A COMPARATIVE STUDY OF SEVOFLURANE SEDATION WITH TCI PROPOFOL SEDATION IN DIALYSIS DEPENDENT END STAGE RENAL FAILURE PATIENTS FOR TRANSPOSITION OF BRACHIOCEPHALIC FISTULA REPAIR

LEE WEN XIN

FACULTY OF MEDICINE
UNIVERSITI MALAYA
KUALA LUMPUR

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LEE WEN XIN

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF ANAESTHESIOLOGY

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A COMPARATIVE STUDY OF SEVOFLURANE SEDATION WITH TCI PROPOFOL SEDATION IN DIALYSIS DEPENDENT END STAGE RENAL FAILURE PATIENTS FOR TRANSPOSITION OF BRACHIOCEPHALIC FISTULA REPAIR

ABSTRACT

Background:

End-stage renal failure (ESRF) is associated with increased anesthetic risks such as perioperative hypotension and cardiovascular events, resulting in higher perioperative morbidity and mortality. The primary objective was to assess whether sedation with sevoflurane would be superior to TCI propofol in maintaining hemodynamic stability among ESRF patients undergoing brachiocephalic fistula repair.

Methodology:

We conducted a prospective study involving thirty-one end-stage renal failure (ESRF) patients scheduled for brachiocephalic fistula repair surgery, randomly assigned to either the SEVOFLURANE or TCI PROPOFOL group. Each participant received ultrasound-guided regional anaesthesia comprising supraclavicular brachial plexus block and pectoralis II block. Sevoflurane was delivered from general anaesthesia machine via nasal CPAP mask, while TCI Propofol was administered intravenously through a TCI pump. Demographics and medical details were retrieved from the hospital's electronic medical record system (EMR) and anaesthetic records. Subsequently, the data was transcribed into a structured data collection form and analyzed utilizing SPSS version 23. Statistical significance was established at $p < 0.05$.

Results:

The sevoflurane group demonstrated a more stable MAP trend without significant changes (p-value: 0.36) notably at 30 minutes compared to the propofol group which exhibited a drop of 20% in MAP (p-value: 0.02). In contrast, the variation in heart rate remained nonsignificant for both groups throughout.

Within the sevoflurane group, there was a notable reduction in mean arterial pressure (MAP) ($F(2.679) = 3.96$, $p = 0.03$) and systolic blood pressure ($F(2.20) = 7.57$, $p = 0.004$. Heart rate within the sevoflurane group also exhibited a significant decrease ($F(2.96) = 3.67$, $p = 0.03$).Within the propofol group, significant variations were observed in mean arterial pressure (MAP) ($F(1.91) = 4.51$, $p = 0.03$) and systolic blood pressure (SBP) also exhibited noteworthy changes within the group ($F(2.14) = 7.35$, $p = 0.005$. However, unlike the sevoflurane group, heart rate (HR) in Group P did not demonstrate significant changes within the group ($F(6) = 1.405$, $p = 0.24$).

The induction time was notably shorter (p-value: 0.007) in the propofol group, on average 5.0 minutes (IQR 2.5-7.5), compared to the sevoflurane group's 8.8 minutes (IQR 7.5-11.3). However, there was no significant difference in recovery time (p value 0.54) between the two groups, with propofol group averaging 5 minutes (IQR 2.5-5 minutes) and sevoflurane group also at same value.

Conclusions:

Sevoflurane may be a better sedation agent compared to TCI propofol for end stage renal failure patients by providing a more stable haemodynamic profile with minimal side effects. However, sevoflurane may take longer time to induce patient compare to TCI propofol.

Keywords: sedation, ESRF, BCF repair, sevoflurane, propofol, TCI.

SATU KAJIAN PERBANDINGAN SEDASI SEVOFLURAN DENGAN SEDASI TCI PROPOFOL PADA PESAKIT YANG BERGANTUNG KEPADA DIALISIS DENGAN KEGAGALAN BUAH PINGGANG TAHAP AKHIR UNTUK PEMBAIKAN TRANSPOSISI FISTULA BRACHIOCEPHALIC

ABSTRAK

Latar belakang:

Tahap kegagalan buah pinggang akhir (ESRF) berkaitan dengan risiko anestetik yang meningkat seperti tekanan darah rendah perioperatif dan peristiwa kardiovaskular, yang menambahkan morbiditi dan mortaliti perioperatif yang lebih tinggi. Objektif utama adalah untuk menilai sama ada sedasi dengan sevoflurane akan lebih baik daripada TCI propofol dalam mengekalkan kestabilan hemodinamik di kalangan pesakit ESRF yang menjalani pembaikan fistula brakiokesefalik.

Methodologi:

Kami menjalankan kajian prospektif melibatkan tiga puluh satu pesakit kegagalan buah pinggang tahap akhir (ESRF) yang menjalani pembedahan pembaikan fistula brakiosefalik, dipilih secara rawak ke dalam kumpulan SEVOFLURANE atau TCI PROPOFOL. Setiap peserta menerima anestesia serantau berasaskan pengimejan ultrasound yang terdiri daripada blok plexus brachialis supraclavicular dan blok pectoralis II. Sevoflurane disampaikan melalui mesin anestesia am melalui topeng hidung CPAP, manakala TCI Propofol diberikan secara intravena melalui pam TCI. Objektif utama adalah untuk menilai sama ada sedasi dengan sevoflurane lebih baik daripada TCI propofol dalam mengekalkan kestabilan hemodinamik yang lebih unggul di kalangan pesakit ESRF yang menjalani pembedahan pembaikan fistula brakiosefalik. Butir-butir demografi dan perubatan telah diperolehi daripada sistem rekod perubatan elektronik (EMR) hospital dan rekod anestetik. Seterusnya, data tersebut telah ditranskripsi ke dalam

borang pengumpulan data yang berstruktur dan dianalisis menggunakan SPSS versi 23. Kepentingan statistik ditetapkan pada $p < 0.05$.

Keputusan:

Kumpulan sevofluran menunjukkan trend MAP yang stabil tanpa perubahan yang signifikan (nilai p: 0.36) berbanding dengan kumpulan propofol yang menunjukkan penurunan yang signifikan sebanyal 20% dalam tekanan arteri min (MAP) sepanjang sedasi (nilai p: 0.02). Walau bagaimanapun, kadar jantung kekal dan tiada perubahan signifikan bagi kedua-dua kumpulan sepanjang sedasi.

Dalam kumpulan sevoflurane, terdapat penurunan yang ketara dalam tekanan arteri minima purata (MAP) ($F (2.679) = 3.96$, $p = 0.03$) dan tekanan darah sistolik ($F (2.20) = 7.57$, $p = 0.004$). Kadar jantung dalam kumpulan sevoflurane juga menunjukkan penurunan yang signifikan ($F (2.96) = 3.67$, $p = 0.03$). Dalam kumpulan propofol, variasi yang signifikan diperhatikan dalam tekanan arteri minima purata (MAP) ($F (1.91) = 4.51$, $p = 0.03$) dan tekanan darah sistolik (SBP) juga menunjukkan perubahan yang ketara dalam kumpulan tersebut ($F (2.14) = 7.35$, $p = 0.005$). Walau bagaimanapun, berbeza dengan kumpulan sevoflurane, kadar jantung (HR) dalam Kumpulan P tidak menunjukkan perubahan yang signifikan dalam kumpulan tersebut ($F (6) = 1.405$, $p = 0.24$).

Masa induksi adalah lebih pendek secara ketara (nilai p: 0.007) dalam kumpulan propofol, dengan purata 5.0 minit (IQR 2.5-7.5), berbanding dengan kumpulan sevoflurane yang mengambil masa 8.8 minit (IQR 7.5-11.3). Walau bagaimanapun, tiada perbezaan yang signifikan dalam masa pemulihan (nilai p 0.54) antara kedua-dua kumpulan, dengan kumpulan propofol purata pada 5 minit (IQR 2.5-5 minit) dan kumpulan sevoflurane juga pada nilai yang sama.

Kesimpulan:

Sevofluran mungkin menjadi agen sedasi yang lebih baik berbanding propofol TCI untuk pesakit tahap akhir kegagalan buah pinggang dengan menyediakan profil hemodinamik yang lebih stabil dengan kesan sampingan yang minima. Walau bagaimanapun, sevoflurane mungkin mengambil masa lebih lama untuk mencapai tahap sedasi berbanding dengan TCI propofol.

Kata Kunci: sedasi, ESRF, pembetulan BCF, sevofluran, propofol, TCI.

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LIST OF SYMPBOLS AND ABBREVIATIONS

ASA: American Society of Anesthesiologists

BCF: Brachiocephalic fistula

CCF: Congestive Cardiac Failure

CPAP: Continuous Positive Airway Pressure

DBP: Diastolic blood pressure

ESRF: End Stage Renal Failure

GA: General Anaesthesia

HR: Heart rate

IQR: Interquartile Range

MAP: Mean arterial pressure

Min: Minute

NIBP: Non-invasive blood pressure

NMDA: N-methyl-D-aspartate (NMDA)

PECS II block: Pectoral nerves block II

pD: Pharmacodynamics

pK: Pharmacokinetics

RA: Regional Anaesthesia

SBP: Systolic blood pressure

SD: Standard Deviation

SpO2: Oxygen saturation

SPSS: Statistical Package for the Social Sciences

TCI: Target Controlled Infusions

TIVA: Total Intravenous Anaesthesia

UMMC: University Malaya Medical Centre

WHO: World Health Organization

VAS: visual analogue score

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CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION:

Regional anesthesia has demonstrated superiority over general anesthesia in end stage renal failure (ESRF) patients undergoing brachiocephalic transposition (BCF) by promoting graft patency, decreasing pharmacokinetic (pK) and pharmacodynamic (pD) variability, and minimizing hemodynamic instability (Bradley et al., 2017). However, the supraclavicular nerve block proves insufficient in BCF transposition procedures, where the surgical incision may extend to the axillary region, necessitating the blockade of the intercostobrachial nerve (T2) dermatome (Quek et al., 2018). In such cases, following supraclavicular and PEC2 block, intraprocedural lignocaine infiltration or intercostobrachial plane block may be necessary to supplement anesthetize this area. Consequently, sedation may be needed and is often recommended to alleviate anxiety and mitigate the sympathetic stress response to surgery.

