BMC Anesthesiology

RESEARCH

Open Access

Effects of balanced opioid-free anesthesia on post-operative nausea and vomiting in patients undergoing video-assisted thoracic surgery: a randomized trial

Xiang Yan[1†], Chen Liang[2†], Jia Jiang[1], Ying Ji[3], An-Shi Wu[1*] and Chang-Wei Wei[1*]

Abstract

Objectives Postoperative nausea and vomiting (PONV) is common after video-assisted thoracic surgery, which may be associated with the use of intraoperative opioids. We tested the hypothesis that balanced opioid-free anesthesia (OFA) might reduce the incidence of PONV after video-assisted thoracic surgery.

Methods One hundred and sixty-eight adults undergoing video-assisted thoracic assisted surgery were randomly assigned to receive balanced opioid-free anesthesia or balanced opioid-based anesthesia (OBA). The primary outcome was the incidence of PONV, which was assessed with the Myles's simplified PONV impact scale during the initial 24 h after surgery.

Results Compared with OBA group, the overall incidence of PONV in OFA group was significant reduced (14.6% vs. 30.1%, $P=0.017$), and OFA reduced the risk of PONV events within 24 h of surgery (HR, 0.44; 95%CI: 0.22–0.87, $P=0.018$). The incidence of other postoperative complications in OFA group was lower than that in OBA group (19.5% vs. 33.7%, $P=0.039$). The quality of recovery, distance of 6-minute walk test, pain scores, and 36-item short form survey were comparable at each time points.

Conclusion In patients undergoing video-assisted thoracic surgery, the use of balanced OFA anesthesia can help reduce the incidence of PONV events. This anesthetic regimen has shown good feasibility without significantly increasing the patient's pain score and complications.

Clinical trial registration number Clinicaltrials.gov, Identifier: NCT05411159. First posted date: 9 Jun, 2022.

Keywords Opioid, Anesthesia, Nausea and vomiting, Video-assisted thoracic surgery, Quality of recovery, 6-min walk test

†Xiang Yan and Chen Liang contributed equally to the study.

*Correspondence:
An-Shi Wu
wuanshi1965@163.com
Chang-Wei Wei
changweiwei2023@163.com
Full list of author information is available at the end of the article

Introduction

Postoperative nausea and vomiting (PONV) is a common complication, with an incidence of 30%~40% in video-assisted thoracic surgery under general anesthesia [1–3]. Severe PONV can affect the early recovery of patients, leading to prolonged post-anesthesia care, increased costs, and increased staffing burden [4–7]. Given the significant population of such patients, reducing the incidence of PONV in patients receiving video-assisted thoracic surgery after anesthesia would have important clinical implications.

Opioids is one of the predictive factors for PONV [8]. Opioids contribute to PONV through various mechanisms, including direct stimulation of opioid receptors, delayed gastric emptying, sensitization of the vestibular system, and triggered release of histamine [9]. Other concerns of opioids use include ventilation disturbances, hyperalgesia, and the potential for addiction [10]. Therefore, the concept of opioid-sparing or opioid-free anesthesia (OFA) is thus gaining attention as a potential strategy to reduce opioid-related side effects and complications [11–13].

The OFA usually involves utilizing alternative analgesic techniques to provide comprehensive pain relief [14–17]. Previous studies suggested that avoiding opioids during video-assisted thoracic surgery could be a viable approach without reported anesthesia-related adverse events [18]. An et al. [19] and Yan et al. [3] in their RCT focused on the effects of OFA on perioperative pain control, and also observed that it was associated with a potential reduction of PONV. In contrast to previous studies, this study applied a widely used standardized scale to evaluate the incidence of PONV as well as the severity of PONV. This approach enhanced the generalizability of the conclusions drawn from this trial. We therefore tested the primary hypothesis that OFA may reduce the incidence of PONV within the initial 24 h after video-assisted thoracic surgery in adult patients.

Methods

This blinded, randomized, parallel-group trial was conducted at the Beijing Chao-Yang Hospital of Capital Medical University, a tertiary hospital. This study was approved by the Institutional Review Board (No. 2022-ke-19) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT05411159). This trial was conducted in accordance with the Declaration of Helsinki principles and followed the Consolidated Standards of Reporting Trials guidelines. The full protocol has been published [20].

Participants

Patients aged 18–65 years with lung space-occupying lesions who were scheduled for video-assisted video-assisted thoracic surgery under general anesthesia were screened for eligibility. Those who met any of the following criteria were excluded: (1) ASA) ≥ IV, (2) BMI > 35 kg/m^2; (3) unable to communicate before surgery; (4) received radiation therapy, chemotherapy, opioids or hormonal drugs within 14 days before surgery; (5) intolerant of the anesthesia protocol, such as nerve block contraindications, allergies to medication; (6) expected to experience prolonged mechanical ventilation usage after surgery; or (7) declined to participate.

