods

This prospective randomized study was conducted at a tertiary care teaching facility in India from November 2019 to October 2021. Ethical approval for this study (IECHR/2019/41/3R) was granted by the Institutional Ethics Committee-Human Research on October 28, 2019, with Prof. Nalin Mehta serving as the chairperson. The trial was registered at ctri.nic.in (CTRI/2019/11/022084). All patients provided written informed consent before participation.

Sixty patients with ASA physical status I or II hip fractures, aged 18-65 years, were enrolled in the study. Patients with pre-existing conditions such as diabetes, pheochromocytoma, pancreatitis, alcoholism, jaundice or liver disorders, bleeding disorders, deranged coagulation profiles, local site infections, neurological or spinal diseases, obesity (body mass index >30 kg m^{2-1}), gastroesophageal reflux, gastric outlet intestinal obstruction, pregnancy, or those who had undergone continuous steroid therapy for more than 5 days in the past year were excluded.

Patients were randomly allocated to two groups, Group F and Group C, using a computer-generated random number table. Randomization was performed using sequentially numbered sealed opaque envelopes. Patients in Group F (n = 30) followed the conventional fasting pattern and refrained from consuming any solids or liquids orally for at least 6 h before surgery. In contrast, patients in Group C (n = 30) abstained from consuming any solids orally for a minimum of 6 h but received 200 mL of Aptonia hydration powder (manufactured by Zeon Lifesciences Limited, Noida, Uttar Pradesh, India) 2 h before surgery. The weight of one sachet is 36 g. Each sachet of the powder contained a combination of sucrose, maltodextrin, dextrose, minerals, vitamins, acidity regulator (INS 330), anticaking agent (INS 551), added food color, and lemon flavor. The powder was dissolved in 300 mL of water, as recommended by the manufacturer, of which 200 mL (nearly 24 g) was administered to the patient.

Following a comprehensive pre-anaesthetic check-up, the patients were taken inside the operating room. Pulse oximetry, electrocardiogram, and automated noninvasive oscillometer blood pressure monitors were attached. An 18-gauge intravenous cannula was inserted, and Ringer's lactate infusion was initiated. In addition, another cannula was inserted to collect blood samples.

With appropriate aseptic measures in place, CSE was administered in the midline lumbar region using 2.5-2.8 mL of heavy bupivacaine (0.5%). After ensuring an adequate level of subarachnoid block, surgery was started. Epidural top-ups with bupivacaine boluses were administered as necessary based on surgical requirements after a negative test

dose. The remaining course of anaesthesia was performed according to the standard protocol.

Blood glucose, insulin, and urea levels were estimated at three time points: at the time of CSE administration (baseline; T0), immediately after surgery (T1), and 24 h postoperatively (T2). POH was considered when the blood glucose level exceeded 180 mg dL^{-1} during the postoperative period (T1 or T2). In addition, patients were enquired about their comfort levels related to hunger, thirst, and anxiety at both T0 and T1. Furthermore, hunger was evaluated using a subjective scoring system known as the "Hunger Level Scale," while thirst was assessed using the "Perioperative Thirst Discomfort Score".[9,10] The presence of anxiety was noted as "yes" or "no". Other parameters, such as admission-to-surgery interval, last-meal-to-surgery interval, last-liquid-to-surgery interval, intraoperative complications, length of hospital stay, 30-day readmission (defined as readmission to the hospital for related complications within 30 days of surgery), and 3-month mortality, were also documented.

Sample Size and Statistical Analysis

Considering the immediate postoperative glucose levels as 105.40±17.47 mg dL^{-1} and 92.43±10.63 mg dL^{-1}, and 24 h postoperative glucose levels as 115.31±23.78 mg dL^{-1} and 100.00±10.63 mg dL^{-1} in the no-POC and POC groups, respectively, as reported in a previous study,[11] a sample size of 20 and 23 cases per group was required to estimate the same difference with a significance level (α) of 5% and a power of 80%. Because of the large sample sizes and to account for potential loss to follow-up, 30 cases were included in each group. Statistical calculations were performed using SPSS v.20.0 and STATA v.15.0. In addition, Student's t-test, Mann-Whitney U test, repeated measures analysis of variance followed by Dunnett's test, and chi-squared/Fisher's test were employed as appropriate. Statistical significance was set at P value < 0.05.

Results

A total of 69 patients were initially screened for eligibility. The CONSORT flow diagram of patient recruitment is shown in Figure 1. Among them, 60 patients were randomized, and all of them successfully completed the study protocol. The demographic characteristics of the patients included in the study were comparable between the two groups, as summarized in Table 1. Table 2 presents the surgical indications and fixation procedures performed.

A significant increase in blood glucose levels was observed in both the groups. However, blood glucose levels at corresponding time points were not statistically different between the two groups. Serum insulin levels at T2 were higher than those at T0 and T1 in Group F. Conversely, in