Administering safe sedation to ESRF patients presents challenges due to their numerous comorbidities, polypharmacy, altered drug pharmacokinetics (pK) resulting from changes in total body water proportion, altered volume of distribution, protein binding, drug metabolism, and excretion (Rutkowska et al., 2009). The commonly used intravenous midazolam can lead to delayed recovery and apnea due to the impaired renal clearance of its active metabolite, α1-hydroxymidazolam (Rutkowska et al., 2009). Target-controlled infusion (TCI) of propofol requires a higher induction dose to achieve the desired level of hypnosis in ESRF patients and can induce hemodynamic disturbances (Virmani et al., 2016) (Zhong et al., 2018).

ESRF patients on dialysis commonly exhibit hypertension and are accustomed to higher baseline blood pressure levels (Xie et al., 2016). Intraoperative hypotension is exacerbated by the residual effects of antihypertensive medications, relative intravascular hypovolemia from preoperative hemodialysis, and preoperative fasting without fluid replacement. Maintaining adequate blood pressure is crucial for ensuring tissue perfusion, as evidence suggests that intraoperative hypotension is linked to adverse outcomes such as stroke, myocardial injury, and delirium (Maheshwari et al., 2020). Major hypertension guidelines recommend a target blood pressure of 140/90 mm Hg for renal disease patients (James et al., 2014).

Sevoflurane, a volatile sedative, has garnered significant praise in intensive care settings for its ability to shorten awakening time, reduce the incidence of delirium, and offer superior sedation compared to conventional intravenous sedatives like midazolam and propofol (Kim et al., 2017). Sevoflurane exhibits rapid onset of action, minimal concerns regarding tolerance and tachyphylaxis, and is cleared primarily via pulmonary exhalation, making it independent of hepatic and renal function (Jerath et al., 2017). Additionally, sevoflurane possesses mild analgesic properties and acts as an opioid-sparing agent through N methyl-D-aspartate receptor blockade, thereby providing a opioid reduction sedation profile (Jerath et al., 2016). Given that ESRF patients are predisposed to ischemic heart disease due to intimal calcification, sevoflurane's ischemic preconditioning and end-organ cytoprotective effects, along with its anti-inflammatory mechanisms, are particularly beneficial (Laferriere-Langlois et al., 2017).

The study aims to explore whether sevoflurane yields a more stable hemodynamic profile in end-stage renal failure patients undergoing brachiocephalic fistula repair under regional block, in comparison to sedation with TCI propofol during the operation.

1.2 OBJECTIVES OF THE STUDY

1.2.1 Primary Objective:

To determine whether sevoflurane sedation would be superior to TCI propofol

in ensuring better hemodynamic stability for ESRF patients going for brachiocephalic fistula repair.

1.2.2 Secondary Objectives:

to determine whether the administration of sevoflurane sedation

is superior to TCI propofol:

(a) Episodes of hemodynamic intervention- administration of vasoactive drugs to maintain hemodynamic within target (sBP> 140 mmHg, dBP > 80 mmHg, MAP within 20% baseline)

(b) Duration of hemodynamic instability

(c) Episodes of bradycardia (HR < 60) or tachycardia (HR >110 or increment of 20% from baseline)

(d) Onset time/ Recovery time

1.3 OPERATIONAL DEFINITIONS

Time of induction: the time taken from starting sedation to maintenance of three consecutive OAAS score of 3 (assessed over 15 mins).

Recovery time: the time taken from stopping sedation to recovery to OAAS score of 5, responding to name in normal tone.

OASS: Observer Assessment of Alertness/ Sedation score

Group S: Sevoflurane sedation group

Group P: TCI propofol sedation group

Hypertension: defined as MAP > 100 mmHg or an increment of >20% from baseline.

Hypotension- Drop in mean arterial pressure (MAP) from baseline or drop in systolic (sBP < 140 mmHg) and diastolic blood pressure (< 90 mmHg)

CHAPTER 2

LITERATURE REVIEW

Arteriovenous fistulas, formed by connecting a vein to an adjacent artery, are the most common type of access for hemodialysis. Research by Bradley et al. (2017) highlights their superiority over grafts, showing better primary patency rates, reduced thrombosis and infection rates, and lower morbidity and mortality.

While local anesthesia (LA) or general anesthesia (GA) may be preferred in certain cases, emerging evidence suggests that regional anesthesia (RA) can yield improved surgical outcomes (Ismail et al., 2017). Upper limb nerve blocks, a form of RA, are particularly advantageous in fistula formation surgeries, minimizing exposure to multiple anesthetic drugs and associated risks of GA. Studies suggest that RA induces vasodilation, aiding both surgical performance and postoperative graft patency (Ismail et al., 2017; Gao et al., 2020). RA leads to an improves venodilatation and vessel flow rates, both of which serve as indicators for successful fistula formation Aitken et al., 2016 RA also correlates with shorter maturation times (Ramadan et al., 2022), reduced failure rates, and improved patency rates (Cerneviciute et al., 2017). Moreover, RA's superior analgesic effect reduces postoperative medication requirements and facilitates faster discharge (Ismail et al., 2017).

However, RA has limitations, such as patient is alert and aware intraoperatively. Yet, careful sedation administration has enhanced patient comfort and acceptance of RA. Sedation techniques, by alleviating anxiety and minimizing pain, offer promise in improving patient tolerance for uncomfortable procedures (Blayney et al., 2012).

The preferred intravenous procedural sedatives, include midazolam, propofol, and remifentanil, among others, aimed at reducing patient awareness and enhancing compliance and comfort during sedation (Ross et al., 2010). Additionally,

dexmedetomidine is also frequently utilized alternatives for sedation in end-stage renal failure patients undergoing procedures.

Benzodiazepines, frequently employed for sedation purposes, exhibit an extended half-life in individuals with end-stage renal failure (ESRF), increasing the likelihood of respiratory depression, delirium, and falls. Both renal and nonrenal mechanisms for drug clearance, including CYP3A4 metabolism of benzodiazepines, may be compromised in chronic kidney disease (CKD) and ESRF, potentially resulting in drug-related side effects and potential renal accumulation effects (Beathard et al., 2011; Blayney et al., 2012). However, according to Beathard et al., the commonly used midazolam does not seem to pose an unacceptable risk to patients undergoing hemodialysis (Beathard et al., 2011).

Propofol, recognized as a short-acting sedative, has been demonstrated to be safe for use in patients with end-stage renal failure (ESRF) when administered at lower doses, with vigilant monitoring of blood pressure and oxygen saturation levels. Its wide utilization in Total Intravenous Anesthesia (TIVA) is attributed to its antiemetic effects, relatively swift recovery time, and enhanced patient satisfaction (Chen et al., 2022). Employing a target-controlled infusion (TCI) system for propofol entails the utilization of a pharmacokinetic model to attain and uphold a specified target concentration of propofol in the blood. Recent meta-analyses have indicated lower odds of cardiopulmonary complications with propofol sedation during advanced endoscopic procedures, such as endoscopic retrograde cholangiopancreatography (ERCP) and diagnostic colonoscopy, compared to conventional sedatives like midazolam (Sethi et al., 2014). As propofol lacks inherent analgesic properties, opioids are frequently administered concurrently, either via bolus dose or continuous infusion, as adjuncts in TIVA (Chen et al., 2022). Propofol is commonly used in combination with other agents, such as alfentanil or midazolam vs fentanyl, for sedation in patients with chronic renal failure (Lee et al., 2010). Notably, studies have shown that when propofol and alfentanil are employed to achieve

comparable levels of sedation and analgesia, patients with chronic renal failure are more prone to experience oxygen desaturation and apnea compared to control subjects (Lee et al., 2010). Moreover, propofol tends to induce hypotension, particularly in elderly individuals, who comprise most end-stage renal failure patients (Jeon et al., 2023). Perioperative hypotension has been associated with an increased risk of delirium in post-operative patients (Maheshwari et al., 2020).

Dexmedetomidine, an alpha-2 agonist, has emerged as a safe and effective sedative option for patients with end-stage renal failure (ESRF), demonstrating minimal impact on hemodynamic stability (Zhong et al., 2018). Its pharmacokinetic parameters in ESRF patients are comparable to those in individuals with normal renal function (Zhong et al., 2018). Dexmedetomidine is predominantly utilized for light sedation in intensive care settings (Jakob et al., 2012; Shehabi et al., 2019; Hughes et al., 2021), as well as for procedural sedation in awake fiber-optic intubation and pediatric patients. Research has shown that low-dose dexmedetomidine premedication reduces propofol consumption during sedation in geriatric patients with end-stage renal disease (Ergenogle et al., 2015). Given that ESRF patients often require fistula creation or repair surgery for hemodialysis access, Rutkowska et al. (2009) demonstrated the ability of dexmedetomidine sedation to prolong the effect of brachial plexus block in this population. However, it's worth noting that the dexmedetomidine regimen may have a slower onset of sedation, as it requires pretreatment with a 10-minute loading infusion (Sneyd et al., 2022). The SPICE III trial reported a significantly higher incidence of adverse effects, including bradycardia, hypotension, and persistent asystole, in the dexmedetomidine group, highlighting potential risks associated with its indiscriminate use (Shehabi et al., 2019). These findings prompted health alerts in Europe and New Zealand regarding the use of dexmedetomidine.

