

BMJ Open Effect of balanced opioid-free anaesthesia on postoperative nausea and vomiting after video-assisted thoracoscopic lung resection: protocol for a randomised controlled trial

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ABSTRACT

Introduction Opioid-free anaesthesia (OFA) may reduce opioid-related side effects such as postoperative nausea and vomiting (PONV) and hyperalgesia. This study aims to investigate the effects of balanced OFA on PONV and pain outcomes in patients undergoing video-assisted thoracoscopic surgery (VATS).

Methods and analysis This randomised controlled trial will be conducted at the First Affiliated Hospital of Soochow University in Suzhou, China. A total of 120 adults scheduled for VATS lung resection will be randomly assigned with a 1:1 ratio to either an OFA group or a control group, stratified by sex (n=60 in each group). Patients will receive balanced anaesthesia with esketamine, dexmedetomidine and sevoflurane (the OFA group), or sufentanil and sevoflurane (the control group). All patients will receive PONV prophylaxis with intraoperative dexamethasone and ondansetron. Multimodal analgesia consists of intraoperative flurbiprofen axetil, ropivacaine infiltration at the end of surgery and postoperative patient-controlled sufentanil. The primary outcome is the incidence of PONV within 48 hours after surgery. Secondary outcomes are nausea, vomiting, need for antiemetic therapy, pain scores at rest and while coughing, postoperative sufentanil consumption, need for rescue analgesia, length of post-anaesthesia care unit stay, length of postoperative hospital stay, and 30-day and 90-day post-surgical pain and mortality. Safety outcomes are hypotension, bradycardia, hypertension, tachycardia, interventions for haemodynamic events, level of sedation, headache, dizziness, nightmare and hallucination. All analyses will be performed in the modified intention-to-treat population.

Ethics and dissemination Ethics approval was obtained from the Ethics Committee of the First Affiliated Hospital of Soochow University (2022-042). All patients will provide written informed consent. The results of this study will be published in a peer-reviewed journal.

Trial registration number Chinese Clinical Trial Registry (ChiCTR2200059710).

INTRODUCTION

Video-assisted thoracoscopic surgery (VATS) has been increasingly performed over the

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The Apfel's postoperative nausea and vomiting risk scores will be calculated preoperatively, based on the number of risk factors.
- ⇒ Anaesthesia depth will be titrated to bispectral index values of 40–60 in both groups.
- ⇒ 3. All patients will receive perioperative multimodal analgesia (flurbiprofen axetil, ropivacaine infiltration and patient-controlled sufentanil).
- ⇒ Anaesthesia providers cannot be blinded due to the differences between techniques, but they will not participate in other parts of the study.
- ⇒ This is a single-centre trial, and more studies evaluating opioid-free anaesthesia will be warranted.

decades, with less postoperative pain and faster recovery compared with thoracotomy.¹ Postoperative nausea and vomiting (PONV) are common for patients undergoing VATS, and moderate to severe pain after VATS is not rare.² PONV and postoperative pain are associated with increased healthcare costs and decreased quality of life after surgery.^{3,4}

Opioids are regarded as the cornerstone of analgesia for patients undergoing surgery. However, use of opioids is associated with increased risks of PONV and hyperalgesia (paradoxical increases in pain and opioid requirements).^{5,6} To overcome these, opioid-free anaesthesia (OFA) appears to be an interesting alternative. OFA is commonly delivered using intravenous dexmedetomidine, ketamine or esketamine, and lidocaine, together with multimodal analgesia (non-steroid anti-inflammatory drugs, nerve blocks or local anaesthetic wound infiltration).^{7,8} Previous reports suggested that OFA was associated with decreased PONV and opioid consumption,^{9,10} but recent studies did not support that association.^{11,12} The

