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CLINICAL PRACTICE

Opioid-free anaesthesia reduces postoperative nausea and vomiting after thoracoscopic lung resection: a randomised controlled trial

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Abstract

Background: Intraoperative opioid use has a positive relationship with postoperative nausea and vomiting (PONV), and opioid-free anaesthesia (OFA) might reduce PONV. We investigated whether OFA compared with opioid-based anaesthesia would reduce PONV during the first 2 postoperative days among patients undergoing thoracoscopic lung resection.

Methods: In this randomised controlled trial, 120 adult patients were randomly assigned (1:1, stratified by sex) to receive either OFA with esketamine, dexmedetomidine, and sevoflurane, or opioid-based anaesthesia with sufentanil and sevoflurane. A surgical pleth index (SPI) of 20–50 was applied for intraoperative analgesia provision. All subjects received PONV prophylaxis (dexamethasone and ondansetron) and multimodal analgesia (flurbiprofen axetil, ropivacaine wound infiltration, and patient-controlled sufentanil). The primary outcome was the occurrence of PONV during the first 48 h after surgery.

Results: The median age was 53 yr and 66.7% were female. Compared with opioid-based anaesthesia, OFA significantly reduced the incidence of PONV (15% *vs* 31.7%; odds ratio [OR]=0.38, 95% confidence interval [CI], 0.16–0.91; number needed to treat, 6; P=0.031). Secondary and safety outcomes were comparable between groups, except that OFA led to a lower rate of vomiting (OR=0.23, 95% CI, 0.08–0.77) and a longer length of PACU stay (median difference=15.5 min, 95% CI, 10–20 min). The effects of OFA on PONV did not differ in the prespecified subgroups of sex, smoking status, and PONV risk scores.

Conclusions: In the context of PONV prophylaxis and multimodal analgesia, SPI-guided opioid-free anaesthesia halved the incidence of PONV after thoracoscopic lung resection, although it was associated with a longer stay in the PACU.

Clinical trial registration: Chinese Clinical Trial Registry (ChiCTR2200059710).

Keywords: dexmedetomidine; esketamine; multimodal analgesia; opioid-free anaesthesia; postoperative nausea and vomiting; surgical pleth index; thoracoscopic lung surgery

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Editor's key points

- Multimodal analgesic strategies are primarily intended to reduce opioid-related adverse effects.
- Many opioid-free anaesthetic regimens are currently being investigated.
- This trial demonstrates that an opioid-free regimen using esketamine and dexmedetomidine reduced postoperative nausea and vomiting after thoracoscopic lung surgery.

Postoperative nausea and vomiting (PONV) are common complications after surgery. Despite prophylaxis, the incidence of PONV still ranges from 20% to 60% according to the recent studies.[1–3] In the Apfel PONV risk scoring system, the risk factors include female sex, non-smoking status, history of motion sickness or PONV, and postoperative opioid use, and patients having three or four risk factors are at a high risk for PONV.[4] In patients undergoing lung surgery, thoracoscopic procedures lead to reduced postoperative pain and enhanced quality of life compared with thoracotomy.[5,6] However, PONV remains an unsolved problem that increases healthcare costs and compromises postoperative recovery.

Opioids produce strong analgesia, but their use is associated with adverse events, such as PONV, hyperalgesia, respiratory depression, gastrointestinal paralysis, chronic pain, and opioid dependence.[7,8] Opioid-free anaesthesia (OFA) has emerged as an alternative option in clinical anaesthesia. Studies have shown the feasibility of OFA in various types of surgical procedures including thoracoscopic surgery.[9–14] The components of OFA commonly comprise dexmedetomidine, N-methyl-D-aspartate antagonists (ketamine or esketamine), lidocaine, magnesium sulfate, and regional anaesthesia.[15,16] The application of OFA could potentially reduce adverse events and improve patient outcomes, but the results are still inconsistent.[11,17–19]

Whether the administration of OFA would benefit patients having thoracoscopic surgical procedures is unclear. Therefore, we conducted this randomised controlled trial to answer the research question: among patients undergoing thoracoscopic lung resection, to what extent does the use of OFA compared with opioid-based anaesthesia alter the incidence of PONV within 48 h of surgery.

Methods

Ethics and study design

This randomised controlled trial was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Approval No: 2022-042) and was registered at the Chinese Clinical Trial Registry (identifier: ChiCTR2200059710; available at: https://www.chictr.org.cn/showprojEN.html?proj=153043) before the first patient enrolment. We conducted this study in accordance with the Declaration of Helsinki and the Consolidated Standards of Reporting Trials guidelines (Supplementary material). All included patients gave their written consent. The study protocol was previously published.[20] No modifications were made during study implementation.

Subjects

Patients older than 18 yr with ASA physical status 1–3 and BMI of 18–30 kg m^{-2} undergoing elective thoracoscopic lung resection were enrolled. Exclusion criteria included sick sinus syndrome, heart rate (HR) <50 beats min^{-1}, second-degree or greater atrioventricular block without a pacemaker, left ventricular ejection fraction <40%, coronary heart disease, myocardial infarction, liver or renal dysfunction, Parkinson's disease, Alzheimer's disease, seizures, epilepsy, pregnancy, breastfeeding, chronic pain (defined as pain that persists or recurs for more than 3 months),[21] preoperative use of sedatives or analgesics (any sedative–hypnotic drugs such as benzodiazepines and non-benzodiazepine receptor agonists, or opioids such as morphine, fentanyl, and oxycodone),[22] and allergies to medications in this study.