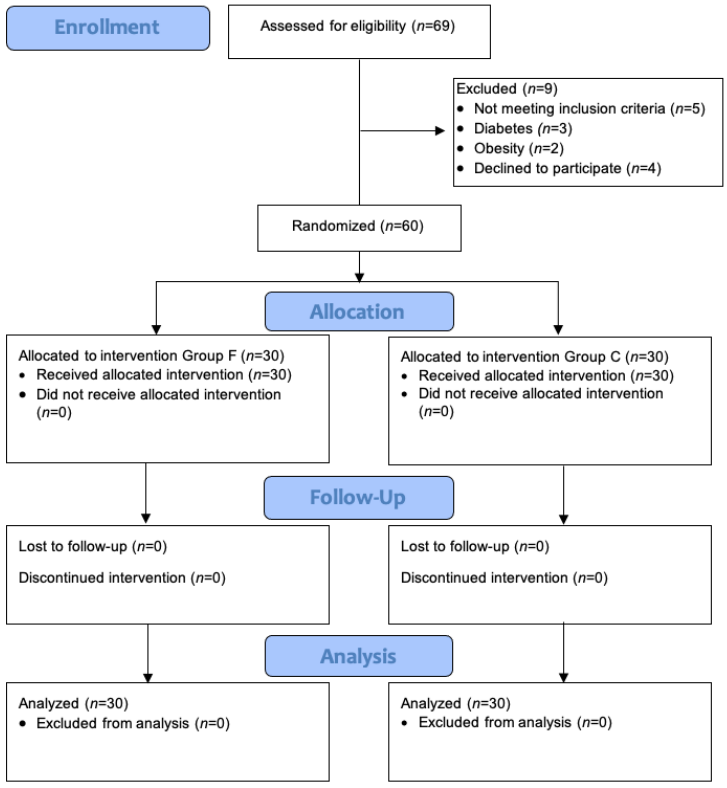

Figure 1. CONSORT flow diagram

Group C, insulin levels were higher at T2 than at T1 but remained not statistically different at T0 and T1 (P=0.472) and T0 and T2 (P=0.074). Insulin levels at the corresponding time points did not significantly differ between the two groups. Furthermore, no significant difference in urea levels was observed within or between the groups, as outlined in Table 3.

Table 1. Demographic Characteristics of the Patients

	Group F (n = 30)	Group C (n = 30)	*P* value
Age* (years)	36.8±13.8	40.9±14.3	0.260
Height* (cm)	163.4±6.7	162.7±8.0	0.740
Weight* (kg)	62.8±10.1	60.2±10.5	0.337
BMI* (kg m^{2-1})	23.5±3.5	22.8±4.0	0.468
Gender (Male:Female)†	27:3	25:5	0.456
ASA (I:II)†	17:13	12:18	0.203

*Values are expressed as mean ± SD, †values are expressed as ratio; $P < 0.05$ is significant.
BMI, body mass index; ASA, American Society of Anesthesiologists; SD, standard deviation.

Table 2. Surgical Indications and Surgical Procedures

	Group F (n = 30)	Group C (n = 30)
Surgical indication		
Intertrochanteric femur fracture*	9 (30)	15 (50)
Neck of femur fracture*	21 (70)	15 (50)
Procedure		
Joint arthroplasty*	3 (10)	6 (20)
Reduction and fixation with CCS*	23 (76.7)	13 (43.3)
Reduction and fixation with DHS*	4 (13.3)	11 (36.7)

*Values are expressed as number (percentage).
CCS, cortico-cancellous screw; DHS, dynamic hip screw.

Table 3. Comparison of Biochemical Markers in the Perioperative Period

	T0	T1	T2	*P* value† Pairwise *P* value
Blood glucose (mg dL^{-1})				
Group F (n = 30)	109.1±18.2	124.4±21.3	145.5±31.3	T0 vs. T1: 0.004 T0 vs. T2: 0.001 T1 vs. T2: 0.003
Group C (n = 30)	104.6±22.1	119.5±24.0	132.6±20.0	T0 to T1: 0.015 T0 to T2: 0.001 T1 to T2: 0.025
P value*	0.400	0.399	0.619	-----
Insulin (microunits mL m^{-1})				
Group F (n = 30)	10.0 [7.7-16.0]	11.5 [7.9-18.5]	19.9 [14.1-29.9]	T0 to T1: 0.540 T0 to T2: 0.003 T1 to T2: 0.015
Group C (n = 30)	9.3 [5.9-15.9]	8.7 [6.2-15.0]	14.2 [10.8-21.1]	T0 to T1: 0.472 T0 to T2: 0.074 T1 to T2: 0.017
P value*	0.778	0.149	0.630	------
Blood urea (mg dL^{-1})				
Group F (n = 30)	25.5 [22.0-38.0]	32.0 [21.0-38.0]	29.5 [24.0-33.0]	T0 to T1: 0.537 T0 to T2: 0.988 T1 to T2: 0.478
Group C (n = 30)	28.0 [24.0-36.0]	29.5 [24.0-34.0]	27.0 [24.0-32.0]	T0 to T1: 0.979 T0 to T2: 0.444 T1 to T2: 0.334
P value*	0.731	0.811	0.651	------

Values are expressed as mean ± SD; *Between-group significance value; †Within-group significance value; $P < 0.05$ is significant; pairwise comparison is shown wherever the overall *P* value is significant.
SD, standard deviation.

Table 4 lists the incidence of POH with blood glucose levels exceeding 180 mg dL^{-1} in both groups. None of the patients developed POH in the immediate postoperative period (T1). However, at the 24th postoperative hour (T2), the incidence of hyperglycemia was notably lower in Group C than in Group F.

Table 5 provides the mean hunger and thirst scores, and the incidence of anxiety in the preoperative and postoperative periods. The mean thirst score was significantly lower in Group C than in Group F at both time points. Nonetheless, hunger scores in the preoperative and postoperative periods were similar between the two groups. Moreover, the incidence of anxiety was significantly lower in Group C than in Group F at both T0 and T1.

The interval between the last liquid intake and surgery was significantly shorter in Group C than in Group F (P=0.001). However, the time from admission to surgery (P=0.075), time from the ingestion of the last solid to surgery (P=0.811), and the length of hospital stay (P=0.348) were not statistically different among the groups. There was one incidence of bradycardia in Group C (3.33%) compared with none in Group F. Nine out of 30 patients in group F (30%) developed hypotension as compared to six out of 30 patients in Group C (20%). Also, the incidence of postoperative nausea and vomiting (PONV) was seen more in Group F (23.33%) as compared to Group C (3.33%). There was no incidence of 30-day readmission or 3-month mortality.

Table 4. Incidence of Postoperative Hyperglycaemia

	Group F (n = 30)	Group C (n = 30)	*P* value
T1	0 (0)	0 (0)	-----
T2	6 (20)	0 (0)	0.045

Values are expressed as number (percentage); T1: immediate postoperative; T2: 24th postoperative hour; $P < 0.05$ is significant.