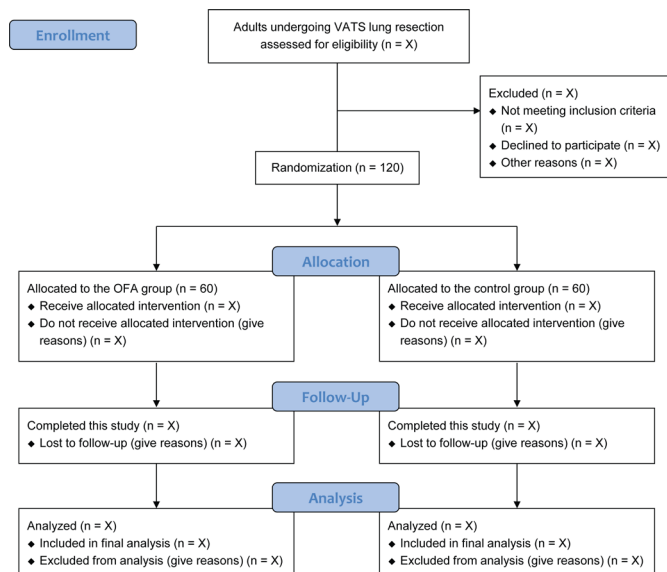


Figure 1 Study flow diagram. OFA, opioid-free anaesthesia; VATS, video-assisted thoracoscopic surgery.

anaesthetic and analgesic components of OFA vary among different institutions, and the benefits as well as potential risks of OFA for surgical patients remain inconclusive.

Objectives

This study aims to compare a balanced OFA versus a balanced opioid-based anaesthesia for patients undergoing VATS lung resection. We hypothesise that our OFA regimen would reduce PONV and improve postoperative pain outcomes after VATS lung procedures.

METHODS AND ANALYSIS

The reporting of this protocol follows the guidelines of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (online supplemental file 1).¹³

Study design and patients

This is a single-centre, prospective, randomised, patient-blind and assessor-blind, parallel-group controlled, superiority clinical trial. A total of 120 patients will be enrolled at the First Affiliated Hospital of Soochow University in Suzhou, China. The First Affiliated Hospital of Soochow University is a tertiary teaching hospital at which approximately 4000 VATS procedures are performed each year. We plan to enrol patients between 18 May 2022 and 30 November 2022. The study flow diagram is presented in figure 1.

Inclusion criteria

To be included in this study, patients should meet the following criteria:

1. Age ≥ 18 years.
2. American Society of Anesthesiologists (ASA) physical status I–III.
3. Body mass index (BMI) 18–30 kg/m².
4. Scheduled for elective VATS lung resection.

Exclusion criteria

The exclusion criteria are as follows:

1. Sick sinus syndrome or severe bradycardia (heart rate (HR) <50 beats/min).
2. Second-degree or greater atrioventricular block without a pacemaker.
3. Left ventricular ejection fraction <40%.
4. Coronary heart disease or history of myocardial infarction.
5. Liver or renal dysfunction (Child-Pugh class C or undergoing renal replacement therapy).
6. Parkinson's disease or Alzheimer's disease.
7. Seizures or epilepsy.
8. Pregnancy or breast feeding.
9. History of chronic pain or preoperative use of sedatives or analgesics.
10. Allergies to medications in this study.

Apfel's PONV risk scores

The Apfel's PONV risk scores will be calculated preoperatively, based on the number of risk factors (female, non-smoker, history of PONV or motion sickness, and postoperative use of opioids).¹⁴ The Apfel's PONV risk scores range from 0 to 4, with each point predicting a 20% increased risk of developing PONV.¹⁴

Randomisation and blinding

An independent research personnel will generate the random numbers using the online tool (<https://www.sealedenvelope.com/simple-randomiser/v1/lists>), with a 1:1 allocation ratio, permuted blocks of 2 and 4, and stratification by sex. The randomisation results will be stored in sealed opaque envelopes. Patients will be randomly assigned to either an OFA group or an opioid-based control group (n=60 in each arm). The anaesthesia providers cannot be blinded to the group allocation due to the differences between the anaesthesia techniques; however, they will not participate in patient recruitment, data collection or statistical analysis. Patients, surgeons, postoperative care providers, outcome assessors and a statistician responsible for analyses will be masked to the group allocation.