Randomisation and blinding

A research personnel (XWM) not involved in patient recruitment, coordination, data collection, or outcome assessment generated the random sequence (1:1, block sizes of 2 and 4, and stratification by sex) using the Sealed Envelope online randomisation tool (https://www.sealedenvelope.com/simple-randomiser/v1/lists). The randomisation was stratified according to sex, as female sex is a significant risk factor for PONV.[4] The random results were concealed in sequentially numbered sealed opaque envelopes. Shortly before anaesthesia induction, a researcher (NS) who was unaware of the randomisation procedure opened the envelopes and assigned patients to either the OFA group or the opioid-based control group. Responsible anaesthesiologists were informed about the study medications, whereas surgeons and other healthcare team members were not. Except for different medications, all patients received a standardised intraoperative management and monitoring. Subjects, clinicians aside from the anaesthesiologists, and the investigators (CDF and YX) responsible for patient recruitment and outcome assessment were fully blinded to group assignment. The two assessors did not access anaesthesia records and were not involved in patient care.

Anaesthesia and study interventions

Baseline HR and mean blood pressure (mBP) were documented during the pre-anaesthetic visit. The PONV risk scores were calculated according to the Apfel risk scoring system (1–2, low risk and 3–4, high risk).[4] The surgical risk was assessed by predicting in-hospital mortality with the use of the Thoracoscore scoring system.[23,24]

In the operating room, subjects were continuously monitored with electrocardiography, pulse oximetry (SpO_2), arterial blood pressure via radial artery cannulation, surgical pleth index (SPI), and anaesthesia end-tidal concentrations (CARESCAPE Monitor B650; GE Healthcare, Helsinki, Finland). Depth of anaesthesia was monitored using the bispectral index (BIS; Medtronic, Minneapolis, MN, USA). General anaesthesia was induced in the OFA group using i.v. dexmedetomidine 0.6 μg kg^{-1} over 10 min, esketamine 0.3 mg kg^{-1}, and propofol 1.5–2.0 mg kg^{-1}, whereas i.v. sufentanil 0.3 μg kg^{-1} and propofol 1.5–2.0 mg kg^{-1} were used in the control group. Tracheal intubation using a double-lumen tube was facilitated by i.v. rocuronium 0.6 mg kg^{-1}, and subjects received one-lung ventilation. Anaesthesia was maintained using sevoflurane

inhalation, adjusted to BIS values of 40–60. Subjects in the OFA group were administered i.v. dexmedetomidine infusion of 0.2–1.0 μg kg^{-1} h^{-1} and esketamine boluses of 0.1 mg kg^{-1}, while subjects in the control group were administered i.v. sufentanil boluses of 0.1 μg kg^{-1}. Adequate intraoperative analgesia was provided with SPI target of 20–50.[25,26] After extubation, subjects were transferred to PACU where the sedation level was assessed using the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) every 5 min.[27,28]

All subjects were managed according to a standardised protocol of enhanced recovery after surgery.[29,30] Briefly, this protocol included preoperative patient education and counselling, smoking cessation, lung function assessment, airway preparation, blood pressure and glucose control, correction of anaemia, correction of electrolyte disturbance, correction of hypoproteinaemia, thromboprophylaxis, oral carbohydrate loading, antibiotic prophylaxis, PONV prophylaxis, multimodal analgesia, euvolaemic fluid therapy, prevention of hypothermia, minimally invasive surgery, avoidance of urinary catheters, early chest drain removal, and early ambulation after surgery.

Postoperative nausea and vomiting prophylaxis and postoperative multimodal analgesia

Subjects in both groups received PONV prophylaxis with i.v. dexamethasone 5 mg and ondansetron 4 mg during anaesthesia. Postoperative rescue antiemetic therapy with additional ondansetron 4 mg i.v. could be administered for subjects having severe PONV (three or more episodes of vomits or inability to have activities of daily living).[31]

The postoperative multimodal analgesia regimen comprised flurbiprofen axetil 50 mg i.v. intraoperatively and daily on postoperative days 1 and 2, wound infiltration with 0.5% ropivacaine 20 ml at the end of surgery, and patient-controlled i.v. sufentanil (1 μg ml^{-1}; a background infusion of 1 ml h^{-1}, a bolus dose of 2 ml, and a lockout time of 10 min). Subjects were encouraged to self-administer sufentanil for pain relief. Postoperative pain was assessed using the numerical rating scale (NRS), ranging from 0 (no pain) to 10 (the most severe pain).[1,19] Rescue analgesia with additional sufentanil 5 μg i.v. could be administered to treat pain with NRS score ≥4.