Table 5. Hunger Score, Thirst Score, and Incidence of Anxiety

	Group F (n = 20)	Group C (n = 20)	*P* value
Hunger score*			
Preoperative (T0)	4.4±1.3	4.7±0.8	0.286
Postoperative (T1)	4.5±1.1	4.6±0.7	0.788
Thirst score*			
Preoperative (T0)	6.9±3.4	3.1±2.9	0.001
Postoperative (T1)	7.5±3.5	4.5±2.7	0.001
Incidence of anxiety†			
Preoperative (T0)	13 (43.3)	2 (6.7)	0.009
Postoperative (T1)	10 (33.3)	1 (3.3)	0.023

*Values are expressed as mean ± SD; †Values are expressed as number (percentage); $P < 0.05$ is significant
SD, standard deviation.

Discussion

This study was conducted in 60 patients of Indian origin undergoing hip fracture fixation. The results revealed that POC administration did not mitigate the perioperative rise in blood glucose and insulin levels, which typically occur in response to surgical stress. However, it was effective in reducing the occurrence of POH in this population. Moreover, POC was effective in reducing the thirst experienced by patients during the perioperative period when adhering to conventional nil per oral guidelines. This approach also contributed to a reduction in anxiety levels among patients during the perioperative period.

Hip fracture is a common cause of hospitalization, surgical intervention, prolonged immobility, and increased morbidity and mortality among the elderly population. In our study, the mean age of the patients ranged from 36 to 40 years, reflecting the higher prevalence of hip fractures among younger age groups in our clinical setup. Notably, the crude incidence of hip fractures in India is substantial, with rates of 105 and 159 per 100,000 among men and women, respectively, accompanied by a one-year mortality of 42%.[12] Given these alarming statistics, it is imperative to implement measures aimed at enhancing patient outcomes and reducing the burden on healthcare resources. Hip fractures include both intertrochanteric and femoral neck fractures, which are typically addressed through surgical interventions such as closed/open reduction with internal fixation using cortico-cancellous screws, dynamic hip screws, or proximal femoral nails. Nevertheless, prolonged preoperative fasting can predispose patients to a catabolic state as they struggle to tolerate the combined stress of trauma, surgery, and fasting.[4] Consequently, patients may experience insulin resistance lasting up to 3 weeks.[5,6]

The POC administered in the study consisted of Aptonia hydration powder. This drink provided approximately 96 kcal of complex carbohydrates as opposed to those provided by canned fruit juices commonly used as preoperative drinks in previous studies.[13,14] The composition aligned with the ideal drink recommended for preoperative administration. With a cost of only ₹20 ($0.24/€0.22) per sachet, it is affordable. Moreover, the drink is highly palatable and is available in lemon and orange flavors, with lemon-flavored powder being utilized in this study. POC was administered 2 h before the planned surgery to ensure gastric emptying before the administration of neuraxial block. In addition, the volume and timing of the drink conformed to the ASA and ERAS guidelines. A study has advocated the use of POC as it improves patient well-being and positively impacts glucose metabolism, insulin resistance, PONV,

and pain management.[15] In contrast, a meta-analysis of randomized controlled trials evaluating POC treatment in elective surgery observed that POC does not confer any beneficial effects on glucose clearance, insulin sensitivity, or postoperative complications.[16] In addition, the latest ERAS guidelines for hip and knee surgeries do not categorize POC as an essential routine intervention, and its administration is left to the discretion of the anaesthesiologist.[17]

The Society for Ambulatory Anesthesia, American Diabetes Association, and Society of Critical Care Medicine recommend target blood glucose levels below 180 mg dL^{-1}. Therefore, a cut-off value for hyperglycemia of >180 mg dL^{-1} was selected in this study.[18-20] Generally, blood glucose levels increase during the perioperative period owing to surgical stress.[21] The findings revealed that POC was not very effective in preventing this increase. However, spikes exceeding 180 mg dL^{-1} were less frequent among patients who received POC. Thus, POC effectively prevents the risk of blood glucose reaching harmful levels, which are associated with adverse perioperative outcomes.

Insulin levels similarly increased in the postoperative period, but values in the POC group consistently remained lower than those in the fasting group, suggesting the beneficial effect of POC. Because POC administration largely prevents the catabolic process to a great extent,[22,23] insulin levels in the blood are thereby reduced, leading to a decrease in insulin resistance. Furthermore, a systematic review examining the role of POC observed its ability to mitigate insulin resistance.[24] However, a sample size of 33 patients per group is required to obtain a statistically significant difference in insulin levels at 80% power and $\alpha = 5\%$.

In addition, increased blood urea levels in the postoperative period can serve as an indicator of nitrogen breakdown,[25] poor renal function, or acute kidney injury.[26] Insulin stimulation may also increase urea clearance.[27] Given that postoperative insulin levels were higher than preoperative levels in our study, it is plausible that insulin-stimulated urea clearance may have increased. Therefore, postoperative blood urea levels may have remained within a range comparable to preoperative values.

Preoperative hunger, thirst, and anxiety are common measures of patient comfort, satisfaction, and overall quality of care during the perioperative period.[28] Thirst can lead to feelings of anxiety, irritability, and weakness.[28] Moreover, discomfort due to thirst may be intensified in tropical countries such as India, where temperatures are often high. Hence, implementing a liberal protocol of fluid administration up to 2 h before surgery may improve patient comfort and decrease anxiety levels. However, it should be noted that the results of the reduction of anxiety and thirst with POC administration are not universal.[15] In our study, we observed a lower incidence of preoperative thirst as well as preoperative and postoperative anxiety in the POC group than in the fasting group; however, hunger scores were not statistically different between the two groups. These findings align with those of previous studies reporting inconsistent results regarding hunger levels following the administration of carbohydrate drinks. For instance, a study performed on patients undergoing gynecological laparoscopic surgery did not observe reduced hunger in those receiving POC,[29] which agrees with our findings. In contrast, according to Imbelloni et al.[28], patients who received POC were not hungry as they received the drink twice: once 2-4 h before surgery and again after spinal block inside the operating theatre.[28] Our results on hunger levels can be attributed to the fact that the Aptonia solution provided only 96 kcal of energy, and hunger assessments were conducted 2 h after consuming this drink. It is possible that the calories provided by the drink were not sufficient to satisfy the hunger of an adult patient who had fasted overnight.