Study interventions

For induction of anaesthesia, the OFA group will receive intravenous dexmedetomidine 0.6 µg/kg over 10 min, esketamine 0.3 mg/kg and propofol 1.5–2.0 mg/kg; the control group will receive intravenous sufentanil 0.3 µg/kg and propofol 1.5–2.0 mg/kg. For maintenance of anaesthesia, the OFA group will receive dexmedetomidine infusion at 0.2–1.0 µg/kg/hour, 1%–3% sevoflurane inhalation and boluses of esketamine 0.1 mg/kg; the control group will receive 1%–3% sevoflurane inhalation and boluses of sufentanil 0.1 µg/kg. The schedule of patient enrolment, study interventions and outcome assessment is in accordance with the SPIRIT statement (table 1).

Table 1 Schedule of patient enrolment, study interventions and outcome assessment

Time point	Study period							
	Enrolment	Allocation	Post-allocation				Close-out	Follow-up
	Preoperative visit	2 hours before surgery	Intraoperatively	PACU	24 hours postoperatively	48 hours postoperatively	Hospital discharge	30 and 90 days
Patient enrolment								
Eligibility criteria	x							
Written informed consent	x							
Demographic data	x							
Baseline characteristics	x							
Randomisation/ allocation		x						
Study interventions								
Opioid-free anaesthesia			x					
Opioid-based anaesthesia			x					
Outcome assessment								
PONV				x	x		x	
Need for antiemetics				x	x		x	
Postoperative pain scores				x	x		x	
Postoperative sufentanil consumption				x	x		x	
Need for rescue analgesia				x	x		x	
Length of PACU stay				x				
Length of hospital stay							x	
30-day and 90-day post-surgical pain								x
30-day and 90-day mortality								x
Hypotension			x	x				
Hypertension			x	x				
Bradycardia			x	x				
Tachycardia			x	x				
Interventions for haemodynamic events			x	x				
Level of sedation				x				
Headache				x	x		x	
Dizziness				x	x		x	
Nightmare				x	x		x	
Hallucination				x	x		x	

According to SPIRIT statement of defining standard protocol items for clinical trials.

PACU, post-anaesthesia care unit; PONV, postoperative nausea and vomiting; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.



Anaesthetic care

Patients will fast for 6–8 hours. No premedication will be given. In a preoperative waiting room, the baseline blood pressure and HR will be obtained. In the operating room, patients will receive continuous monitoring with ECG, non-invasive blood pressure, pulse oximetry (SpO₂) and bispectral index (BIS) (Aspect Medical Systems, Newton, Massachusetts, USA).

After anaesthesia induction, a catheter will be inserted into the radial artery for arterial blood pressure monitoring. Rocuronium 0.6 mg/kg will be administered to facilitate the intubation of a double-lumen endotracheal tube. The location of the tube will be confirmed by capnography, auscultation and fiberoptic bronchoscopy. One-lung mechanical ventilation will be started on the non-surgical side with tidal volume of 6–8 mL/kg (predicted body weight) and positive end-expiratory pressure of 5–10 cm H₂O. The inspired oxygen fraction and respiratory frequency will be adjusted to maintain SpO₂ ≥95% and end-tidal carbon dioxide within 35–45 mm Hg. Lung recruitment manoeuvres will be applied when clinically indicated.