Study outcomes

The primary outcome was the occurrence of PONV during the first 48 h after surgery, defined as any episodes of nausea, retching, or vomiting.[32] PONV was assessed in the ward at 24 h and 48 h after surgery by the blinded assessors (CDF or YX). Subjects were asked to rate their PONV episodes in the preceding 24 h on the simplified PONV impact scale (consisting of two questions: Q1. Have you had vomiting or retching? Q2. Have you experienced nausea? If yes, has the feeling of nausea interfered with activities of daily living?).[31]

Secondary outcomes included nausea, retching, vomiting, use of rescue antiemetics, postoperative sufentanil consumption, and need for rescue analgesia during 0–24 h and 24–48 h, NRS pain scores at rest and on coughing at 24 h and 48 h, length of PACU stay, length of postoperative hospital stay, 30- and 90-day postsurgical pain (defined as a NRS pain score ≥1),[33] and 30- and 90-day mortality. Safety outcomes included hypotension (defined as a reduction in mBP >30% of the baseline value for at least 1 min), bradycardia (defined as HR <50 beats min^{-1} for at least 1 min), hypertension (defined as an increase in mBP >30% of baseline for at least 1 min), tachycardia (defined as HR >100 beats min^{-1} for at least 1 min) during anaesthesia and in the PACU, interventions for haemodynamic events (using ephedrine, phenylephrine, atropine, urapidil, or esmolol), sedation in the PACU (defined as MOAA/S scores ≤3), and the occurrence of headache, dizziness, nightmare, or hallucination within 0–48 h after surgery.

The NRS pain scores and symptoms (headache, dizziness, nightmare, and hallucination) were recorded by the blinded assessors during ward visits. Haemodynamic events, interventions, sedation in PACU, and length of PACU stay were recorded in the DoCare Anaesthesia Clinical Information System (V5.0; Suzhou MedicalSystem Co., Ltd, Suzhou, China). Use of rescue antiemetics, postoperative sufentanil consumption, rescue analgesia, and length of postoperative hospital stay were documented in the electronic medical records and nursing notes. Data at 30 and 90 days were obtained by telephone. All data were collected in the electronic case report form, which was checked by the principal investigator (KP) and an independent data monitoring committee.

Statistical analysis

Based on existing data,[11,17] we hypothesised that the incidence of PONV in the OFA group was 16% compared with 40% in the opioid-based control group. To achieve a statistical power of 80% and a significance level of 0.05, we calculated that 106 patients were required in this trial, with 53 in each group (PASS 11.0.7; NCSS, LCC, Kaysville, UT, USA). To account for possible dropouts, we set the sample size to 120 patients (n=60 in each group).

Data distribution was assessed using the Shapiro–Wilk test. Data are presented as mean (standard deviation [SD]), median (interquartile range [IQR]), or number (%), as appropriate. Patient characteristics and baseline data were analysed using descriptive statistics only. Perioperative data and study outcomes were compared using the Mann–Whitney rank-sum test, χ^2 test, or Fisher's exact test, as appropriate. The treatment effects of OFA *vs* control were assessed using the median difference (MD) or odds ratio (OR) with its 95% confidence interval (CI). Moreover, prespecified subgroup analyses on the primary outcome of PONV were conducted according to sex (female *vs* male), current smoking (no *vs* yes), and PONV risk scores (1–2 *vs* 3–4). For the secondary outcomes, multiple comparisons were not corrected; thus, these results should be interpreted as exploratory.

Data were analysed in the modified intention-to-treat population, including all randomised patients who had undergone surgery and had available outcome data. We did not perform an interim analysis or missing data imputation. The SPSS software (version 19.0; IBM SPSS, Chicago, IL, USA) was used for analyses. A two-sided P<0.05 denotes a statistically significant difference.

Results

From May 2022 to November 2022, a total of 176 patients were screened (Fig. 1). Of these, 56 patients were excluded, and 120 patients were randomly assigned to the OFA group and the control group. All randomised patients underwent their surgical procedures with the designated anaesthesia regimens. Primary outcome data were available at all time points in all