Randomization and masking

Eligible patients were randomized to OFA group (opioid-free anesthesia) or OBA group (opioid-based anesthesia) with a 1:1 ratio. The randomization sequence with a block size of 4 or 6 was generated by an independent researcher. The generated random results were sealed in sequentially numbered opaque envelopes and kept by a research assistant. After participants entered the operating room, the randomized envelopes were opened according to the recruitment sequence by an attending anesthesiologist, who then prepared the study medications accordingly. The research assistant was not involved in anesthesia management, perioperative care, and postoperative follow-up. Patients, surgeons, nurses, and the investigator performing follow-up assessments were blinded to the allocation.

Anesthesia, perioperative care, and intervention

Intraoperative monitoring included electrocardiogram, peripheral oxygen saturation, invasive blood pressure, end-tidal carbon dioxide tension, end-tidal anesthetic concentration, and wavelet index (WLi), which was calculated from the changes in EEG signals by multifunction combination monitor [2]. The WLi ranges from 0 to 100, with 0 indicating the disappearance of EEG while 100 indicating awake status.

Dexamethasone (5 mg) and atropine (0.25 mg) were administered before anesthesia induction for prevention of PONV and reduction of bronchial secretions. All participants received flurbiprofen (50 mg, twice) as adjunctive analgesics before induction and skin closure. A single thoracic paravertebral block (20 ml of 0.5% ropivacaine) was performed at T_5 level on the surgical side before incision to reduce pain during incision.

Anesthesia was induced with intravenous propofol (2–3 mg/kg), rocuronium (0.6–0.8 mg/kg) in both groups. Participants in the OFA group received dexmedetomidine (0.5 ug/kg for 15 min) before induction,

lidocaine (1.5 mg/kg) intravenous for induction, and followed by dexmedetomidine (0.5 ug/kg/h) and lidocaine (1.5 mg/kg/h) infusion during surgery. While participants in the OBA group received sufentanil (0.3–0.4 ug/kg) intravenous for induction, and followed by remifentanil (0.1–0.2 ug/kg/min) infusion during surgery. The anesthesia was maintained with desflurane (0.5–1.0 MAC) in both groups. Continuous or intermittent additions of propofol were allowed to maintain a reasonable depth of sedation (WLi between 40 and 60) [19]. All participants received a double-lumen endobronchial tube intubation to facilitate lung isolation. During anesthesia, the vasoactive drugs were used to maintain the heart rate and blood pressure within 25% of baseline.

After surgery, patients in both groups received the same multimodal analgesia regimen, including ibuprofen orally at a dosage of 0.2 g every 8 h for 48 h, and patient-controlled analgesia pump with sufentanil (1 μg/h background, 2 μg bolus, and a 10-minute lock-out). Medications available for the treatment of PONV included ondansetron, metoclopramide, and dexamethasone.

Measurements

Baseline data included patients' characteristics, preoperative comorbidities, current diagnosis, smoking and alcohol consumption, and pulmonary function measures. All participants finished lung CT, pulmonary function test, 6-minute walk test (6-MWT), and PONV risk assessment one day before surgery [5]. Intraoperative data included surgical type, medications during anesthesia, fluid infusion, blood loss and transfusion, and the length of anesthesia and surgery.

PONV and pain severity were assessed at 24 and 48 h after surgery. The severity of PONV was assessed with the Myles's simplified PONV impact scale [21]. According to this scale, the frequency of vomiting/retching (Once, Twice, three or more times) and the duration of nausea (Sometimes, Often or most of the time, All of the time.) directly contribute to the score, with a maximum of 6 points. A total score of 3 or higher indicates severe PONV. The time to first PONV after surgery was also recorded. Postoperative pain at rest and with movement were assessed with the Numerical Rating Scale score (NRS, 0–10 points, higher score represents worse). Postoperative quality of recovery was assessed through the Quality of Recovery 15-item scale (QoR-15, 0–150 points, higher point indicates better) at 24 h after surgery [22]. The 6-MWT (farther distance is better) was tested on the 48 h after surgery [23]. The 36-item short form survey (SF-36) was performed at 180 days after surgery.