This study determined the efficacy of POC on glucose and insulin levels during the perioperative period. To adhere to the ERAS pathway, we opted against the use of general anaesthesia and opioids during the perioperative period. Instead, we employed epidural catheters for perioperative and postoperative analgesia, specifically for prolonged surgeries, to ensure adequate pain relief and maintain patient comfort. Meanwhile, PONV was actively monitored and promptly addressed with appropriate treatment whenever it occurred. In addition, perioperative patient comfort was measured in terms of objective hunger and thirst scores, providing a more comprehensive evaluation than previous studies that only assessed the presence or absence of these symptoms.

Study Limitations

In addition, the study has certain limitations that should be acknowledged. Despite observing a lower incidence of PONV in patients receiving POC,[30] the study was not adequately powered to detect differences in PONV. Therefore, any potential differences in PONV between the groups may not have been readily clear. Additionally, while the ERAS protocol is known to reduce the length of hospital stay, only a portion of this protocol was implemented in our study through the administration of POC. Therefore, no beneficial effects on the length of hospital stay were observed.[31,32] Furthermore, insulin resistance could not be accurately calculated in our study because of the limitations in our setup. Specifically, the hyperinsulinaemic clamp technique, which is considered the gold standard for dynamic insulin resistance assessment, was not feasible to implement. Moreover, the homeostatic model assessment of the insulin resistance equation could not be applied because it measures static insulin resistance and may not accurately reflect the

situation in the perioperative setting. The potential clinical benefits of POC about surgical site infections, renal failure, and cardiovascular events were also not evaluated.

Conclusion

Based on the findings of this study, it can be concluded that POC administration does not effectively prevent the perioperative increase in blood glucose levels, although it leads to a modest increase in insulin levels among Indian patients undergoing hip surgery under neuraxial block. Despite this, the practice of administering POC remains beneficial as it reduces the incidence of POH and improves patient comfort by considerably alleviating perioperative thirst and anxiety. Therefore, we recommend the administration of 200 mL POC containing maltodextrin and a suitable flavoring agent up to 2 h before surgery, particularly in countries like India where the climatic conditions are hot and thirst levels are prevalent. This intervention can improve the overall quality of perioperative care.

Ethics

Ethics Committee Approval: Ethical approval for this study (IECHR/2019/41/3R) was granted by the Institutional Ethics Committee-Human Research on October 28, 2019, with Prof. Nalin Mehta serving as the chairperson. The trial was registered at ctri.nic.in (CTRI/2019/11/022084).

Informed Consent: All patients provided written informed consent before participation.

Author Contributions: Surgical and Medical Practices - E.E.M., R.S., A.T., A.D.A., M.M., S.M., V.G.T., A.E.A.; Concept - E.E.M., R.S., A.T., A.D.A., M.M., S.M.; Design - E.E.M., R.S., A.T., S.M.; Data Collection and Processing - E.E.M., R.S., A.T., A.D.A., M.M., V.G.T.; Analysis and Interpretation - E.E.M., R.S., A.T., M.M., V.G.T., A.E.A.; Literature Review - E.E.M., R.S., A.T., A.D.A., M.M., S.M.; Writing - E.E.M., R.S., A.T.

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Original Article
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Comparison of the Effects of Sevoflurane and Desflurane on Endothelial Glycocalyx in Patients Undergoing Laparoscopic Hysterectomy: A Randomized, Double-Blind Trial

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Abstract

Objective: Various enzymes, reactive oxygen species, inflammatory conditions, and major surgeries cause endothelial glycocalyx breakdown. Inhalation of anaesthetic agents may have protective effects on the endothelium. This study compared syndecan-1 and heparan sulfate levels to evaluate the effects of sevoflurane and desflurane on the endothelial glycocalyx.

Methods: This prospective randomized, double-blind study included 46 patients undergoing laparoscopic hysterectomy. The participants were allocated into sevoflurane and desflurane groups. Subsequently, blood samples were drawn at three time points: before anaesthesia induction for a baseline value (T0), after pneumoperitoneum (T1), and after extubation (T2). Heparan sulfate and syndecan-1 levels were measured.

Results: There was no statistical difference between the sevoflurane and desflurane groups in terms of heparan sulfate and syndecan-1 levels at any time point. A significant difference was found only in the desflurane group in the intragroup comparisons of the measurements of heparan sulfate levels (χ^2=29.826, $P < 0.001$). Matched pairs of the time points in the desflurane group showed that P=0.036 (Z=-2.099) for T1-T0, $P < 0.001$ (Z=-3.924) for T2-T0, and $P < 0.001$ (Z=-4.197) for T2-T1. The change in percentage between T2 and T1 of heparan sulfate in the desflurane group was found to be statistically significant (P=0.034).

Conclusion: The damage caused by surgical stress on the endothelial glycocalyx can be reduced by both desflurane and sevoflurane. The protective effect of desflurane is more prominent than that of sevoflurane.

Keywords: Desflurane, endothelium, glycocalyx, heparan sulfate proteoglycans, sevoflurane, syndecans

Main Points

- The endothelial glycocalyx is a crucial element of endothelial function.
- Disrupting endothelial glycocalyx integrity results in interstitial edema and coagulation disorders.
- Inhalation agents prevent endothelial glycocalyx degradation compared with intravenous anaesthetics.
- The damage caused by surgical stress on the endothelial glycocalyx can be reduced by both desflurane and sevoflurane.
- The protective effect of desflurane is more prominent than that of sevoflurane.