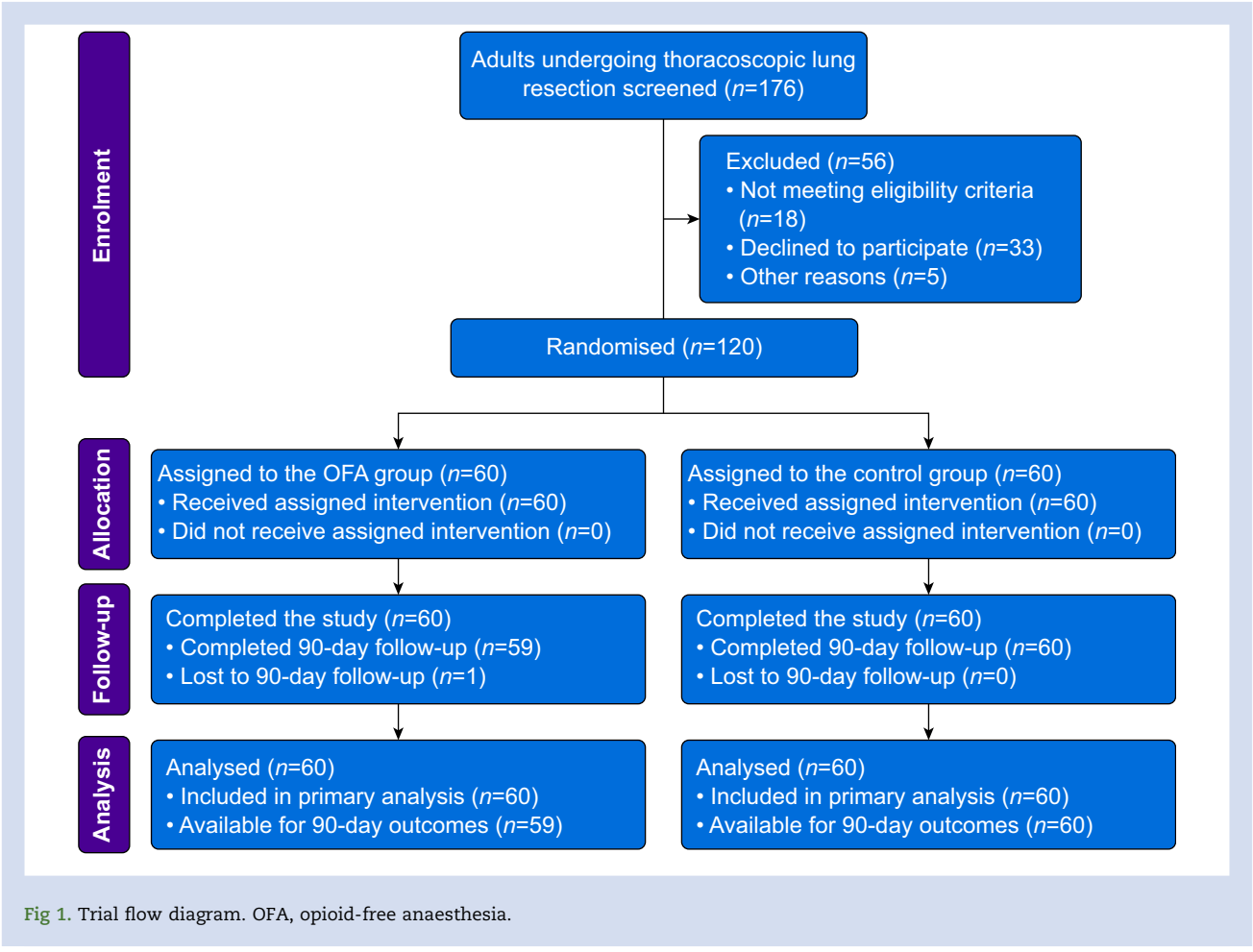

Fig 1. Trial flow diagram. OFA, opioid-free anaesthesia.

subjects. There were no missing data on secondary outcomes, except that 90-day outcome data was missing in one subjects in the OFA group owing to loss to follow-up.

Subject characteristics and baseline data were well balanced between the two groups (Table 1). The median (IQR) age was 52 (42.5–60) yr in the OFA group and 53.5 (43–60) yr in the control group. In both groups, 66.7% of subjects were female. Most subjects were at ASA physical status 1 and 2. The two groups had comparable preoperative baseline lung function. The median (IQR) predicted mortality by Thoracoscore was 0.34 (0.22–0.68)% and 0.47 (0.22–0.59)% in the OFA group and control group, respectively. The median (IQR) PONV risk score was 3 (1.3–3) in the OFA group and 3 (2–3) in the control group.

Perioperative data

Compared with control, OFA led to higher values of mBP from the time of intubation (mean [SD]: 115 [16] *vs* 106 [16] mm Hg; P=0.002) to 1 h in surgery (88 [12] *vs* 83 [11] mm Hg; P=0.021) and higher values of HR at the time of skin incision (74 [12] *vs* 66 [12] beats min^{-1}; P=0.001) (Table 2). The two groups had comparable SPI values throughout the anaesthesia and surgery.

The propofol requirement was higher in the OFA group (median [IQR]: 185 [160–200] *vs* 150 [120–200] mg; P=0.020). In the OFA group, the median (IQR) dose of esketamine was 30 (25–35) mg, and the mean (SD) consumption of dexmedetomidine was 97 (29) μg. In the control group, the median (IQR) dose of sufentanil was 50 (50–55) μg. The median sevoflurane end-tidal concentration was 2% in both groups. The median (IQR) length of surgery was 120 (66–169) min and 125 (86–156) min in the OFA group and the control group, respectively.

Primary outcome

During 0–48 h after surgery, nine of 60 (15%) subjects in the OFA group and 19 of 60 (31.7%) subjects in the control group experienced PONV episodes (Table 3, Fig. 2). The incidence of PONV was significantly reduced in the OFA group (OR=0.38; 95% CI, 0.16–0.91; absolute risk reduction, 16.7%, number needed to treat [NNT], 6; P=0.031).

Secondary outcomes

During 0–24 h after surgery, episodes of nausea occurred in nine subjects (15%) in the OFA group *vs* 19 subjects (31.7%) in the control group (OR=0.38; 95% CI, 0.16–0.91; P=0.031; Fig. 2a), retching in four subjects (6.7%) in the OFA group *vs* 15 subjects (25%) in the control group (OR=0.21; 95% CI, 0.07–0.68; P=0.011; Fig. 2b), and vomiting in four subjects (6.7%) in the OFA group *vs* 14 subjects (23.3%) in the control group (OR=0.23, 95% CI, 0.08–0.77; P=0.019; Fig. 2c) (Table 3). During 24–48 h

Table 1 Subject and baseline characteristics. Data are presented as mean (SD), median (interquartile range), or *n* (%). FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF, maximum mid-expiratory flow; MVV, maximal voluntary ventilation; OFA, opioid-free anaesthesia; PEF, peak expiratory flow; PONV, postoperative nausea and vomiting. *Preoperative lung function test data available: OFA (*n*=55), control (*n*=54). †Predicted in-hospital mortality by the Thoracoscore scoring system, including nine risk factors: age, sex, American Society of Anesthesiologists (ASA) physical status score, performance status classification, dyspnoea score, priority of surgery, procedure class, diagnosis group, and comorbidity score.