Study endpoints

The primary outcome was the cumulative incidence of PONV (Myles's simplified PONV impact scale ≥ 1) during the first 24 h after surgery [21]. The secondary outcomes included the severity of PONV within 24 h after surgery, the score of QoR-15 at 24 h after surgery, the pain severity at rest and with movement at 24 and 48 h after surgery, the 6-MWT at 48 h after surgery, the length of hospital and PACU stay, and the score of SF-36 at 180 days after surgery. Perioperative complications were recorded as newly occurring adverse conditions that required therapeutic interventions, and the severity of complications were classified by the ClassIntra [24] and Clavien-Dindo [25] surgical complication categories from interventions to 48 h after surgery.

Safety outcomes included intraoperative, postoperative complications, and mortality. Intraoperative complications included the occurrence of hypotension, bradycardia, newly occurred arrhythmias, delayed awakening, and desaturation. The occurrence of local anesthetic toxicity and hematoma due to nerve block puncture were also recorded. Postoperative complications of interest within 2 days after surgery included hypoxemia, hypotension, pulmonary embolism based on lung imaging, pruritus, drowsy, dizziness, fatigue, constipation, and uroschesis.

Statistics

Outcome analyses were mainly conducted in the modified intention-to-treat population, that was, all subjects who were randomized and received surgery under general anesthesia without withdrawing consent. For the primary outcome, a per-protocol analysis was planned after excluding patients with major protocol deviations.

Baseline characteristics were described with mean [standard deviation (SD)], median [inter-quartile range (IQR)], or number (percentage). For perioperative data, normally distributed continuous variables were described by mean (SD) and compared by Student's t-test, while skewed distributed continuous variables were described by median (IQR) and compared by *Mann-Whitney U* test. Categorical variables were reported as number (percentage) and compared by χ [2] test or *Fisher's* test.

For the primary outcome, log-binomial model was applied to calculate the relative risk (RR) with 95% confidence interval (CI). The time to the first PONV after surgery was represented by Kaplan-Meier curve, and compared by log-rank test between groups as sensitivity analysis. The hazard ratio and 95% CI were calculated from cox regression. Secondary and exploratory outcomes were analyzed by χ [2] test, Student t-tests, or *Mann-Whitney U* test as appropriate. Between groups, the median differences (MD) with 95% CIs were

calculated for normal or skewed continuous variables by Hodges-Lehman Estimation. Safety outcomes were evaluated with χ [2] tests or *Fisher's* exact tests. No imputation was performed for missing data. Predefined subgroup analyses (sex, smoker, history of PONV/motion sickness, and the length of anesthesia) were conducted. Two-sided $P<0.05$ was considered statistically significant. Statistical analyses were conducted with SAS 9.4 (SAS Inc., Cary, NC, USA).

Sample size estimation

Sample size estimation was based on previous publications [26, 27], and our pilot results, the incidence of PONV within the first day among patients after VATs was about 40%. And we assumed that there would be a 50% reduction in the OFA group. Therefore, a total of 168 subjects (84 per group) were required to provide 80% power at a two-sided alpha level of 0.05 with a dropout rate of 5%.

Results

One hundred ninety-six patients were assessed for eligibility, and 168 were enrolled and randomized to OFA or OBA group. Finally, 165 subjects were included in the modified intention-to-treat analysis. During the operation, no major protocol deviations were observed in all cases, so the modified intention-to-treat and per-protocol population were identical (Fig. 1).

The baseline characteristics were reported in Table 1. For participants assigned to OBA group, the median dosage of sufentanil and remifentanil during surgery were 20 ug (IQR: 20, 25) and 1080 ug (IQR: 800,1600) ug, respectively. No significant differences were observed in the dose and infusion rate of sufentanil, or other medications between groups postoperatively (Table 2).

Primary outcome

The incidence of PONV within 24 h after surgery was 14.6% in OFA group and 30.1% in OBA group (RR, 0.49; 95%CI: 0.26 to 0.90, $P=0.017$; Table 3; Fig. 2). And the