Anaesthesia depth will be titrated to BIS values of 40–60 via adjusting inhalational sevoflurane concentration. Sufficient intraoperative analgesia will be provided via adjusting the infusion rate of dexmedetomidine and using boluses of esketamine (the OFA group) or boluses of sufentanil (the control group), at the discretion of the attending anaesthesiologist. For intraoperative muscle relaxation, patients will receive additional rocuronium administration. Patients will receive Lactated Ringer's solution for intravenous fluid repletion. A warming blanket will be used to maintain the nasopharyngeal temperature at 36°C–37°C. After surgery, all patients will be transferred to the post-anaesthesia care unit (PACU). The Modified Observer's Alertness/Sedation Scale (MOAA/S) and modified Aldrete score will be assessed every 5 min.^{15 16} A modified Aldrete score ≥9 indicates readiness for PACU discharge to surgical wards.¹⁷

All patients will receive PONV prophylaxis using intravenous dexamethasone 5 mg and ondansetron 4 mg during anaesthesia. If patients experience vomiting in the PACU and surgical wards, they will receive an additional administration of ondansetron 4 mg as antiemetic therapy.

For multimodal analgesia, the patients in both groups will receive intraoperative flurbiprofen axetil 50 mg, wound infiltration with 0.5% ropivacaine 20 mL at the end of surgery and postoperative patient-controlled sufentanil until 48 hours postoperatively. The patient-controlled analgesia (PCA) device contains sufentanil 100 µg diluted with normal saline to a total volume of 100 mL (ie, sufentanil 1 µg/mL), with a background infusion of 1 mL/hour, a bolus dose of 2 mL and a lockout time of 10 min. Postoperative pain will be assessed using the Numerical Rating Scale, ranging from 0 to 10 (0=no pain and 10=the worst pain imaginable). If pain scores remain ≥4 despite the use of patient-controlled sufentanil, rescue analgesia with additional intravenous sufentanil 5 µg will be given.

Primary and secondary outcomes

The primary outcome of this trial is the incidence of PONV during the first 48 hours postoperatively. We will assess PONV as the combined incidence of nausea, retching and vomiting. The secondary outcomes are nausea, vomiting, need for antiemetic therapy, pain scores at rest and while coughing, postoperative sufentanil consumption, need for rescue analgesia, length of PACU stay, length of postoperative hospital stay, and 30-day and 90-day post-surgical pain and mortality.

Nausea, vomiting, need for antiemetic therapy and need for rescue analgesia will be recorded within 48 hours postoperatively. Postoperative pain scores at rest and while coughing and postoperative sufentanil consumption will be recorded at PACU discharge and 24 and 48 hours postoperatively. Follow-up data on post-surgical pain and mortality will be collected via telephone calls at 30 and 90 days after surgery.

Safety outcomes

The safety outcomes include perioperative hypotension (reduction in mean blood pressure >30% of baseline for at least 1 min),¹⁸ bradycardia (HR <45 beats/min for at least 1 min), hypertension (increase in mean blood pressure >30% of baseline for at least 1 min), tachycardia (HR >100 beats/min for at least 1 min), interventions for haemodynamic events, MOAA/S sedation levels, headache, dizziness, nightmare and hallucination. These haemodynamic events will be assessed during anaesthesia and in the PACU, and interventions will be at the discretion of the attending anaesthesiologist, via adjusting dexmedetomidine infusion, using additional esketamine or sufentanil, and using intravenous vasopressors (ephedrine 6–10 mg or phenylephrine 50–100 µg), atropine 0.3–0.5 mg, urapidil 5 mg or esmolol 10 mg, as appropriate. The episodes of headache, dizziness, nightmare and hallucination within 48 hours postoperatively will be recorded.

Data collection and monitoring

An independent research staff will collect demographic data (age, sex, height, weight and BMI), baseline characteristics (preoperative medications, comorbidities, ASA physical status, smoking status, education level and Apfel's PONV risk score) and perioperative data (BIS values, haemodynamic data, end-tidal sevoflurane concentration, and doses of propofol, sufentanil, esketamine, dexmedetomidine, and all other medications). All data will be collected in the case report forms and then entered into the electronic database under the supervision of the principal investigator (KP). An independent data monitoring committee (DMC) will conduct an ongoing review of data collection. The electronic database will be locked once the data registration is completed. Datasets without personally identifiable information will be sent to the independent statistician for final analyses based on the prespecified statistical plan.