	Opioid-free anaesthesia (*n*=60)	Control (*n*=60)
Age (yr)	52 (42.5–60)	53.5 (43–60)
Female	40 (66.7)	40 (66.7)
Height (cm)	163 (6.9)	164 (7.1)
Weight (kg)	59.4 (10.2)	61.2 (9.3)
BMI (kg m^{-2})	21.7 (20.1–24.2)	22.9 (21.5–24.5)
Current smokers	15 (25)	10 (16.7)
ASA physical status		
1	40 (66.7)	35 (58.3)
2	20 (33.3)	24 (40)
3	0	1 (1.7)
Comorbidities		
Hypertension	11 (18.3)	13 (21.7)
Diabetes mellitus	2 (3.3)	3 (5)
Anaemia	2 (3.3)	1 (1.7)
History of stroke	0	1 (1.7)
History of malignancy	2 (3.3)	4 (6.7)
Other	4 (6.7)	3 (5)
Preoperative lung function*		
FVC (L)	3.13 (2.66–3.71)	3.17 (2.67–3.89)
Predicted percentages of FVC (%)	103.3 (91.3–110.8)	101.7 (93.4–111.7)
FEV_1 (L)	2.68 (0.69)	2.64 (0.67)
Predicted percentages of FEV_1 (%)	99.1 (15.1)	96.8 (13.6)
MVV (L min^{-1})	101.1 (29.2)	99.1 (29.9)
Predicted percentages of MVV (%)	97.1 (19.2)	94 (20.5)
FEV_1 to FVC ratio (%)	100.8 (96.3–105.2)	100 (95.2–103.2)
Predicted percentages of PEF (%)	102.5 (90.5–119.8)	99.7 (92.8–110.4)
Predicted percentages of MMEF 75 to 25 (%)	76.4 (23.2)	71.6 (22.0)
MVV <80% predicted	7 (12.7)	11 (20.3)
FEV_1 to FVC ratio <80%	1 (1.8)	2 (3.7)
Haemoglobin (g L^{-1})	131 (122–143)	128 (119–140)
Albumin (g L^{-1})	42.1 (40.7–44.7)	42.1 (40.1–44.4)
Preoperative mean blood pressure (mm Hg)	102 (13)	99 (12)
Preoperative heart rate (beats min^{-1})	77 (10)	76 (11)
Preoperative surgical pleth index	69 (65–74)	69 (62–72)
Apfel PONV risk score		
1	15 (25)	10 (16.7)
2	5 (8.3)	10 (16.7)
3	35 (58.3)	37 (61.7)
4	5 (8.3)	3 (5)
Risk scores	3 (1.3–3)	3 (2–3)
Predicted mortality† (%)	0.34 (0.22–0.68)	0.47 (0.22–0.59)

after surgery, no subjects in the OFA group *vs* four subjects in the control group had PONV (*P*=0.12). Only three subjects (5%) having three or more vomits in the control group needed rescue antiemetics (Table 3, Fig. 2d).

The two groups were comparable in terms of postoperative NRS pain scores and sufentanil consumption (Table 3). Rescue analgesia was not required in either group. Length of PACU stay was longer in the OFA group (MD=15.5 min; 95% CI, 10–20 min, *P*<0.001). The median (IQR) length of postoperative hospital stay was 5 (3–6) days in the OFA group *vs* 4 (3–6) days in the control group (*P*=0.22). The 30-day postsurgical pain occurred in 18 subjects (30%) in the OFA group and 24 subjects (40%) in the control group (*P*=0.25); all these subjects reported their pain as mild (NRS pain score ≤3). Of them, six subjects (10.2%) in the OFA group and eight (13.3%) in the control group still had mild pain at 90 days after surgery (*P*=0.59).

Safety outcomes

All safety outcomes were comparable between the two groups (Table 3). Twenty-three subjects (38.3%) in the OFA group and 19 subjects (31.7%) in the control group had hypotension, while bradycardia was uncommon in either group. Furthermore, 40% of subjects in the OFA group and 31.7% of subjects in the control group received interventions for haemodynamic events.

Table 2 Perioperative data. Data are median (interquartile range) or *n* (%).