The mechanism of volatile anesthetic agents is complex and not entirely understood. They reduce presynaptic excitation and inhibit the release of neurotransmitters, inhibit

postsynaptic neurotransmitter function, and demonstrate anti-NMDA and anticonvulsant properties (Matthieu et al., 2024). Volatile anesthetics take effect rapidly, typically within 1-2 minutes, and wear off quickly within 4-7 minutes (Matthieu et al., 2024). These medications induce sedation in a dose-dependent manner and are traditionally used for general anesthesia. However, recent surveys conducted in French ICUs have expanded their applications, particularly in cases of severe asthma or bronchospasm, acute respiratory distress syndrome (ARDS), and when intravenous sedation fails (Blondonnet et al., 2021; Blondonnet et al., 2022). Sevoflurane, a non-irritating inhalational anesthetic with rapid onset and elimination, is widely used for induction, particularly in pediatric dentistry and MRI procedures (Ross et al., 2010). However, there is limited research on the use of sevoflurane for procedural sedation in adults, especially in those with end-stage renal failure.

Sevoflurane presents a promising alternative, if not superior, option for procedural sedation due to its titratability and pharmacological profile, allowing for precise tailoring of sedation levels for individualized treatment (Matthieu et al., 2024). One of its key advantages is its rapid clearance through the lungs and minimal hepatic metabolism (2-5% for sevoflurane), resulting in negligible production of active metabolites (fluorine ions) or significant alterations in hepatic or renal function tests in certain ICU patients as observed in published trials (Matthieu et al., 2024). Clinical trials have indicated that using inhaled sedation in ICU patients leads to shorter wake-up and extubation times compared to intravenous midazolam or propofol (Mesnil et al., 2011). Additionally, sevoflurane exhibits some analgesic properties (Jung et al., 2020), making it potentially beneficial as part of multimodal analgesic strategies, particularly in patients undergoing fistula repair surgery. While the use of sevoflurane for procedural sedation or analgesia is off-label due to its approval limited to the induction and maintenance of general

anesthesia, administering low doses for short durations for analgesia or sedation purposes is generally considered safe (Sneyd et al., 2022).

Sedation in patients with ESRF can be challenging due to altered drug metabolism and clearance. Benzodiazepines should be used with caution, while propofol and dexmedetomidine are safer alternatives for sedation in patients with ESRF. Sevoflurane may be an option for sedation for ESRF patients going for fistula repair surgery with a result of a more stable haemodynamic profile. However, careful monitoring of vital signs and titration of drug doses are essential to minimize the risks associated with sedation in this patient population. Further research is needed to optimize sedation strategies in patients with ESRF.

Sedating patients with end-stage renal failure (ESRF) presents challenges due to altered drug metabolism and clearance. Benzodiazepines should be used cautiously, while propofol and dexmedetomidine offer safer alternatives for sedation in this population. Sevoflurane might be considered for sedation in ESRF patients undergoing fistula repair surgery, potentially resulting in a more stable hemodynamic profile. However, close monitoring of vital signs and careful titration of drug doses are crucial to mitigate the risks associated with sedation in these individuals. Further investigation is necessary to refine sedation approaches for patients with ESRF.

CHAPTER 3

METHODOLOGY

3.1 Study design

This was a randomized, controlled, single blinded study. Patients were randomized to sevoflurane (Group S) or TCI propofol (Group P) using computer-generated sequences in blocks of six. The allocation concealment was carried out by having an independent investigator placing randomization sequence into sealed envelopes, which were numbered accordingly. The next available envelope was then placed on the folder of the next recruited patient and opened prior to induction of anaesthesia.

3.2 Data Collection

The patients recruited were from a university-affiliated teaching hospital. All patients undergoing transposition of brachiocephalic fistula repair with regional anaesthesia between September 2023 to February 2024 were screened for eligibility and all eligible patients were approached for consent. A total of 48 patients were assessed for eligibility. Among them, two patients (n=2) did not meet the inclusion criteria, while 15 patients (n=15) were unable to proceed with the study due to logistical issues, such as insufficient operating theater time or failure to complete payment for the operation leading to cancellation of surgery. Of the remaining participants, 31 were randomized without any dropouts or attrition. All patients underwent successful sedation, adhering to the study's protocol. These individuals were randomly assigned to either the Sevoflurane group (n = 16) or the TCI group (n = 15). (refer to Figure 3.1)

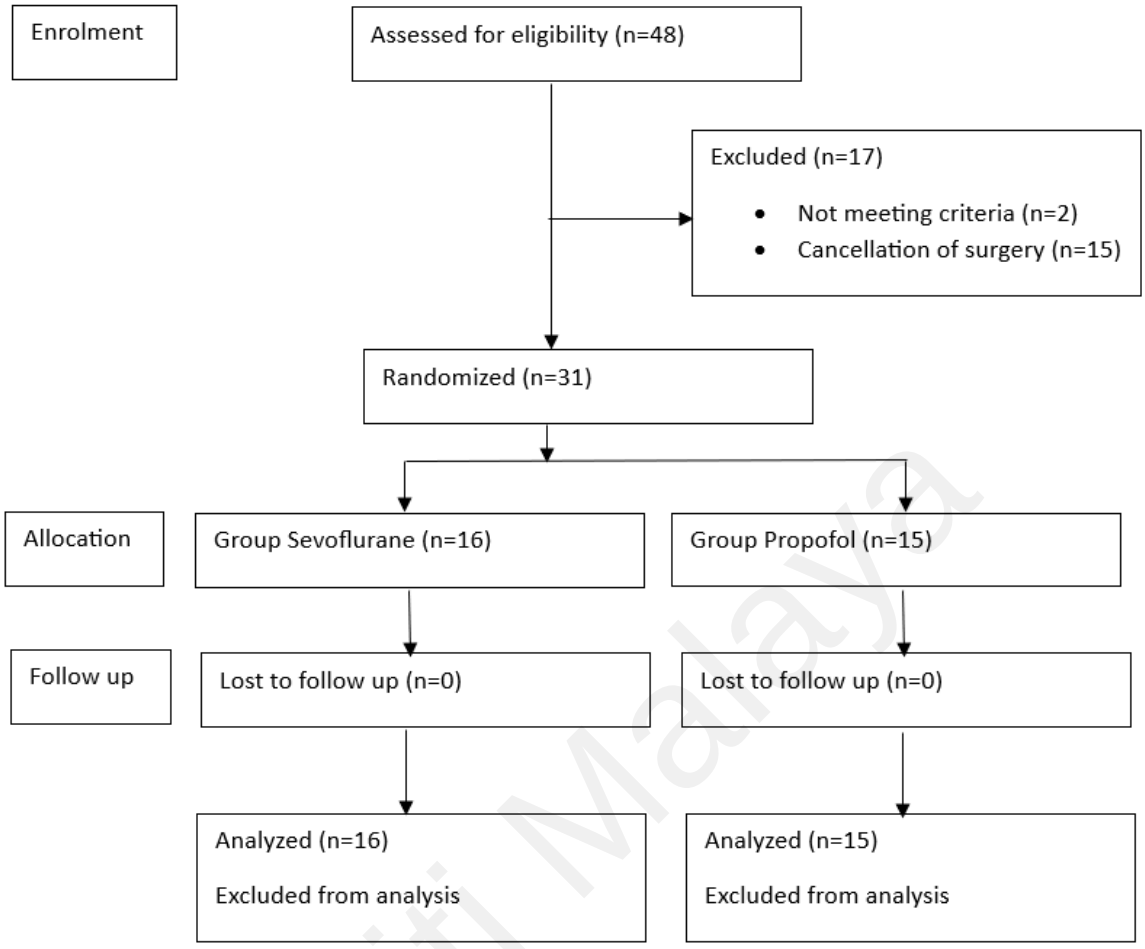


Figure 3.1 Flow diagram of the study from data collection to data analysis.

Inclusion Criteria

1. 18 to 80 years old

2. Patient with end stage renal failure, dialysis dependent undergoing transposition of brachiocephalic fistula repair

3. ASA II or III

Exclusion Criteria

1. Patient refusal

2. History or family history of malignant hyperthermia

3. Known allergy to propofol or local anaesthetic agent

4. Patients who have taken neuroleptics, benzodiazepine over 2 weeks within 1 month

5. Chronic use of alcohols/ opioid

6. Active lungs disease (e.g. acute exacerbation of COPD)

7. Active and significant cardiac disease (e.g. decompensated CCF, recent myocardial infarction)

8. End stage heart failure with left ventricular ejection fraction < 30% 9. Recent (< 3 months) cerebrovascular accident

Preoperative:

All eligible patients were seen by the investigator (blinded) 1 day prior to operation for consent. Patient also done their regular haemodialysis prior to the surgery. Information from prescribed haemodialysis, baseline vital signs and blood investigations were taken. Patients were assessed for level of anxiety using Hamilton Anxiety Score during the interview. All patients fasted for 6hours prior to operation. The morning antihypertensive was managed by treating physician blinded to this study. Patients were not be prescribed with anxiolytic, sedatives, or anti-emetic prior to the surgery.

Intraoperative:

In the operating theatre, all patients received regional anaesthesia by a consultant anaesthetist trained in regional anaesthesia. Supraclavicular block and PECs II block was performed using 15 mls 0.5% ropivacaine and 20 mls 0.25% ropivacaine respectively under ultrasound guidance. Adequacy of sensory and motor block was tested and charted by surgeon prior to skin incision. Subsequently, patients were randomized into 2 group:

Group S (received sevoflurane as sedation) and group P (received TCI propofol as sedation). It was a computer-generated randomized number. Sealed envelope was given to anaesthetist registrar who would administer sedation based on allocation group. The anaesthetist who administered the sedation were aware of randomization assignment but did not take part in randomization allocation. They were blinded to study objective and data collection. Minimum standard anaesthesia monitoring was applied to patients. These included noninvasive blood pressure (NIBP) monitoring, pulse oximetry (SpO2), electrocardiograph (ECG continuous lead II) monitoring and capnography. The end point of sedation was Observer Assessment of Alertness/ Sedation score (OAAS score) of 3 (Table 3.1). Before starting intervention, baseline vital signs such as Blood pressure (BP), heart rate (HR), mean arterial pressure (MAP) were recorded. The vital signs monitoring were recorded to average of 2.5 mins interval.