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Introduction

The glycocalyx is a dynamic and complex biochemical structure that consists of glycosaminoglycans (hyaluronic acid, heparan sulfate, chondroitin sulfate), glycoproteins (syndecan), and plasma proteins (albumin, antithrombin-III).[1] The endothelial glycocalyx forms a thick and physiologically active layer on the vessel surface that regulates oncotic pressure and prevents leukocyte and platelet adhesion to the endothelium.[2,3] Glycocalyx damage causes increased fluid permeability, resulting in interstitial edema and increased leukocyte and platelet adhesion, resulting in coagulation disorders.[4,5] Various enzymes, reactive oxygen species, inflammatory conditions, severe multiple traumas, and major surgical procedures lead to alterations in the endothelial glycocalyx.[6]

Compared with laparotomic surgery, laparoscopic surgery causes less surgical trauma, stress, and inflammatory response.[7] However, abdominal distension during pneumoperitoneum, which is necessary to create sufficient vision and working space in laparoscopic surgery, may also decrease splanchnic blood flow and organ ischemia. Moreover, deflation of the pneumoperitoneum may cause ischemia-reperfusion injury and oxidative stress.[8,9] These conditions, which are highly associated with endothelial glycocalyx degradation, can cause adverse outcomes.[6,9]

Hydrocortisone and anti-TNF-α agents help reduce surgical stress-induced mediator release and inflammation.[10] In addition, although inhalational and intravenous anaesthetic agents are thought to have protective effects against endothelial glycocalyx damage, previous studies have produced conflicting results. For instance, sevoflurane is effective in preventing endothelial glycocalyx degradation compared with controls.[11,12] However, neither sevoflurane nor desflurane was found to be superior to propofol in protecting the endothelial glycocalyx.[13-15] In contrast, another study suggested that sevoflurane resulted in lower syndecan-1 and heparan sulfate levels than propofol.[16]

Based on the existing literature, no studies have compared the effects of sevoflurane and desflurane on the endothelial glycocalyx. With the hypothesis that the effects of sevoflurane and desflurane on endothelial glycocalyx may vary depending on the differences in their chemical structures, we aimed to compare the serum syndecan-1 and heparan sulfate levels of patients undergoing laparoscopic hysterectomy under sevoflurane- or desflurane-based anaesthesia.

Methods

Ethics

Ethical approval of the study protocol was provided by the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Kartal City Hospital, Clinical Research Ethics Committee with protocol #514/192/32 and dated December 30, 2020. The trial was registered on www.clinicaltrials.gov with the reference NCT05068336. Written informed consent for participation was obtained from all patients before the trial. The study was conducted in accordance with the Declaration of Helsinki and reported in adherence to the CONSORT guidelines for randomized trials.

Study Design

This prospective, randomized, double-blind study was conducted at a university hospital between August 15, 2021, and November 5, 2021. The primary outcome was to compare serum syndecan-1 and heparan sulfate levels with sevoflurane- and desflurane-based anaesthesia. The secondary outcome was to explore the variation in syndecan-1 and heparan sulfate levels.

Participants

Patients scheduled for elective laparoscopic hysterectomy who were 18-65 years old with American Society of Anesthesiologists I and II were asked to participate in the trial. The predetermined exclusion criteria were refusal to participate in the study, risk of malignant hyperthermia, difficult airway, need for blood product transfusion, emergency surgery, and conversion from laparoscopy to laparotomy for any reason.

Anaesthesia Protocol

All participants received a standard anaesthesia regimen. Standard monitoring techniques, including electrocardiogram, pulse oximetry, end-tidal carbon dioxide, and noninvasive blood pressure, were applied to the patients in the operating room. A bispectral index monitor was not used. Body temperature was measured using an esophageal probe, and all patients were heated intraoperatively with a warming blanket. No premedication was administered. After establishing intravenous access, standard anaesthesia induction was performed with 1-1.5 mg kg^{-1} propofol, 1-2 μg kg^{-1} fentanyl, and 0.6 mg kg^{-1} rocuronium (lidocaine was not used). After endotracheal intubation, general anaesthesia was maintained with the inhalational anaesthetics sevoflurane or desflurane (according to the allocation) in 2 L min of 50-50% oxygen-air mixture. For the maintenance of anaesthesia, sevoflurane at a 2-2.5% concentration or desflurane at a 6-8% concentration was used to maintain a minimum alveolar concentration of 1. The patients were ventilated in the pressure-controlled, volume-guaranteed mode, with the tidal volume set at 8 mL kg^{-1} of ideal body weight.

All patients received a standard fluid treatment protocol. Crystalloids (ringer lactate) were infused at a rate of 1-1.5 mL kg^{-1} h^{-1} during surgery. No colloids were used. Tramadol (100 mg) and paracetamol (1 g) were administered for

postoperative analgesia to all patients 20 min at the end of the surgery. At the end of the surgery, the neuromuscular blocker was antagonized with the administration of 0.015 mg kg^{-1} atropine and 0.04 mg kg^{-1} neostigmine. After extubation, the patients were transferred to the post-anaesthesia care unit following adequate muscle strength and spontaneous ventilation.

Collection of Blood Samples

Venous blood samples to analyze syndecan-1 and heparan sulfate levels were drawn at three time points: intravenous access placement in the operating room, before anaesthesia induction for a baseline value (T_0), 5 min after gas insufflation for pneumoperitoneum but before the initiation of surgery (T_1), and 5 min after extubation of the endotracheal tube at the end of surgery (T_2). Blood samples were placed in a 5 mL vacuum tube. The samples were immediately centrifuged at a rate of 1500 × g for 10 min at 4 °C to separate the serum, and the supernatant was stored at 80 °C for further analysis of syndecan-1 and heparan sulfate.

Biochemical Analysis

Studies for the analysis of heparan sulfate and syndecan-1 parameters as indicators of endothelial glycocalyx injury were performed at the institutional medical biochemistry laboratory. The serum concentrations of these indicators were measured with the enzyme-linked immunosorbent assay (ELISA) technique using commercial ELISA kits (BT-Lab, Shanghai Korain Biotech Co., Ltd., Shanghai, China) according to the manufacturer's instructions.