	Opioid-free anaesthesia (*n*=60)	Control (*n*=60)	*P*-value
Mean blood pressure (mm Hg)			
Intubation	115 (16)	106 (16)	0.002
Skin incision	105 (15)	99 (14)	0.031
0.5 h in surgery	86 (13)	78 (12)	0.001
1 h in surgery	88 (12)	83 (11)	0.021
End of surgery	87 (11)	91 (14)	0.12
Heart rate (beats min^{-1})			
Intubation	83 (14)	78 (14)	0.07
Skin incision	74 (12)	66 (12)	0.001
0.5 h in surgery	72 (11)	70 (10)	0.46
1 h in surgery	69 (9)	68 (10)	0.38
End of surgery	70 (10)	70 (11)	0.71
Surgical pleth index			
Intubation	37 (33–42)	39 (32–46)	0.37
Skin incision	39 (32–48)	38 (31–54)	0.89
0.5 h in surgery	34 (31–38)	34 (29–39)	0.77
1 h in surgery	39 (35–45)	39 (33–44)	0.16
End of surgery	51 (39–59)	54 (48–59)	0.46
Anaesthetics and analgesics			
Propofol (mg)	185 (160–200)	150 (120–200)	0.02
Esketamine (mg)	30 (25–35)	–	–
Dexmedetomidine (μg)	97 (29)	–	–
Sufentanil (μg)	–	50 (50–55)	–
Sevoflurane (%)			
Skin incision	2 (2–2.4)	2 (2–2)	0.004
0.5 h in surgery	2 (1.6–2)	2 (1.5–2)	0.51
1 h in surgery	2 (1.5–2)	2 (1.1–2)	0.55
Surgical characteristics			
Surgical procedure			
Wedge resection	25 (41.7)	25 (41.7)	0.89
Segmentectomy	13 (21.7)	15 (25)	
Lobectomy	22 (36.7)	20 (33.3)	
Number of ports			
Single	33 (55)	29 (48.3)	0.47
Two or three	27 (45)	31 (51.7)	
Pathological diagnosis			
Benign	10 (16.7)	7 (11.7)	0.43
Malignant	50 (83.3)	53 (88.3)	
Length of surgery (min)	120 (66–169)	125 (86–156)	0.46

Sedation in the PACU was observed in five subjects (8.3%) in the OFA group and one subject (1.7%) in the control group.

Subgroup analyses

In the prespecified subgroup analyses, the treatment effects of OFA *vs* control on PONV did not differ in the subgroups of sex (female *vs* male, *P*=0.43), smoking (no *vs* yes, *P*=0.66), and PONV risk scores (1–2 *vs* 3–4, *P*=0.43) (Fig. 3).

Discussion

In adult patients who underwent thoracoscopic lung resection with PONV prophylaxis and multimodal analgesia, the SPI-guided opioid-free anaesthesia (OFA) led to a statistically and clinically significant reduction (NNT=6) in the incidence of PONV within the first 48 h after surgery, when compared with opioid-based anaesthesia. Opioid-free anaesthesia was associated with a longer length of PACU stay. The safety outcomes were comparable between the two anaesthesia regimens.

Studies suggested that OFA was feasible and safe for thoracic surgery and may be associated with reduced postoperative pain and opioid consumption.[9,10] A randomised study found that OFA of dexmedetomidine and sevoflurane achieved equal intraoperative analgesia to that of remifentanil and sevoflurane.[11] Another study showed that OFA using esketamine (i.v. injection and epidural infusion) reduced the incidence of chronic pain after thoracoscopic surgery.[12] However, none of the previous studies aimed PONV as the primary outcome when assessing the effects of OFA in thoracoscopic lung surgery. In a trial by An and colleagues,[11] the rate of PONV was 4.3% in the OFA group, which was significantly lower than 41.7% in the opioid-based control group. However, our study showed a reduced PONV incidence of 15% in the OFA group compared with 31.7% in the control group. The potential reasons for this difference are as follows. Firstly, An and colleagues[11] assessed pain intensity as their primary outcome, whereas PONV was recorded as non-outcome data, without details on its definition and measurement (such as the assessor, method, and

Table 3 Primary, secondary, and safety outcomes. Data are median (interquartile range) or *n* (%). CI, confidence interval; PONV, postoperative nausea and vomiting.