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking
0	Does not respond to noxious stimulus

Table 3.1 Observer Assessment of Alertness/ Sedation score (OAAS score)

Intervention

Group S (Sevoflurane sedation):

The patient was given time to familiarize with the nasal CPAP mask and nasal breathing with oxygen 3L/min via a Bain anaesthetic circuit before the introduction of sevoflurane. Once patient started to adapt to nasal continuous positive airway pressure CPAP mask (Fig 3.2), sevoflurane was delivered, starting with a concentration of 0.2% and increased

stepwise by 0.2% every 30s until sedation score of OAAS of 3 is achieved. Anaesthetist in charge assessed and maintained sedation endpoint to OAAS 3. If patient was over sedated, sevoflurane concentration was reduced by 0.2% until OAAS 3. The deepest level of sedation was then recorded.

Figure 3.2 Nasal continuous positive airway pressure CPAP mask.

Group P (TCI propofol sedation):

For TCI propofol group, all patients also received nasal CPAP mask and nasal breathing with oxygen of 3L/min. We utilized the Schinder model to target effect site (Cet) starting from 0.5 mcg/ml and with gradual 0.5mcg/ml increment every 30s until OAAS score of 3 was achieved. For any patients with OAAS score < 3, Cet was decreased by decremental 0.5 mcg/ml. The deepest level of sedation was then recorded.

Rescue therapy

Hypotension was treated with intravenous phenylephrine or ephedrine while bradycardia with atropine 0.5 mg. Hemodynamic interventions were measured in term of number of

doses and total amount of vasoactive drugs administered. The dose units were standardized as phenylephrine 20 mcg, ephedrine 6mg, atropine 0.5 mg. Occurrence of hypertension in event of pain was treated with intravenous fentanyl 0.5 mcg/kg. Critical respiratory event was classified into i) transient where SpO2 < 90% for < 60 seconds or ii) severe when SpO2 < 75% at any time or prolonged SpO2 < 90% for > 60 seconds. Desaturation was rescued by reassessing OAAS, adjusted the sedation dose to OAAS 3 or increased fractionate inspired oxygen flow rate. Obstructed airway was rendered patent by head tilt chin lift, support ventilation with positive end expiratory pressure (PEEP), insertion of nasopharyngeal airway, or bag valve mask ventilation. Apnea or hypopnea was rescued by converting spontaneous breathing to supported breathing (pressure support) with backup rate.

Excitation-disinhibition phenomenon throughout sedation was documented and severity was graded. Surgeon was blinded from type of sedation administered with an opaque screen between patient and patient.

At the end of procedure, patient was given 100% oxygen to breath for 10 mins before returning to post anaesthesia care unit and monitor for recovery agitation. After 30 mins of re-establishing verbal contact, investigator performed a brief questionnaire, inquiring about procedural recall, pain score, hallucination recall and sedation satisfaction on 0-10 score where 0 is ‘pleasant’, 10 being ‘unpleasant’.

Patient co-operation during the procedure was scored by the anaesthetist registrar and surgeon separately, using a Likert 5-point scale. In addition, the surgeon also was asked to indicate his/her satisfaction with sedation given using 0-10cm visual analogue score (VAS) (0 poor; 10 excellent).

3.3 Sample size

Sample size estimation was based on clinical importance reduction of mean arterial pressure (MAP) of > 20% from baseline. We calculated sample size based on a pilot study of 6 subjects (3 subjects per arm). The response within each arm was normally distributed (normality of data assessed by Shapiro Wilk test). The drop of mean artery pressure was 15 ± 9.8 mmHg and 29± 11 mmHg for sevoflurane and TCI propofol sedation respectively. Effect size calculated using Gpower version 3.1.9.2 is 1.3. Sample size calculated using a two-tailed independent t-test at 90% power and $\alpha = 0.05$ will be 13 subjects in each arm. Total sample size would account to 30 subjects accounting 20% dropout rate. We decided to recruit 36 subjects for the trial.

3.4 Data Analysis

In this study, all the variables were firstly presented using descriptive statistics to understand the data distribution. For the categorical variables, we summarized using counts and percentage whereas the continuous variables were presented using mean and standard deviation. The assumption of normality test was conducted using Shapiro-Wilk test to assess data normality for continuous variables. In the univariate analysis, the comparison between two groups were conducted. The Mann-Whitney U-test was used to analyze time to induction. The 95% confidence interval (CI) for the median difference in time between groups was calculated. The incidence of airway events and respiratory interventions was evaluated using either the Chi-squared test or Fisher exact test. Significant factors identified in the univariate analysis were further examined in multivariate analysis. Binary logistic regression was employed to determine the odds ratio and 95% confidence interval for categorical data, ensuring their significance to the model. Additionally, repeated measures ANOVA analysis was utilized to explore the hemodynamic response (MAP, SBP, DBP and HR) to sevoflurane and TCI propofol. This

is to test the statistical analysis for the variables between groups and within the group. Greenhouse-Geisser test was employed for correction of data which did not fulfill Mauchly's sphericity test. Multivariate analysis was used to analyze the difference of MAP, SBP, DBP and HR within group. All statistical tests were 2-tailed analysis, with p-values less than 0.05 were considered statistically significant. Data analysis was conducted using IBM SPSS Statistics version 23.

3.5 Ethical Concerns

Prior to the initiation of this study, ethical approval was diligently secured from the UMMC Medical Research Ethics Committee (MREC) on 5th May 2023, under the reference number 2021116-9722. (Refer to Appendix B for details.)

All data gathered during this study was treated with utmost confidentiality, adhering strictly to relevant laws and regulations. The statistical data was meticulously stored and managed through SPSS version 23 software. To enhance security measures, access to the data was restricted by implementing password protection, thus mitigating the risk of unauthorized access by third parties. The identity of the patients will not be disclosed in any publication or presentation of the study results without their explicit consent.

Access to the research data is exclusively granted to designated investigators, facilitated by the generation of unique passwords. This precautionary measure ensures the safeguarding of sensitive information against unauthorized access by external entities. Furthermore, in compliance with regulatory guidelines, the data will be securely retained for a minimum duration of seven years.

CHAPTER 4

RESULTS

4.1 Patient's Demographics and Medical Diseases

In Table 4.1, which summarizes the baseline characteristics of the patients, it's evident that there were no significant differences among them. Analysis of factors such as history of hypertension, diabetes mellitus, ischemic heart disease, respiratory disease, obstructive sleep apnea, years of renal replacement therapy (RRT), and smoking revealed no notable distinctions between the two groups. Moreover, Table 4.2 reinforced this finding, demonstrating no significant disparity in baseline hemodynamic profile and biochemical parameters between the two groups. Both Group S and Group P did not show significant difference in terms of number types of antihypertensive for their regular medications (p value= 0.79)

Table 4.1 Baseline demographics of the patients

Demographics		SEVO (n=16)	PROPOFOL (n=15)	
Mean age (years)		60.1 SD 11.2	58.5 SD 11.6	0.71*
Race	Chinese	4 (25%)	1 (6.7%)	0.38**
	Indian	1 (6.3%)	1 (6.7%)	
	Malay	11 (68.8%)	13 (86.7%)	
Sex	F	5 (31.3%)	7 (46.7%)	0.38**
	M	11 (68.8%)	8 (53.3%)	
Median dry weight (kg)		67.3 SD 11.3	65.3 SD 12	0.54*
Median height (cm)		161.9 SD 9	154.6 SD 8.8	0.03*

Table 4.1 continued

Demographics		SEVO (n=16)	PROPOFOL (n=15)	
Median body mass index (kg/m2)		26.1 SD 4.7	26.9 SD 5.7	0.65*
Number of types of antihypertensive	0	7 (46.7%)	7 (43.8%)	
	1	3 (20.0%)	1 (6.3%)	
	2	2 (13.3%)	3 (18.8%)	
	3	2 (13.3%)	3 (18.8%)	
	4	1 (6.7%)	2 (12.5%)	0.79**

* t-test

** chi-square test

Table 4.2 Baseline haemodynamic profile and biochemical parameters

	SEVO	PROPOFOL	SIG
Baseline hemodynamic profile			
SBP (mmHg)	139 SD 15	140 SD 16	0.84*
DBP (mmHg)	74 SD 12	72 SD 14	0.67*
MAP (mmHg)	96 SD 11	96 SD 12	0.99*
HR (bpm)	79 SD 8	79 SD 8	0.91*
Pre-op biochemical parameters			
Haemoglobin (g/dL)	10.8 SD 2.5	10.4 SD 1.6	0.62*
Sodium (mmol/L)	136 (IQR 133-138)	137 (IQR 135-139)	0.22*
Albumin (d/dL)	32.6 SD 6.8	33.8 SD 4.1	0.57*

* t-test

Table 4.3 Shapiro-Wilk Test of Normality

Tests of Normality[c]			
	Statistic	df	Sig.
Age	0.96	31	0.28
Dry weight (kg)	0.96	31	0.24
Height (cm)	0.98	31	0.91
Body mass index (kg/m2)	0.95	31	0.14
Years of RRT (year)	0.77	31	0.00
SBP	0.97	31	0.49
DBP	0.95	31	0.15
MAP	0.96	31	0.29
HR	0.95	31	0.12
urea	0.94	31	0.07
potassium	0.94	31	0.08
Hemoglobin	0.95	31	0.19
Sodium	0.30	31	0.00
Albumin	0.95	31	0.11
Volume extraction/Ultrafiltration (mls)	0.91	31	0.01
sedation total duration (mins)	0.96	31	0.39

surgery total duration (mins)	0.96	31	0.24
induction time (mins)*	0.90	31	0.01
Recovery time (mins)**	0.77	31	0.00
Total dose phenylephrine (episodes)	0.54	31	0.00
Total dose ephedrine (episodes)	0.34	31	0.00
MAP < 20% baseline (duration/mins)	0.53	31	0.00
MAP within 20% (duration/mins)	0.98	31	0.86
MAP > 20% baseline (duration/mins)	0.41	31	0.00

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

c. Total dose atropine (mg) is constant. It has been omitted.