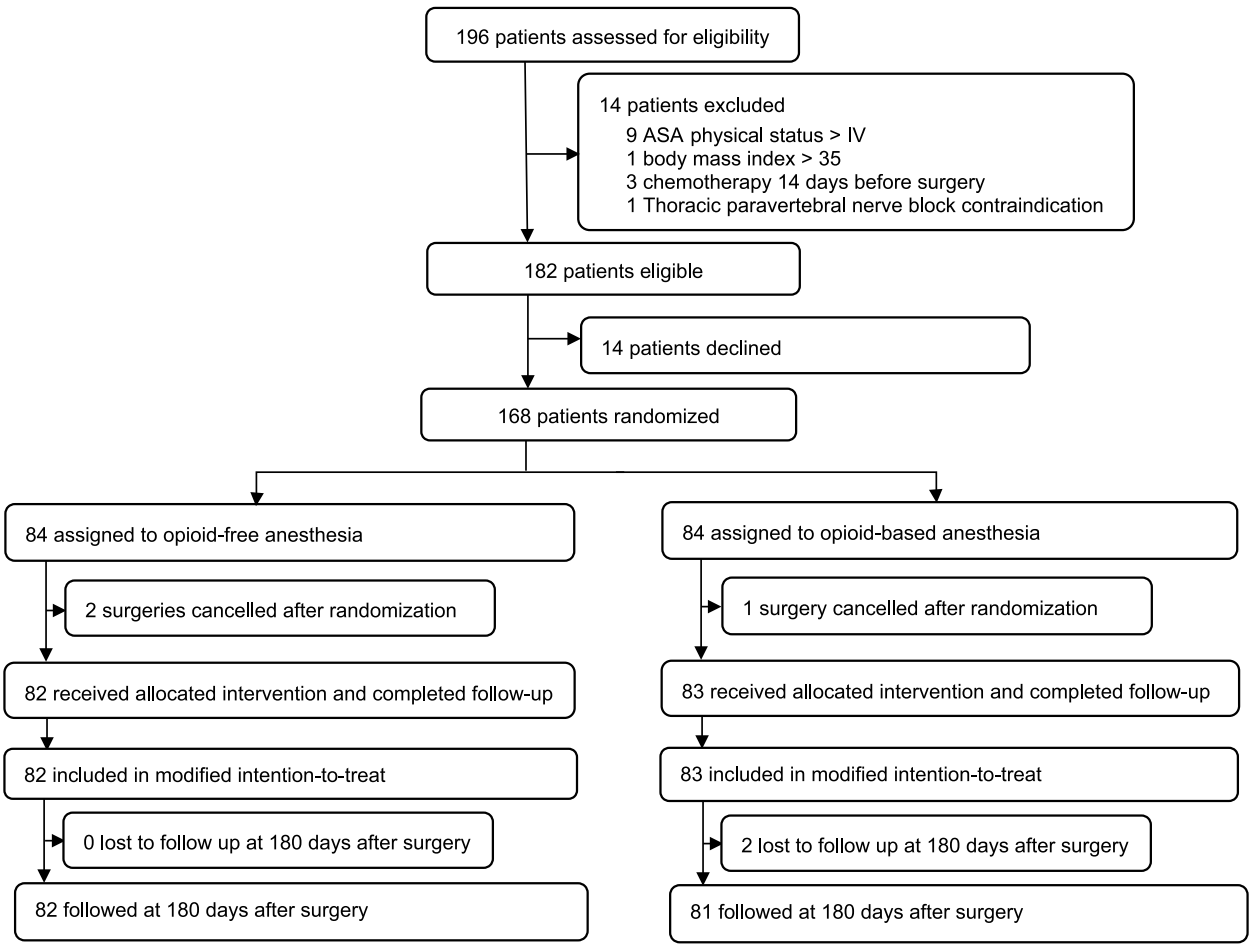

Fig. 1 Flowchart. ASA, American Society of Anesthesiologists

Table 1 Baseline characteristics

Variables	OFA group *n* = 82	OBA group *n* = 83	ASD
Demographics			
Age, year	56[50,60]	56[50,60]	0.043
Female sex	47(57.3%)	55(66.3%)	0.146
Body mass index, kg/m^2	24.5 ± 3.5	23.9 ± 3.6	0.169
Preoperative comorbidities			
Smoker	17(20.7%)	12(14.5%)	0.163
Alcoholism[a]	10(12.2%)	7(8.4%)	0.125
Hypertension	29(35.4%)	21(25.3%)	0.220
Diabetes	14(17.1%)	9(10.8%)	0.182
Coronary artery disease	4(4.9%)	4(4.8%)	0.005
Chronic obstructive pulmonary disease	3(3.7%)	2(2.4%)	0.076
Hyperlipidemia	18(22.0%)	21(25.3%)	0.078
Pulmonary disease			
Side of lesion (left/right)	36/46	35/48	0.034
Maximum diameter of lesion, mm	14[10,24]	13[10,18]	0.239
Lung cancer	68(82.9%)	67(80.7%)	0.057
FEV1/FVC%	77[74,80]	77[74,80]	0.017
Baseline assessment			
age-adjusted Charlson Comorbidity Index	1[1,2]	1[1,2]	0.187
ASA physical status			0.236
I	29(35.4%)	39(47.0%)	
II	49(59.7%)	40(48.2%)	
III	4(4.9%)	4(4.8%)	
6-MWT, meter	461[415,514]	450[408,500]	0.044
KPS status, point	100[90,100]	100[100,100]	0.219
Apfel score			0.242
1	16(19.5%)	9(10.8%)	
2	14(17.1%)	11(13.3%)	
3	34(41.4%)	40(48.2%)	
4	18(22.0%)	23(27.7%)	