	Opioid-free anaesthesia (*n*=60)	Control (*n*=60)	Odds ratio or median difference (95% CI)	P-value
Primary outcome				
PONV 0–48 h after surgery	9 (15)	19 (31.7)	0.38 (0.16–0.91)	0.031
Secondary outcomes				
Nausea				
0–24 h	9 (15)	19 (31.7)	0.38 (0.16–0.91)	0.031
24–48 h	0	4 (6.7)	–	0.119
Retching				
0–24 h	4 (6.7)	15 (25)	0.21 (0.07–0.68)	0.011
24–48 h	0	4 (6.7)	–	0.12
Vomiting				
0–24 h	4 (6.7)	14 (23.3)	0.23 (0.08–0.77)	0.019
24–48 h	0	4 (6.7)	–	0.12
Use of rescue antiemetics				
0–24 h	0	3 (5)	–	0.24
24–48 h	0	0	–	1.0
Pain scores at rest				
at 24 h	1 (0–2)	1 (0–2)	0 (−1–0)	0.53
at 48 h	0 (0–1)	1 (0–1)	−1 (0–0)	0.19
Pain scores while coughing				
at 24 h	3 (2–3)	3 (2–3)	0 (0–0)	0.94
at 48 h	1 (1–2)	2 (1–3)	−1 (−1–0)	0.20
Sufentanil consumption (μg)				
0–24 h	24 (20.3–28)	22 (19–27)	2 (0–4)	0.07
24–48 h	23 (19.3–27.8)	22 (13.3–25)	1 (0–4)	0.15
Rescue analgesia 0–48 h	0	0	–	1.0
Length of PACU stay (min)	50.5 (40–65)	35 (30–49.3)	15.5 (10–20)	<0.001
Length of postoperative hospital stay (days)	5 (3–6)	4 (3–6)	1 (0–1)	0.22
30-day postsurgical pain	18 (30)	24 (40)	0.64 (0.30–1.34)	0.25
90-day postsurgical pain	6 (10.2) (*n*=59)	8 (13.3)	0.72 (0.23–2.36)	0.59
90-day mortality	0 (*n*=59)	0	–	1.0
Safety outcomes				
Hypotension	23 (38.3)	19 (31.7)	1.34 (0.64–2.86)	0.44
Bradycardia	1 (1.7)	3 (5)	0.32 (0.02–2.23)	0.62
Hypertension	16 (26.7)	13 (21.7)	1.32 (0.58–3.15)	0.52
Tachycardia	6 (10)	2 (3.3)	3.22 (0.76–16.10)	0.27
Interventions for haemodynamic events	24 (40)	19 (31.7)	1.44 (0.70–3.06)	0.34
Sedation in PACU	5 (8.3)	1 (1.7)	5.36 (0.69–64.13)	0.21
Headache or dizziness 0–48 h	8 (13.3)	9 (15)	0.87 (0.30–2.36)	0.79
Nightmare or hallucination 0–48 h	3 (5)	2 (3.33)	1.53 (0.30–8.82)	1.0

frequency). Secondly, the precision of their result might be affected by a smaller number of subjects (*n*=49 in the OFA group). Next, 55% of subjects in the OFA group were female in their study compared with 66.7% in our study, which also contributes to the different rate of PONV.

In contrast, PONV was designated as the primary outcome in our trial, with an explicit definition and detailed measurement. Our trial was based on a randomised design; the implementation strictly adhered to the published protocol; and all analyses were done in accordance with the prespecified statistical plan.[20] Therefore, our results provide robust clinical evidence supporting the OFA administered, in combination with PONV prophylaxis and multimodal analgesia, for reducing PONV after thoracoscopic lung resection. SPI is an index of the nociceptive–antinociceptive balance and reflects noxious stimuli and analgesic effects better than other clinical parameters such as entropy and HR.[34] SPI with a target of 20–50 has been used to guide intraoperative analgesia provision in the previous studies,[25,26] and in our recent studies of patients undergoing thoracoscopic lung surgery.[35,36] Owing to intraoperative SPI-guided analgesia and postoperative multimodal analgesia (flurbiprofen axetil, ropivacaine wound infiltration, and patient-controlled sufentanil), patients of both groups had adequate pain control (median NRS pain scores of 0–1 at rest and 1–3 on coughing), without the need for rescue analgesics. Additionally, the two groups had comparable postoperative sufentanil consumption and 30- and 90-day pain outcomes.

In a recent study, Beloeil and colleagues[37] showed that the balanced OFA led to serious adverse events of hypoxaemia and bradycardia, with a mean (SD) dexmedetomidine of 1.2 (2) μg kg^{-1} h^{-1} in the OFA group. A high dose of dexmedetomidine is undoubtably associated with severe bradycardia and even asystole. With an overdosage of dexmedetomidine, the risk of OFA outweighs its benefits. Here, in our OFA regimen, dexmedetomidine (0.6 μg kg^{-1} over 10 min), esketamine (0.3 mg kg^{-1}), and propofol (1.5–2.0 mg kg^{-1}) were administered to induce anaesthesia, followed by dexmedetomidine infusion (0.2–1.0 μg