4.2 Fluid balance prior to surgery

Fluid balance status remained consistent across both groups. Typically, intravenous fluids were not administered during the preoperative fasting period, with 81.3% (n=13) of the sevoflurane group and 100% (n=15) of the propofol group refraining from such fluids. Moreover, there were no significant discrepancies (p value 0.576) between the groups regarding volume extraction during preoperative hemodialysis, with the sevoflurane group recording an median extraction 2050 (IQR 1750-2600) and the propofol group extracting 2200 (IQR 2000-2800). There was no statistically significant variance in the

number of days of hemodialysis (HD) preceding the operation. Specifically, 53.3% of Group S underwent HD two days before the operation, compared to 56.3% of Group P who underwent dialysis one day prior to the operation (p-value=0.65).

Table 4.4 Fluid balance before the operation

		SEVO	PROPOFOL	SIG
Intravenous fluid given during fasting (mls)	100 ml	2 (12.5%)	0 (0%)	
	300 ml	1 (6.3%)	0 (0%)	0.21**
	NIL	13 (81.3%)	15 (100%)	
Volume extraction (mls)		2050 (IQR 1750-2600)	2200 (IQR 2000-2800)	0.58*
Last HD (days pre-op)	0	1 (6.7%)	1 (6.3%)	
	1	6 (40.0%)	9 (56.3%)	
	2	8 (53.3%)	6 (37.5%)	0.65**

*t-test

**chi-square test

4.3 Haemodynamic changes

The sevoflurane group demonstrated a relatively stable MAP trend without significant changes (p-value: 0.36) compared to the propofol group which exhibited a significant drop 20% from baseline in mean arterial pressure (MAP) at 30 minutes in this study (p-value: 0.02) (Figure 4.1). Heart rate did not show significant differences between the groups (p value= 0.88) (Figure 4.2).

Within the sevoflurane group, notable alterations were detected in mean arterial pressure (MAP) ($F(2.679) = 3.96$, $p = 0.03$). At 5 minutes, there was a reduction of 19 mmHg compared to the baseline MAP, reaching a maximum decrement of 25 mmHg at 60, 90, and 120 minutes. Systolic blood pressure also exhibited significant within-group changes ($F(2.20) = 7.57$, $p = 0.004$), experiencing a decrease of 27 mmHg at 10 minutes, and a maximal drop of 47 mmHg at 90 and 120 minutes. Heart rate within the sevoflurane group showed significant changes ($F(2.96) = 3.67$, $p = 0.03$), noticeable as early as 5 minutes post-sedation. However, diastolic blood pressure did not demonstrate a significant change ($F(6) = 1.652$, $p = 0.15$).

Within the propofol group, significant variations were noted within the group for mean arterial pressure (MAP) ($F(1.91) = 4.51$, $p = 0.03$). There was a reduction of up to 23 mmHg compared to baseline MAP at 30 minutes, with the maximum decrement of 26 mmHg observed at 90 minutes. Systolic blood pressure (SBP) also displayed notable changes within the group ($F(2.14) = 7.35$, $p = 0.005$), showing a decrease of up to 23 mmHg at 10 minutes, and reaching a maximum drop of 50 mmHg at 90 minutes. Conversely, diastolic blood pressure (DBP) for the propofol group did not exhibit a significant difference ($F(2.09) = 2.36$, $p = 0.13$), akin to the findings in the sevoflurane group. Unlike the sevoflurane group, however, heart rate (HR) for Group P did not demonstrate significant changes within group ($F(6) = 1.405$, $p = 0.24$).

Figure 4.1 Changes of MAP for Group S and Group P throughout the procedure

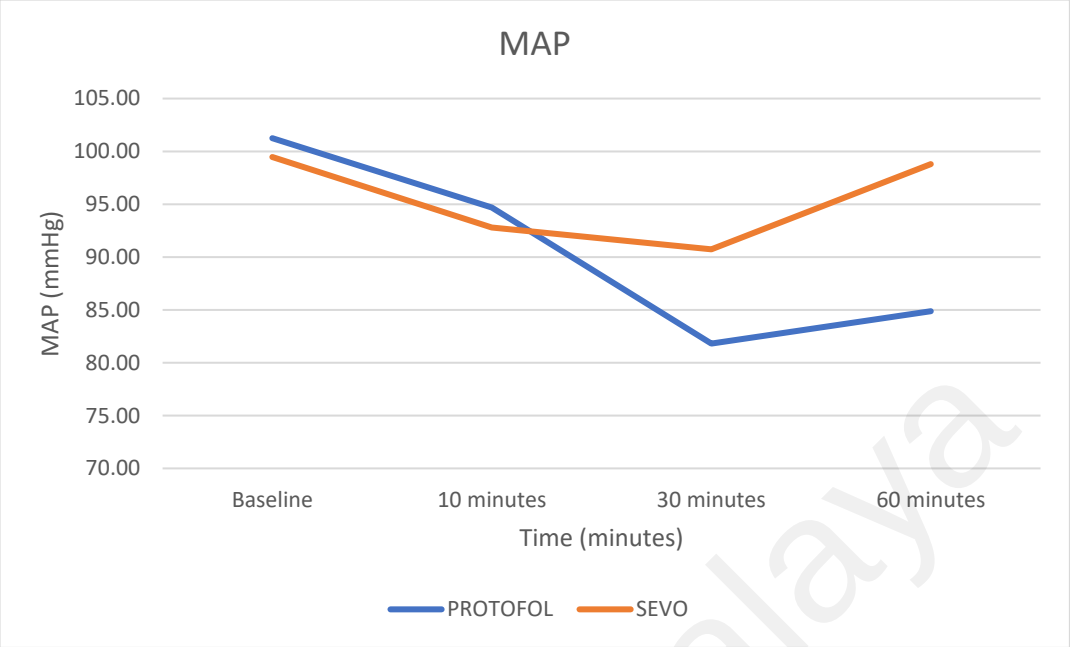


Figure 4.2 Changes of heart rate for Group S and Group P throughout the procedure

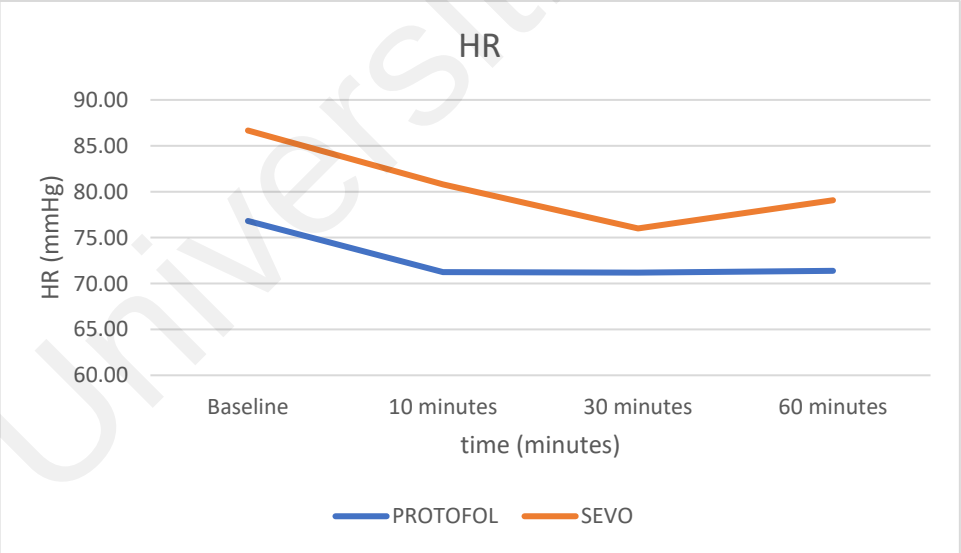


Table 4.5 Repeated measure Anova for Group S

		Type III Sum of Squares	df	Mean Square	F	Sig.
MAP	Sphericity Assumed	2095.30	6	349.22	3.96	.003
	Greenhouse-Geisser	2095.30	2.68	782.00	3.96	.025
HR	Sphericity Assumed	1308.64	6	218.11	3.67	.004
	Greenhouse-Geisser	1308.64	2.96	442.87	3.67	.027
SBP	Sphericity Assumed	7652.60	6	1275.43	7.57	.000
	Greenhouse-Geisser	7652.60	2.20	3479.79	7.57	.004
DBP	Sphericity Assumed	628.86	6	104.81	1.65	.153
	Greenhouse-Geisser	628.86	2.89	217.80	1.65	.206

Table 4.6 Repeated measure Anova for Group P

		Type III Sum of Squares	df	Mean Square	F	Sig.
MAP	Sphericity Assumed	1687.18	6	281.20	4.51	.001
	Greenhouse-Geisser	1687.18	1.91	883.34	4.51	.030
HR	Sphericity Assumed	288.61	6	48.10	1.41	.240
	Greenhouse-Geisser	288.61	1.61	179.42	1.41	.279
SBP	Sphericity Assumed	7324.21	6	1220.70	7.35	.000
	Greenhouse-Geisser	7324.21	2.14	3423.09	7.35	.005
DBP	Sphericity Assumed	751.21	6	125.20	2.36	.047
	Greenhouse-Geisser	751.21	2.09	358.94	2.36	.128

The duration of MAP below 20% of baseline did not significantly (p value 0.20) differ between the groups, with propofol group (5 minutes, IQR 0-32.5 minutes) and sevoflurane group (1.3 minutes, IQR 0-7.5 minutes). Mean duration of MAP within 20% of baseline also showed no significant distinction (p value 0.17), with sevoflurane group (113.4 minutes, SD 57.3 minutes) and the propofol group (97 minutes, SD 51.9 minutes). Similarly, the duration of MAP exceeding 20% from baseline did not significantly differ (p value 0.76) between the two groups, with the sevoflurane group (0 minutes, IQR 0-15 minutes) and the propofol group (0 minutes, IQR 0-15 minutes) (Figure 4.3). Moreover, there was no substantial difference observed in the instances of phenylephrine administration between the groups (p-value 0.438). In the sevoflurane group, 80% did not necessitate the drug, while in the propofol group, this figure stood at 43.8%. (Figure 4.4) The utilization of ephedrine was minimal and lacked significance across both groups (p-

value 0.40), with 87.5% in the sevoflurane group and 93.3% in the propofol group not requiring ephedrine. (Figure 4.5) Additionally, no injection of atropine was required for either group.