Serum syndecan-1 levels were analyzed using the SDC1 ELISA kit (catalog #E3344Hu). The intra-assay coefficient of variation (CV) of Syndecan-1 was <8% and the inter-assay CV was <10% for this parameter. The serum concentration of heparan sulfate was analyzed using the HS/HPS ELISA Kit (catalog #E9005Hu). The intra-assay CV of heparan sulfate was <10% and the inter-assay CV was <12% for this parameter. The results are expressed in ng mL^{-1}.

Randomization and Blinding

Before anaesthesia induction, the patients were randomly allocated to sevoflurane-based or desflurane-based anaesthesia using the closed envelope method. The anaesthesia and surgery team and the statistician were blinded to the study goals. A data collector who was not involved in the study coded the blood samples and collected patient data. The research team members were blinded to the allocation until the statistical analysis was completed.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp., 2017). Percentage and frequency values were used for categorical variables, and the median, minimum, and maximum [med. (min.-max.)] were presented for quantitative data. The chi-square test was used to compare the two qualitative variables. The comparison of the two continuous variables was analyzed using the Mann-Whitney U test. Friedman variance analysis was performed for repeated measures of dependent variables. The Wilcoxon signed rank test was used for pairwise comparisons if statistical significance was found in the variance analysis. The type I error rate (α) was taken as 0.05 in the study.

The sample size was determined according to the change in mean heparan sulfate levels in the postoperative period based on the findings of a previously published study (allocation 1:1, two-sided).[1] Accordingly, 22 patients per group were needed to obtain a 0.80 power with a large effect size and an alpha error of 0.05.

Results

By considering possible dropouts, 50 patients were asked to participate in the study. Two patients declined to participate, and the other two were excluded from the study because of protocol violations (blood transfusion and conversion to laparotomy). Finally, data from 46 patients were analyzed (Figure 1).

The demographic and surgical characteristics of the participants in both groups were similar (Table 1). None of the patients received blood products. There was no intraoperative hypotensive period in any patient. The body temperature remained >36 °C during the surgery.

There was no statistical difference between the sevoflurane and desflurane groups in terms of heparan sulfate and syndecan-1 levels at any time point (Figure 2). A statistically significant difference was found only in the desflurane group in the intragroup comparisons of the measurements of heparan sulfate levels (χ^2=29.826, $P < 0.001$). Further analysis of the matched pairs of the time points showed that P=0.036 (Z=-2.099) for T_1-T_0, $P < 0.001$ (Z=-3.924) for T_2-T_0, and $P < 0.001$ (Z=-4.197) for T_2-T_1 (Figure 2). There was no significant difference at any time point in syndecan-1 levels between the desflurane and sevoflurane groups.

A final analysis was performed to determine the difference in the change percentage of syndecan-1 and heparan sulfate at the time points. Accordingly, the change percent between the T_2 and T_1 of heparan sulfate in the desflurane group was found to be significantly higher than that in the sevoflurane group (P=0.034) (Figure 3).

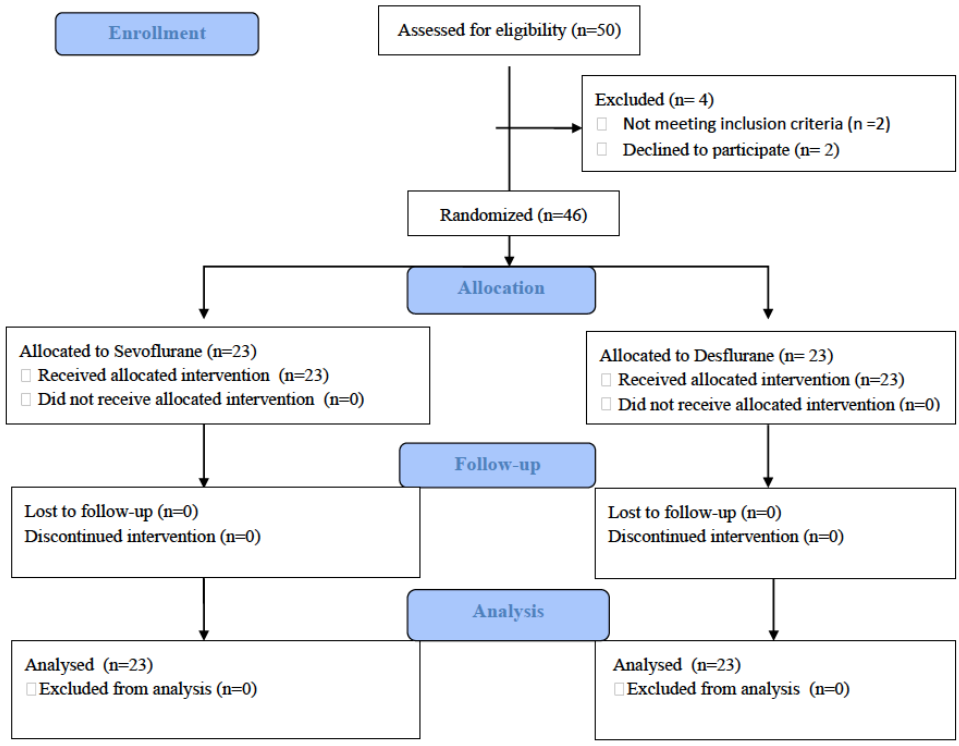

Figure 1. Flowchart of the study.