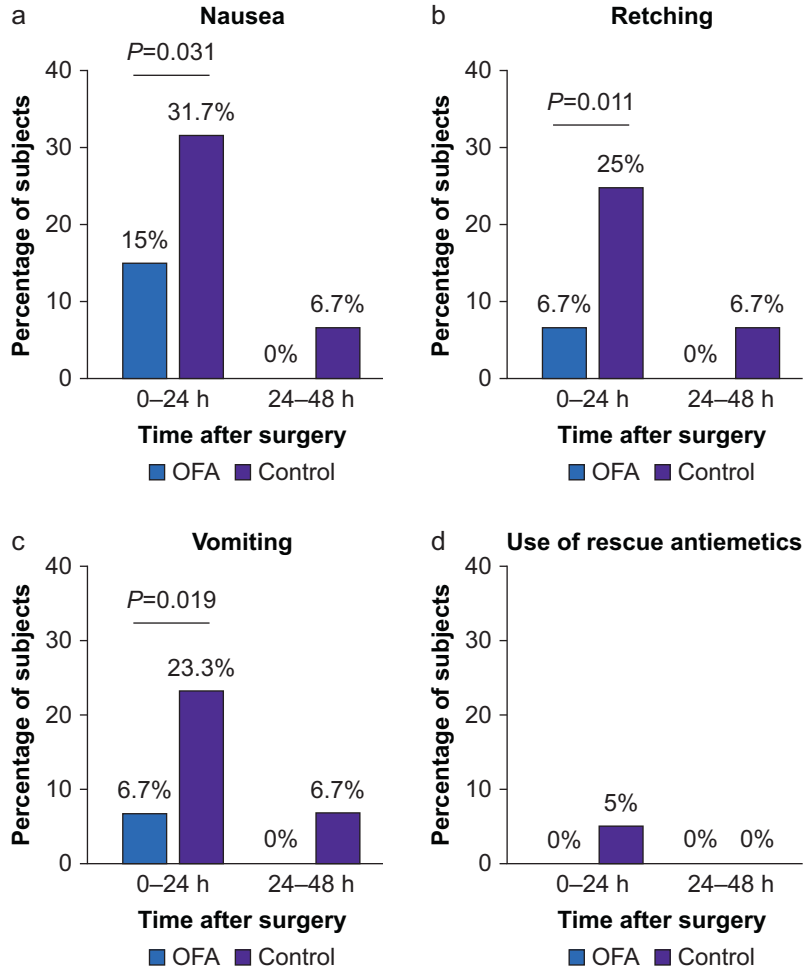

Fig 2. Nausea, retching, vomiting, and use of rescue antiemetics during 0–24 h and 24–48 h after surgery. Incidence of (a) nausea, (b) retching, (c) vomiting, and (d) using rescue antiemetics. OFA, opioid-free anaesthesia.

Subgroup	OFA No./total (%)	Control No./total (%)	Odds ratio (95% CI)	*P*-value for interaction
Sex				
Female	9/40 (22.5)	16/40 (40)	0.44 (0.16–1.15)	0.43
Male	0/20 (0)	3/20 (15)	0.12 (0.01–2.53)	
Smoking				
No	9/45 (20)	18/50 (36)	0.44 (0.18–1.13)	0.66
Yes	0/15 (0)	1/10 (10)	0.20 (0.01–5.54)	
PONV risk score				
1–2	0/20 (0)	3/20 (15)	0.12 (0.01–2.53)	0.43
3–4	9/40 (22.5)	16/40 (40)	0.44 (0.16–1.15)	
Overall	**9/60 (15)**	**19/60 (31.7)**	**0.38 (0.16–0.91)**	

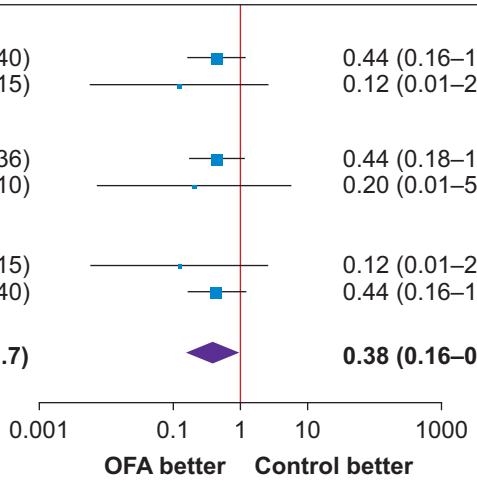

Fig 3. Subgroup analysis of postoperative nausea and vomiting (PONV). CI, confidence interval; OFA, opioid-free anaesthesia.

kg^{-1} h^{-1}), esketamine boluses (0.1 mg kg^{-1}), and 1–3% sevoflurane inhalation intraoperatively. The dosage of each component in the OFA was well within the clinical norms, without increasing the associated adverse events. Of note, the OFA was associated with a moderately longer length of PACU stay (~15 min). We considered that this finding was mainly attributable to the sedative effect of dexmedetomidine. In healthy adults, dexmedetomidine 1 μg kg^{-1} i.v. produced a median sedation duration of 203 (95% CI, 105–225) min.[38] In our study, five subjects in the OFA group exhibited excessive sedation in the PACU compared with one subject in the control group, although the between-group difference was not significant.

This study has limitations. Firstly, the OFA regimen delivered to our subjects was informed by recent literature and pilot observations in our clinical practice. We acknowledge that it is not definitive, and more efforts are still required to ascertain the optimal OFA regimen in thoracoscopic and other types of surgery. Secondly, the subgroup analysis did not show differences in subjects with low *vs* high risk of PONV. This result might be affected by the small number of subjects included in each subgroup. Whether OFA would be more beneficial for patients with a high PONV risk needs further investigations. Thirdly, this study showed a relatively wide 95% CI for the treatment effect of OFA on PONV, which can also be attributed to the limited sample size. Finally, our subjects had a low surgical risk, and the generalisability of the findings from this single-centre trial needs to be corroborated in future larger studies.

In conclusion, the SPI-guided opioid-free anaesthesia halved the incidence of PONV in patients having thoracoscopic lung resection with PONV prophylaxis and multimodal analgesia, and moderately prolonged the length of PACU stay. The opioid-free anaesthesia regimen is feasible in thoracoscopic surgery and could be considered for patients at a higher risk of PONV.

Authors' contributions

Study design: CDF, YX, FHJ, KP
Data acquisition: CDF, YX, SC, NS, XWM
Manuscript drafting: CDF, YX, SC, NS
Statistical analysis: CDF, YX, KP
Data interpretation: CDF, YX, SC, NS, XWM, HL, FHJ, KP
Manuscript revision: XWM, HL, FHJ, KP
Final approval of the version to be published: all authors

Declaration of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2023.11.008.

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