We defined 'failed OFA' as that haemodynamics preclude continued dexmedetomidine administration (severe bradycardia despite the use of atropine). In this situation, the dexmedetomidine infusion will be discontinued, and the patients will receive treatment at the clinician discretion. Sufentanil may have to be administered to these patients for the completion of anaesthesia and surgery. Serious adverse events (such as persistent haemodynamic instability or asystole) associated with the study medications or not should be immediately reported to the principal investigator (KP). In such situations, the perioperative care team should provide relevant treatment to ensure patient safety. Such events should also be reported to the DMC within 24 hours. The DMC will discuss and make recommendations on whether the study interventions should be modified and whether the study should be stopped.

Sample size calculation

A recent study suggested that 41.7% of patients who received VATS and opioid-based anaesthesia experienced PONV and OFA reduced the incidence of PONV by ~90% (ie, from 41.7% to 4.3%).¹⁹ However, a previous study showed that the use of OFA reduced the risk of PONV by ~45% (ie, from 37.3% to 20%) in bariatric surgery.⁹ For power analysis in this study, we hypothesise that the incidence of PONV is 40% in the opioid-based control group. Based on the assumption of an average PONV reduction by 60%, we expect that our balanced OFA strategy would reduce the PONV incidence to 16%. To detect such a between-group difference in PONV at two-sided $\alpha=0.05$ and power=80%, 53 patients in each group are required. Considering potential dropouts, we plan to enrol a total of 120 patients, with 60 in each group. The sample size calculation is performed using the PASS software (V.11.0.7, NCSS, Kaysville, Utah, USA).

Statistical analysis

Continuous data will be checked for normal distribution with the Shapiro-Wilk test. Means (SDs) will be used for normally distributed data, and medians (IQRs) for data that are not normally distributed. Continuous data will be analysed using the independent t-test, Mann-Whitney rank-sum test or repeated measures analysis of variance, as appropriate. Categorical data will be presented as numbers (percentages) and analysed using the χ^2 test or Fisher's exact test. The between-group differences for the primary, secondary and safety outcomes will be analysed using mean difference or OR with 95% CIs. The primary outcome of PONV incidence will be further analysed in the subgroups of sex, smoking status and PONV risk scores. Multiple testing corrections for the secondary outcomes are not planned, so these outcomes should be considered exploratory.

All study outcomes will be analysed in the modified intention-to-treat population, including all patients who undergo randomisation with relevant data available. Patients will be included in the analysis according to their

original allocation. No interim analysis will be planned. Missing data will not be imputed. Statistical analyses will be conducted with the use of SPSS software (V.19.0; IBM SPSS). A two-sided p value of <0.05 indicates a statistically significant difference.

Patient and public involvement

Patients and public will not be involved in the design, recruitment, conduct or report of the study. The study results will be disseminated to the participants via email.

Ethics and dissemination

This study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (2022-042) on 28 April 2022. The protocol was registered at the Chinese Clinical Trial Registry (ChiCTR2200059710) on 9 May 2022. All patients will provide written informed consent (online supplemental file 2), and the implementation of this study will conform to the Declaration of Helsinki. The results of this study will be published in a peer-reviewed journal.

DISCUSSION

In this randomised controlled trial, we will enrol a total of 120 adult patients who undergo VATS lung resection to evaluate the effects of balanced OFA versus balanced opioid-based anaesthesia on PONV and postoperative pain outcomes. In addition, we will compare the two anaesthesia regimens in terms of length of PACU stay, length of postoperative hospital stay, perioperative safety outcomes, and 30-day and 90-day post-surgical pain and mortality. This study will be implemented in accordance with the Consolidated Standards of Reporting Trials guidelines.²⁰

From the existing literature, OFA has been used for patients undergoing several of types surgery. Ziemann-Gimmel and colleagues suggested that opioid-free total intravenous anaesthesia was associated with reduced risk of PONV for patients undergoing bariatric surgery.⁹ Bakan and colleagues reported that opioid-free propofol anaesthesia in laparoscopic cholecystectomy reduced postoperative fentanyl consumption, pain scores and need for ondansetron administration.¹⁰ However, Massoth and colleagues showed that their balanced OFA strategy did not decrease PONV, postoperative pain or morphine requirement after gynaecological laparoscopy.¹¹ Beloeil and colleagues showed that the balanced OFA led to an increased incidence of hypoxaemia, serious bradycardia, delayed extubation and prolonged PACU stay.¹² Hence, the effects of OFA in different surgical setting are inconsistent.