Table 1. Demographic and Surgical Characteristics of Patients Randomized to Sevoflurane and Desflurane Groups

	Sevoflurane (n = 23)	Desflurane (n = 23)	*P* value
ASA II; n	16 (69.6)	17 (73.9)	1.00
Hypertension/Diabetes; n	13/3 (56.5/13.0)	14/3 (60.9/13.0)	0.765
Age; years	47 (41-64)	49 (41-65)	0.775
BMI; kg m^{2-1}	29 (20-35)	28 (22-35)	0.834
Anaesthesia duration; minutes	135 (120-210)	150 (90-210)	0.930
Surgery duration; minutes	120 (100-200)	135 (80-200)	0.930
Amount of bleeding; mL	50 (0-300)	50 (50-300)	0.855
Total crystalloids; mL	2000 (1500-3000)	1800 (1000-3000)	0.195
Baseline HR; beats min^{-1}	83 (63-111)	85 (56-104)	0.367
End of operation HR; beats min^{-1}	74 (57-108)	76 (55-120)	0.921
Baseline MAP; mmHg	93 (63-128)	103 (73-143)	0.047
End of operation MAP; mmHg	84 (57-114)	88 (58-107)	0.582
Baseline SpO_2; %	99 (97-100)	99 (97-100)	0.944
End of operation SpO_2; %	100 (97-100)	100 (98-100)	0.502
Baseline $EtCO_2$; mmHg	34 (26-39)	35 (29-42)	0.193
End of operation $EtCO_2$; mmHg	35 (29-51)	38 (30-48)	0.071

Results are presented as n (%) and median (min.-max.).

ASA, American Society of Anesthesiologist; BMI: body mass index; $EtCO_2$, end tidal carbon dioxide; HR, heart rate; MAP, mean arterial pressure; SpO_2, peripheral capillary oxygen saturation; min.-max., minimum-maximum.

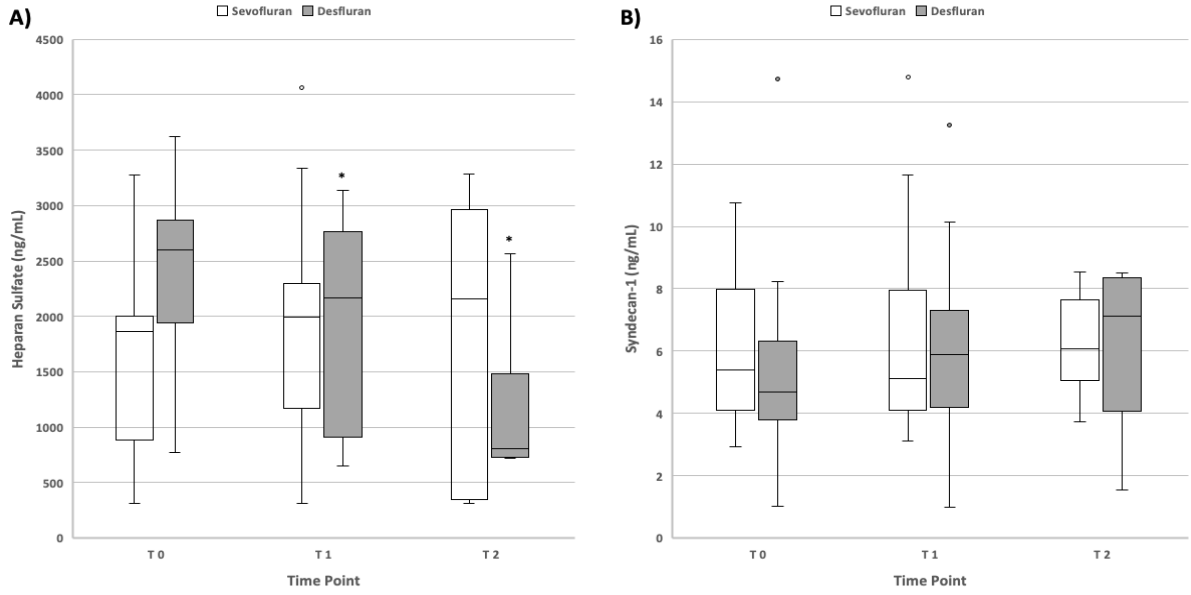

Figure 2. Alteration of heparan sulfate and syndecan-1 levels at the time points.

Box and whisker plots of heparan sulfate (A) and syndecan-1 (B) according to sevoflurane and desflurane anaesthesia before induction (T_0), 5 min after pneumoperitoneum (T_1), and 5 min after extubation of the endotracheal tube (T_2). The bottom and top of each box represent the 25th and 75th percentiles, respectively, the line inside the box is the median, the bottom and top of whiskers show the minimum and maximum range, respectively, and open circles indicate the outliers.

***Significant difference ($P < 0.05$) in heparan sulfate levels in the desflurane group compared with the values at T_0 and T_1 time points.**

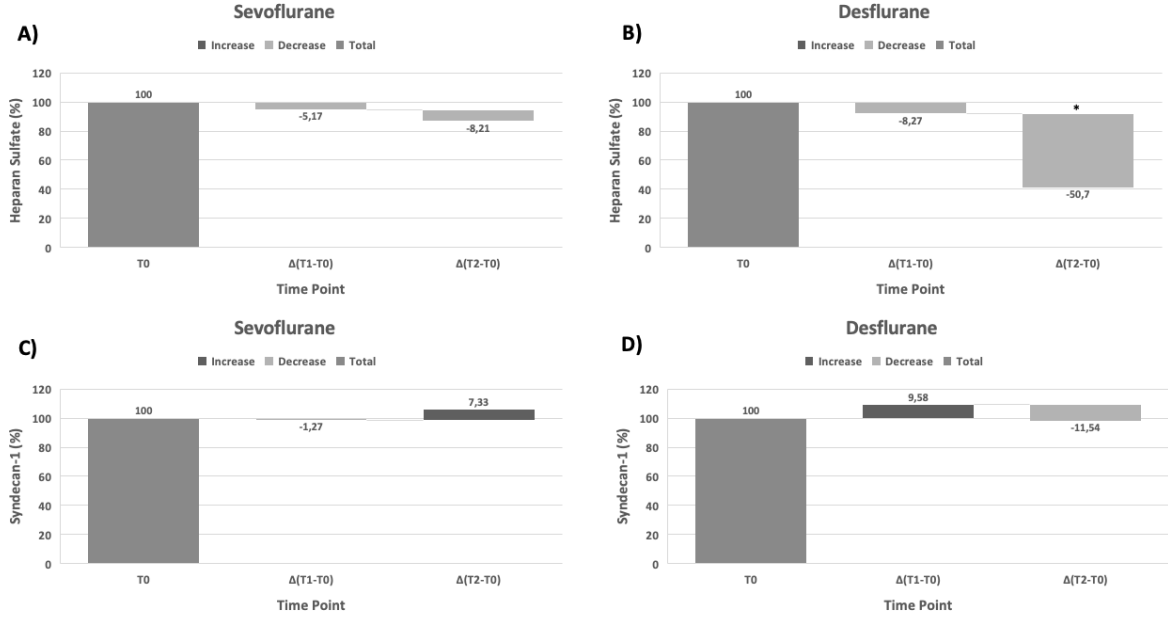

Figure 3: Comparison of the change percentage of heparan sulfate and syndecan-1.