Figure 4.3 MAP duration for Group P and Group S

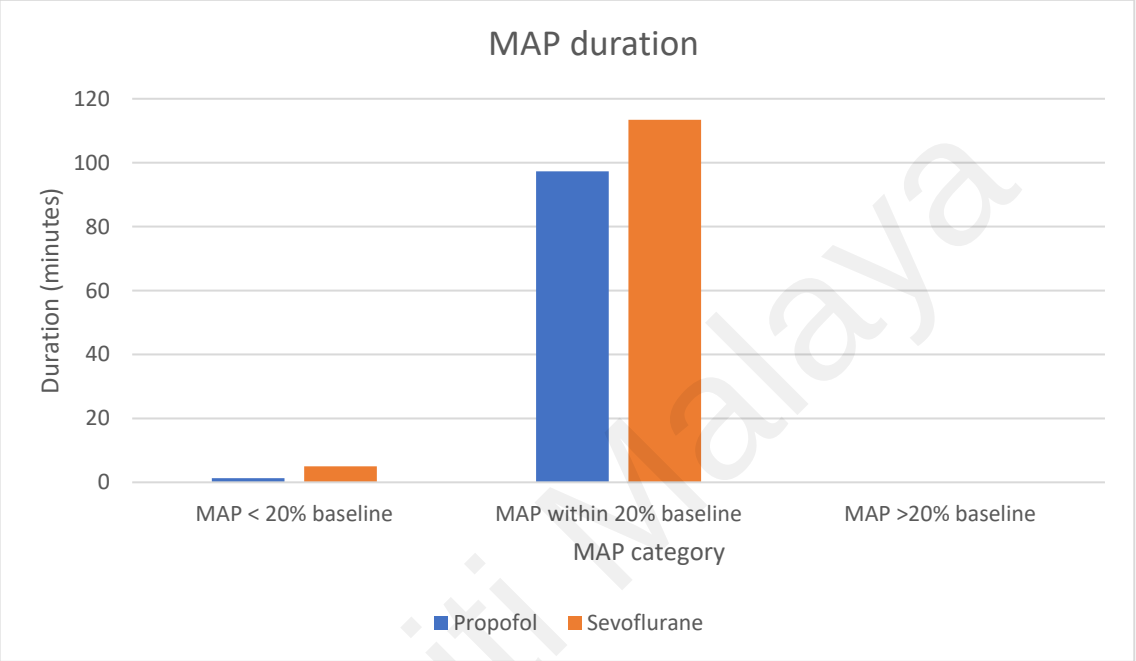


Figure 4.4 Episodes of phenylephrine required

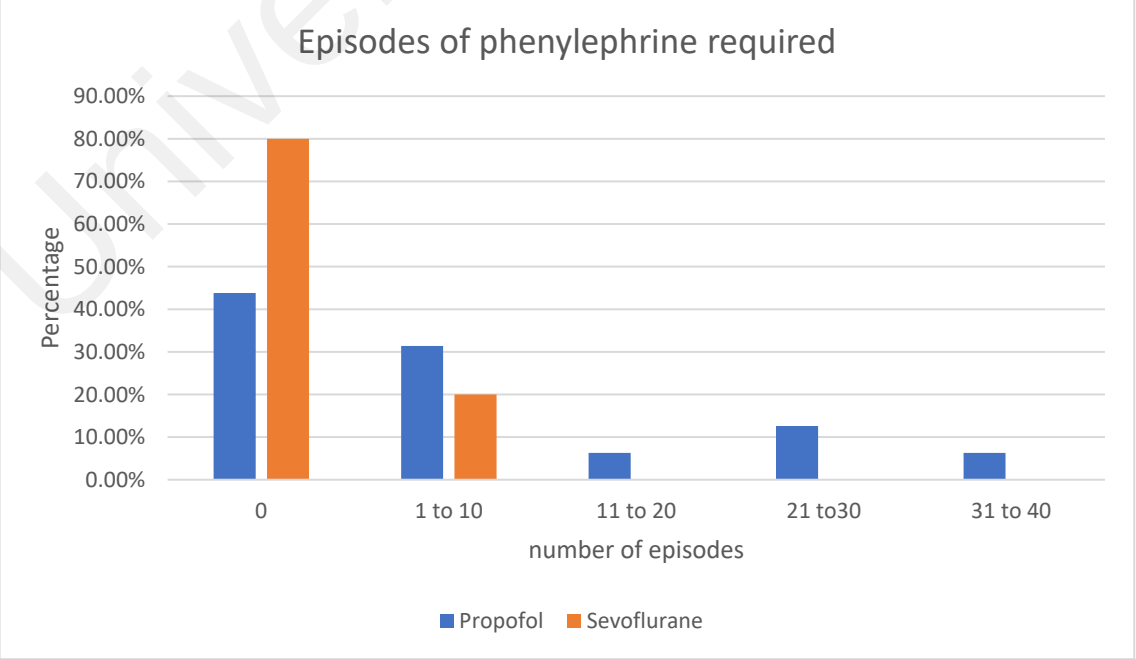
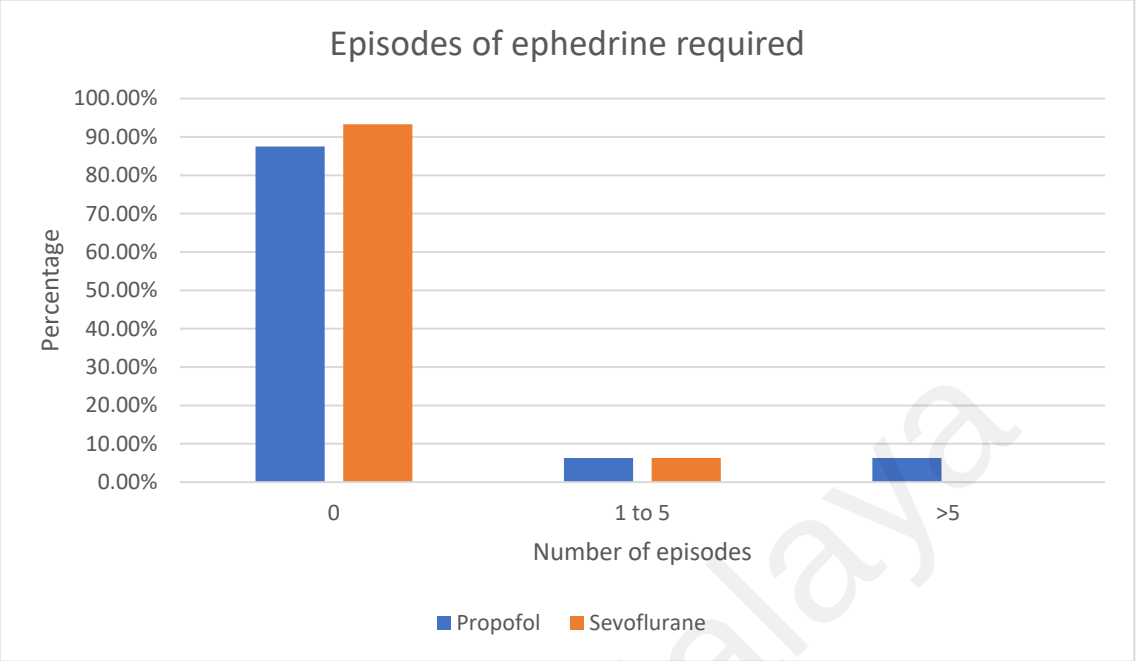


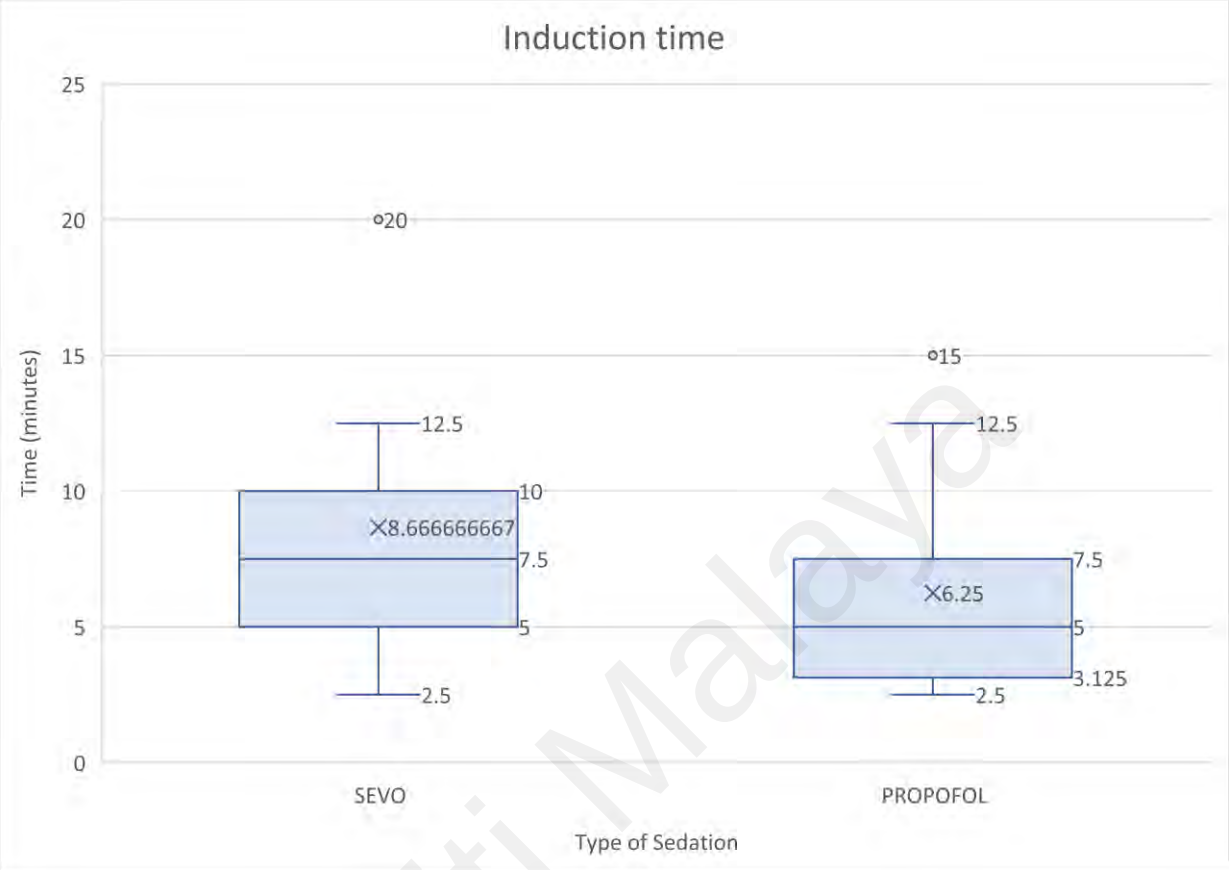
Figure 4.5 Episodes of ephedrine required