In a recent study, we reported the characteristics (opioid usage, PONV, pain scores, PACU stay, intensive care unit (ICU) admission and hospital stay) for VATS lung resection at our institution.²¹ The results showed that: (1) the mean intraoperative sufentanil consumption was 0.74 $\mu\text{g}/\text{kg}$; (2) the incidence of PONV during postoperative

0–48 hours was 26.7%; (3) the mean pain scores were 2.2 at PACU discharge, 3.0 at postoperative 24 hours and 1.0 at postoperative 48 hours; (4) the mean length of PACU stay was 35 min; (5) no patient needed ICU admission; and (6) the mean length of postoperative hospital stay was 5 days. The observed PONV incidence in the previous study is lower than that of opioid-based control group (40%) in our power analysis, possibly because of the small number of patients (n=30). For postoperative pain control in that study, using tramadol on patients' request or when pain scores ≥ 4 provided adequate analgesia after surgery, and patient-controlled opioids were not used. In the present study, all patients will receive multimodal analgesia (wound infiltration with ropivacaine at the end of surgery, intraoperative flurbiprofen axetil and postoperative PCA with sufentanil). Wound infiltration is a safe and simple technique that is widely used for pain management in thoracic surgery.^{22–24} Yang and colleagues also suggested that wound infiltration was not inferior to PCA with fentanyl in VATS lung resection.²⁵ Actually, the PCA used in our study is to provide rescue analgesia, with low background infusion rate and patient-controlled additional dose.

Two recent studies have investigated the use of OFA in VATS procedures. A retrospective study reported that OFA with dexmedetomidine, ketamine, lidocaine, and sevoflurane was safe and associated with reduced postoperative pain and morphine consumption.²⁶ A randomised study suggested that analgesia-antinociception offered by OFA with dexmedetomidine and sevoflurane was as effective as opioid-based anaesthesia with remifentanyl and sevoflurane.¹⁹ However, the effects of OFA on postoperative pain and PONV for patients undergoing VATS are still unclear. Our balanced OFA regimen includes dexmedetomidine (0.6 $\mu\text{g}/\text{kg}$ over 10 min), esketamine (0.3 mg/kg) and propofol (1.5–2.0 mg/kg) for anaesthesia induction, followed by dexmedetomidine (0.2–1.0 $\mu\text{g}/\text{kg}/\text{hour}$), esketamine (0.1 mg/kg boluses), and sevoflurane for anaesthesia maintenance and intraoperative analgesia. As far as we know, this is the first randomised controlled trial powered to assess the effects of OFA on PONV after VATS lung resection.

This study has some limitations. First, the balanced OFA regimen is not definitive, and the optimal way to administer OFA in VATS lung procedures needs further investigation. Second, the sample size calculation is based on the incidence of PONV. The pain outcomes and other secondary outcomes should be interpreted as exploratory. Third, the anaesthesiologist cannot be blinded due to the differences between techniques. Nonetheless, they will not participate in other parts of the study, and the primary outcome of PONV is reported by patients themselves. Fourth, we do not use PONV severity scoring in this study. We will assess nausea, vomiting and need for antiemetic therapy separately as secondary outcomes. Last, as this is a single-centre trial, further studies evaluating the OFA regimen will be warranted to corroborate our findings.

In summary, this randomised controlled trial will determine the effects of balanced OFA on PONV, postoperative pain and postoperative sufentanil consumption after VATS lung resection. The results of this study will offer a new insight into improving anaesthetic care for patients undergoing VATS lung procedures.

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