The waterfall chart shows the change in the percent of heparan sulfate (A), (B), and syndecan-1 (C), (D) from the baseline measurement at T_1 and T_2 time points according to sevoflurane and desflurane anaesthesia.

***Significant difference ($P < 0.05$) in heparan sulfate change percentage in the desflurane group between T_2 and T_1.**

Discussion

The results of this study illustrated that heparan sulfate levels had decreased gradually in the desflurane group, indicating that desflurane had more protective effects on the endothelium than sevoflurane.

Many factors, such as major trauma and surgery, lead to endothelium damage and change endothelial functions.[6] Surgical stress causes the release of cathepsin B, a lysosomal protease stored in endothelial cells, and subsequent degradation of the glycocalyx.[17] Sevoflurane exerts a protective effect on the endothelial glycocalyx by stabilizing the lysosomal membrane.[18,19] and suppressing the proinflammatory agents responsible for inducing lysosomal discharge.[20]

Annecke et al.[11] in an animal study using electron microscopy, we demonstrated that heparan sulfate, syndecan, and cathepsin B release increased after ischemia, in addition to a massive increase in endothelial glycocalyx degradation. They also observed that these adverse effects due to ischemia were attenuated after sevoflurane administration. Similarly, another experimental study reported that endothelial glycocalyx components increased in serum after ischemia/reperfusion; this increase was more prominent with sevoflurane than with propofol-based anaesthesia.[20]

Although sevoflurane was emphasized to have protective effects on the endothelial glycocalyx in previous experimental studies on animals, the results in human studies were contradictory. Kim et al.[9] found that syndecan levels increased after laparoscopic surgery, indicating endothelial glycocalyx impairment. In addition, the authors stated that the increase in syndecan levels was more pronounced with sevoflurane than with propofol. Similarly, another study comparing the effects of sevoflurane and propofol against ischemia/reperfusion damage in patients who underwent knee surgery concluded that sevoflurane did not have a protective effect on the endothelial glycocalyx.[14] In contrast, Fang et al.'s[21] study's results denoted the endothelial protective effects of sevoflurane in cardiac surgery patients. Our study results can also be interpreted as suggesting that sevoflurane may have protective effects on the endothelium because the serum syndecan-1 and heparan sulfate levels remained unchanged.

Decomposition of syndecan from the endothelial glycocalyx structure requires protease activity, whereas lyase heparinase activity is required to degrade heparan sulfate in humans.[22] Our findings showed no evident alteration in syndecan-1 levels with desflurane, but heparan sulfate levels significantly decreased compared with baseline values. These findings can be interpreted as desflurane preventing endothelial glycocalyx degradation by affecting lyase heparinase activity and incorporating heparan sulfate molecules into the glycocalyx structure. In the literature, very few studies have examined desflurane's effects on endothelial glycocalyx. Contrary to our results, Oh et al.[15] found no difference between desflurane and propofol in protecting the endothelial glycocalyx from ischemia/reperfusion injury knee arthroplasty patients. The main difference between Oh et al.[15] and our study was that the mean age of the participants was higher in the trial conducted by Oh et al.[15] than in our patients. The endothelial glycocalyx structure becomes more prone to deterioration with advanced age. Therefore, we can hypothesize that the protective effect of desflurane may be obscured by age.

Although syndecan-1 levels were similar between desflurane and sevoflurane, the results of our study suggested that desflurane was more effective than sevoflurane in protecting endothelial glycocalyx integrity, depending on the obvious decrease in heparan sulfate values. Although injury and protection of the endothelium are multifactorial, there is clear evidence that anaesthetics are somehow involved in this process. Despite these findings, there is a need for large-scale human studies to reveal more definitive results because there are conflicting studies on sevoflurane and very limited studies on desflurane in the literature.

Study Limitations

The main limitation of this study is the lack of a control group comprising total intravenous anaesthesia. In addition, the study depicts endothelial glycocalyx degradation by measuring its components in plasma instead of directly visualizing the endothelial glycocalyx structure with electron microscopy. Furthermore, another limitation is that the enzyme levels that affect endothelial glycocalyx are not included. We believe that the analysis of these enzymes will further support our results. Finally, early postoperative pain levels were not evaluated in this study. Although inflammation can lead to pain, it does not always accompany overt inflammation.[23]

Conclusion

The damage caused by surgical stress on the endothelial glycocalyx can be reduced by both desflurane and sevoflurane. However, the protective effect of desflurane is more prominent than that of sevoflurane.

Ethics

Ethics Committee Approval: Ethical approval of the study protocol was provided by the University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar Kartal City Hospital, Clinical Research Ethics Committee with protocol #514/192/32 and dated December 30, 2020.

Informed Consent: Written informed consent for participation was obtained from all patients before the trial.

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- K.T.S., T.S., H.G.; Data Collection and Processing - T.S., F.D.G, E.K., R.G.M.K., A.K., A.S.; Analysis and Interpretation - H.G., K.N.B., A.S.; Literature Review - K.T.S., T.S., H.G., R.G.M.K., A.K., A.S.; Writing - K.T.S., T.S., H.G., R.G.M.K., A.K., A.S.

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