4.4 Induction time and recovery time

The induction time was notably shorter (p-value: 0.007) in the propofol group, on average 5.0 minutes (IQR 2.5-7.5), compared to the sevoflurane group's 8.8 minutes (IQR 7.5-11.3). However, there was no significant difference in recovery time (p value 0.54) between the two groups, with propofol group averaging 5 minutes (IQR 2.5-5 minutes) and sevoflurane group also at same value.

Figure 4.6 Induction time Sevoflurane VS Propofol



4.5 Post-procedural recall and satisfaction scores

Post-procedural recall did not show significant differences between the sevoflurane group (n=6, 37.5%) and the propofol group (n=3, 20%). There was no notable contrast in the Visual Analog Scale readings between Group S and Group P (p-value 0.49), with 60% of Group S at score 0 and 75% of Group P at score 0. In terms of preference for the same sedation method for future procedures, most patients in both groups expressed willingness, with the sevoflurane group at 87.5% (n=14) and the propofol group at 93.3% (n=14).

Patients from both groups reported high levels of satisfaction, with 50% (n=8) in the sevoflurane group and 60% (n=9) in the propofol group indicating they were 'very satisfied'. Sedation providers rated the sevoflurane group as 'very satisfied' (n=6, 37.5%) and the propofol group as 'satisfied' (n=7, 46.7%). Furthermore, surgeons expressed

general satisfaction as 'satisfied' with both sedation methods, with 50% (n=8) in the sevoflurane group and 60% (n=9) in the propofol group.

4.6 Complications of the sedation method

The dermatomes blocked by both the supraclavicular and PECS 2 blocks showed similar outcomes for both the sevoflurane and propofol groups (refer to Table 7). (VAS score data) Additionally, complications, aside from those related to hemodynamic profiles, demonstrated no significant differences between the two groups (refer to Table 4.3).

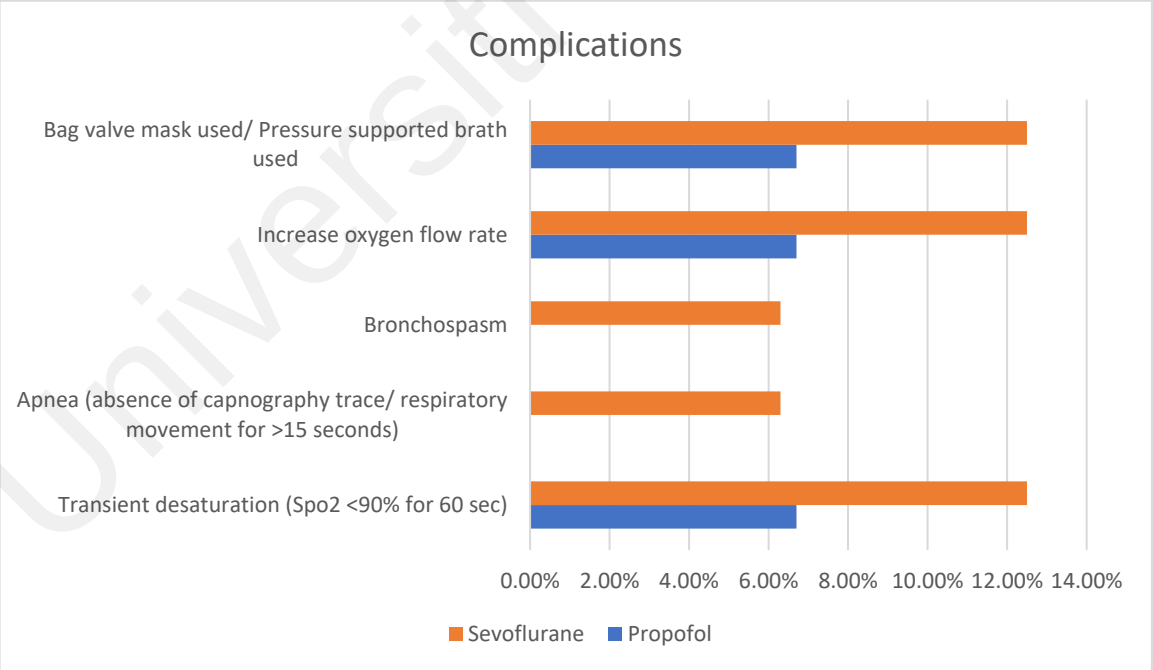
Table 4.7 Complications between the sevoflurane and the propofol group.

	SEVO	PROPOFOL	SIG
Transient desaturation (Spo2 <90% for 60 sec)	2 (12.5%)	1 (6.7%)	1.00
Apnea (absence of capnography trace/ respiratory movement for >15 seconds)	1 (6.3) %	0.0%	1.00
Bronchospasm	1 (6.3%)	0.0%	1.00
Increase oxygen flow rate	2 (12.5%)	1 (6.7%)	1.00
Bag valve mask used/ Pressure supported breath used	1 (6.3%)	1 (6.7%)	1.00

Table 4.7, continued

		SEVO	PROPOFOL	SIG
Patient's intraprocedural conduct	COMPLIANCE	9 (56.3%)	10 (66.7%)	0.21
	INTERFERENCE WITH PROCEDURE	3 (18.8%)	0.0%	
	MILD AGITATION	4 (25%)	5 (33.3%)	

Figure 4.7 Complications during sedation



CHAPTER 5

DISCUSSION

5.1 Discussion

To date, extensive research has focused on sevoflurane as a sedative in critical care settings (Blondonnet et al., 2021; Blondonnet et al., 2022), while TCI propofol remains the standard for most procedures. Our study highlights the efficacy of sevoflurane in sedating patients with end-stage renal failure undergoing fistula repair, demonstrating superior hemodynamic stability compared to traditional TCI propofol sedation. Notably, the propofol group experienced a significant 20% decrease in mean arterial pressure (MAP) at 30minutes of sedation, which is more than double in magnitude compared to sevoflurane MAP reduction of 8%. The reduction of MAP for both groups mainly contributed by decrement of systolic blood pressure (SBP) as the diastolic blood pressure changes were not significant for both groups. The drop of SBP in both groups primarily determined by the vasodilatation and reduction in systemic vascular resistance (SVR).

Maintaining hemodynamic stability is crucial, particularly in patients with end-stage renal failure who often contend with multiple comorbidities, including angiopathy. Chronic hypertension, prevalent in these patients, leads to a rightward shift in blood pressure autoregulation (Chowdhury et al., 2022), exacerbating the challenge. Such outcomes encompass increased mortality, prolonged hospitalization (Abbott et al., 2018; Sessler et al., 2018), heightened all-cause morbidity, and heightened risk of stroke (Meng, et al., 2018; Brunaud, et al., 2015; Bijker, et al., 2012).

Various factors can contribute to intraoperative hypotension in ESRF population, including low fluid balance resulting from haemodialysis ultrafiltration (Cronin B et al., 2023), patients being nil by mouth without intravenous drips, and the ingestion of antihypertensive medication on the morning of surgery. In this study, TCI propofol

delivered via Schnider model likely induces more vasodilation and subsequent hypotension due to its initial dose at the start of infusion. Whereas for sevoflurane sedation, it was initiated at a lower concentration and titrated upward to achieve the desired sedative effect. Additionally, TCI propofol was developed based on a pharmacokinetic model for healthy individuals, not specifically tailored to patients with end-stage renal failure (Al-Rifai, et al., 2016), potentially resulting in inappropriate dosing for this population, as observed in the study. Gotoda et al., (2016) noted that elderly patients typically require lower propofol doses with the TCI/BIS system compared to younger patients. ESRF patients routinely undergo pre-operative hemodialysis with ultrafiltration to reach dry weight. In this study, the patients' volume status was similar (p value 0.576) based on ultrafiltrate volume: the sevoflurane group exhibited a median extraction of 2050 mLs (IQR 1750-2600 mLs), while the propofol group extracted 2200 mLs (IQR 2000-2800 mLs). This effectively eliminated the confounding factor of retracted intravascular volume for both groups, enabling a direct comparison of the pharmacodynamic effects of sevoflurane versus propofol.

In the 1990s, Ickx et al. (1998) reported that end-stage renal disease (ESRD) did not significantly influence the pharmacokinetic and pharmacodynamic profiles of propofol. Chen et al., (2022) demonstrated that Propofol TCI with brachial plexus block is an effective and safe anesthesia regimen for ESRD patients receiving AV access surgery. It provides less blood pressure fluctuation than inhalational anesthesia. Unfortunately, the condition of Chen et al., (2022) study is different in that they conducted the study under general anaesthesia rather than sedation. Moreover, they did not employ an objective anesthesia depth monitoring system and the depth of anesthesia was assessed by clinical judgment. Therefore, it was not certain whether all patients were maintained at the same depth of anesthesia.

In our study, the Group S has a more stable haemodynamic profile compare to Group P. Husedzinovic et al. (19) conducted a study comparing the impact of sevoflurane and propofol anesthesia on myocardial contractility using transesophageal echo-Doppler. They observed a notably higher stroke volume in the sevoflurane group compared to the propofol group (P) thus providing a better haemodynamic profile. Propofol exhibits a direct arterial vasodilator effect, contributing substantially to the reduction in arterial pressure upon its administration during anesthetic induction. (Sahinovic et al., 2018) Furthermore, group S superior haemodynamic stability likely attributable to the self-regulating nature of sedation depth in spontaneously breathing patients. Inhalation of potent volatile anesthetics (VAs) leads to a dose-dependent reduction in spontaneous ventilation. Consequently, in spontaneously breathing patients, there is an inherent autoregulatory mechanism wherein the uptake of anesthetic agent decreases as the depth of anesthesia intensifies. This self-regulation offers a level of safety not observed in ventilated patients, as they risk receiving excessive doses of inhaled anesthetics if a vaporizer is mistakenly configured to deliver overpressure (Groper et al., 2020). Consequently, the dosage of the volatile agent maintaining sedation in this context may not have reached levels sufficient to induce a significant decrease in blood pressure. Sevoflurane thus presents a distinct advantage in promoting superior hemodynamic stability, rendering it a potentially preferred sedation agent, particularly in high-risk patients with compromised cardiovascular reserves. Also Li et al. (2015) demonstrated that sevoflurane potentially offers a more advantageous cardioprotective effect compared to propofol. This effect holds particular significance for patients with end-stage renal failure (ESRF), who frequently present with ischemic heart disease.

Volatile sedation utilizing sevoflurane in intensive care settings has garnered widespread acclaim for its remarkable reduction in awakening time, superior compared to conventional midazolam/propofol intravenous sedation (Kim et al., 2017). Sevoflurane

boasts a rapid onset of action without significant concerns regarding tolerance or tachyphylaxis (Ross et al., 2010). However, this study revealed a significantly prolonged induction time for sevoflurane (mean time = 9.5 mins, SD = 4 mins), nearly twice the duration compared to TCI propofol (mean time = 5.7 mins, SD = 2.9 mins). This delay could be attributed to the initial delivery of a low inspired fraction of sevoflurane, coupled with a fixed low fresh gas flow of 3L/min at the onset of sedation, leading to a low alveolar-venous concentration gradient (Khan K.S., 2014). Additionally, the loss of the agent via mouth opening (leak not compensated by circuit), as sevoflurane is administered through a nasal CPAP mask, may further contribute to diluting its concentration. Consequently, the accuracy of MAC measurements in this study may be compromised by these equipment-related factors (no scavenging device). Heart rate variations were minimal in both the sevoflurane and TCI propofol groups. This phenomenon could be attributed to patients' regular use of beta blockers or the presence of autonomic dysregulation associated with long-standing diabetes mellitus, resulting in a blunted baroreceptor response.

The utilization of sevoflurane in conjunction with carbon dioxide absorbents within the circuit can generate compound A, which has demonstrated nephrotoxic properties in animal models (Chowdhury, et al., 2022). Nonetheless, the concentrations of these compounds produced during clinical practice are deemed inadequate to evoke nephrotoxic effects. Consequently, sevoflurane is regarded as safe for use in patients with end-stage renal failure (Chowdhury et al., 2022).

The incidence of sedation-related complications in both study groups was not statistically significant. Notably, no instances of apnea were reported among the patients, in contrast to findings by Syaed El Ahl et al. (2015), which highlighted a higher frequency of apnea attacks, need for airway intervention, and general anesthesia occurrences within the Propofol group compared to the Sevoflurane group. While disinhibition and paradoxical

excitement were observed in both groups, the Sevoflurane group encountered three cases (18.8%) where intraoperative behavior interfered with surgical proceedings.

Guedel's classification outlined four stages of ether anesthesia (Calverley, et al., 1985). In the second stage, known as the delirium stage, patients often display excessive motor activity, occasionally reaching levels of agitation or even violence. Such agitation or involuntary movements can pose risks, potentially leading to self-injury or disruption of dressing, surgical positioning, or indwelling devices, thereby elevating the likelihood of perioperative complications. Despite its occurrence, the precise mechanisms underlying sevoflurane-induced agitation or paradoxical excitation remain elusive. Zhao et al., (2021) provided preliminary evidence suggesting that genetic polymorphisms in Methionine Synthase Reductase (MTRR), involved in folate metabolism, may influence susceptibility to agitation. The risks associated with pollution and patient excitement have historically positioned sevoflurane as a "second choice" for sedation (Höhener et al., 2008).

In this study, 5 out of 15 patients (33%) receiving propofol experienced mild agitation. Propofol is renowned for its dose-dependent sedative effects and non-dose-related anxiolysis (Smith et al., 1994). However, it can paradoxically induce behavioral and electroencephalographic (EEG) signs of excitation, rather than sedation, particularly at lower doses. Such neuronal excitation is unexpected given the drug's GABA-potentiating properties. MacCarthy M et al (2008) proposed interneuron anti-synchrony as a potential network mechanism underlying the generation of propofol-induced paradoxical excitation. Moreover, Lee et al (2019) demonstrated that propofol-induced paradoxical reactions are more likely to occur in individuals with underlying anxiety, especially among younger patients.

Herzog-Niescery et al (2015) demonstrated that sevoflurane application results in measurable concentrations of sevoflurane in the air, regardless of the induction method,

airway management technique, or airflow technology utilized. This exposure poses a concern for anesthesia providers during their routine clinical work. In this study, sevoflurane was administered via nasal CPAP, which, due to the lack of a closed circuit, may lead to potential leaks of sevoflurane into the operating room, thereby exposing healthcare workers to higher atmospheric concentrations of the gas. It is crucial to note that volatile anesthetics, such as sevoflurane, are potent greenhouse gases (GHGs) capable of absorbing infrared radiation and trapping energy within the atmosphere (Ishizawa et al., 2011). Therefore, their contribution to global warming should not be underestimated. Only a small fraction (less than 5%) of the volatile anesthetics administered are metabolized by the patient, with the majority being released into the atmosphere (Gadani et al., 2011). Recognizing the environmental impact, the FDA recommended in 2023 that sevoflurane usage should be limited to less than 2 minimum alveolar concentration-hours, with flow rates ranging from 1 to less than 2 L/min, as part of a transition toward more environmentally friendly anesthesia practices.

5.2 Strength of the study

This study represented a pioneering investigation into the hemodynamic impacts of employing sevoflurane as a sedative agent during fistula repair procedures in end-stage renal failure patients under regional block anesthesia. It endeavored to compare these effects with those observed during sedation with the conventional choice, TCI propofol.

This randomized controlled trial (RCT) meticulously addressed selection bias by ensuring equitable allocation of interventions (sevoflurane) and controls (TCI propofol) among participants. Employing computer-generated sequences in blocks of six and the sealed envelope method for randomization, patients were assigned to either the sevoflurane (Group S) or TCI propofol (Group P) cohorts. This strategic approach substantially

mitigated the risk of systematic disparities between treatment and control groups, thereby fortifying the reliability of the outcomes. The prospective nature of the study empowered it to elucidate causal relationships between the chosen sedation method and ensuing hemodynamic changes. By attributing observed differences in outcomes directly to the interventions rather than confounding variables, the study contributed robust evidence to the field. While the study maintained single-blinding to shield researchers from treatment allocation knowledge and minimize influence on outcome assessments, full blinding of the sedation provider and patients was impractical due to the nature of sedation administration. Nonetheless, these measures were instrumental in enhancing the credibility and validity of the study.

5.3 Limitations of the study

The small sample size and single-center design of this study present potential limitations regarding the generalizability of findings beyond the study population and setting. Findings may not fully capture the diversity of patients encountered in various healthcare contexts or geographic regions. Such limitations can introduce selection bias, where enrolled participants' characteristics may not adequately represent the broader population, compromising the external validity of the study. Furthermore, the small sample size diminishes statistical power, posing challenges in discerning clinically significant differences between treatment groups and increasing the risk of type II errors—instances where true effects remain undetected due to insufficient sample size. Additionally, heightened variability in participant characteristics and outcomes may lead to less precise estimates of treatment effects, undermining the reliability of findings. Lastly, the study's limited ability to detect rare adverse events or outcomes associated with the intervention raises concerns, particularly for interventions with potential safety implications that may not be evident in a small sample size.

5.4 Future research

To mitigate the risk of intraoperative hypotension, the use of the Bispectral Index System (BIS) to guide sedation in patients undergoing fistula repair surgery could be beneficial. Frisella et al. (1997) demonstrated that adding a low-dose ketamine regimen improved haemodynamic stability. While this study may offer valuable initial insights, it is imperative to conscientiously acknowledge its limitations when interpreting findings and informing clinical decisions. Larger, multicenter trials, employing robust methodologies, are essential to corroborate and extrapolate the results concerning the hemodynamic stability of sevoflurane as a sedation modality for end-stage renal failure patients undergoing fistula repair surgery under regional block.

CHAPTER 6

CONCLUSION

Sevoflurane may be a better sedation agent compared to TCI propofol for end stage renal failure patients by offering a more consistent hemodynamic profile with few adverse effects. This is particularly significant given the prevalence of underlying comorbidities in this population, who frequently require anesthesia for fistula repair surgeries. Patients with end-stage renal failure often exhibit compromised cardiovascular function and are less tolerant to perioperative hypotensive episodes thus it is vital to ensure their safety by opting to a sedation agent with a more stable haemodynamic. However, the time taken for induction to reach the desired sedation level with sevoflurane is longer compared to TCI propofol, although the recovery time is similar in both groups. Nonetheless, further comprehensive studies are imperative to ascertain and thoroughly evaluate potential side effects, thereby confirming the safety profile of sevoflurane as a procedural sedative agent.

CHAPTER 7

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