Data are mean ± standard deviation, median [inter-quartile range], or n (%). An absolute standardized difference > 0.305 is considered imbalanced between the two groups. [a]Two drinks or more daily, or weekly consumption of the equivalent of 150 ml of alcohol. *OFA* Opioid-free anesthesia, *OBA* Opioid-based anesthesia, *SMD* Absolute standardized difference, *ASA* American Society of Anesthesiologists, *6-MWT* 6-minute walk test, *KPS* Karnofsky Performance Status Scale. Apfel score including four variables (female sex, non-smoking status, history of PONV or motion sickness, and use of postoperative opioids) that are assigned one point each, and the total score was used to evaluate the risk of developing PONV

OFA group showed significant lower the risk of PONV within 24 h of surgery (HR, 0.44; 95%CI: 0.22 to 0.87, $P = 0.018$; Fig. 3).

Secondary outcomes

The median score of PONV severity was lower in the OFA group than in the OBA group (0 vs. 0, MD 0, 95%CI 0 to 0; $P = 0.018$; Table 3; Fig. 2). The quality of recovery 15-item scale at 24 h after surgery were comparable (median 113 vs. 112, MD 1.00, 95CI%: −3.11 to 5.11, $P = 0.358$; Table 3). The distance of 6-minute walk test of patients in the two groups was also similar (median 305 vs. 298 m, MD 5.00, 95 CI%: −37.65 to 47.65, $P = 0.545$; Table 3). The scores of each dimension of SF-36 at 180 days were comparable between groups (Table 3). Subjects randomized to OFA group did not have more intraoperative complications than those in the OBA group (7.3% vs. 3.6%, $P = 0.328$). In subgroup analyses, patients without history of PONV or motion sickness in OFA group had lower incidence of PONV (6.9% vs. 24%, $P = 0.022$; Supplementary Table 1). The incidence of postoperative complications within 2 days in OFA group was lower than that in OBA group (19.5% vs. 33.7%, $P = 0.039$; Supplementary Table 2).

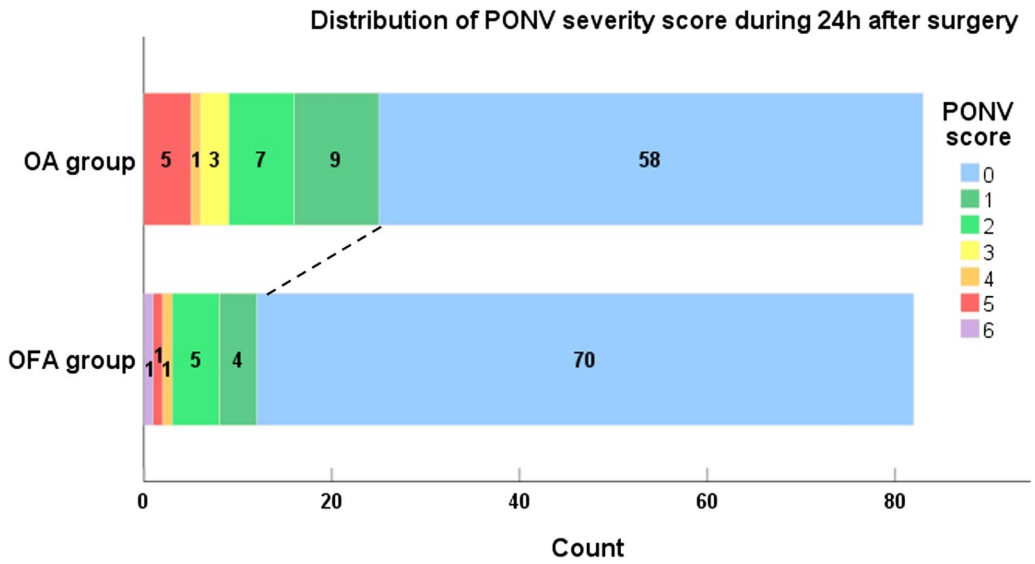

Fig. 2 Distribution of PONV severity score during 24h after surgery. PONV, postoperative nausea and vomiting. OFA, opioid-free anesthesia. OBA, opioid-based anesthesia

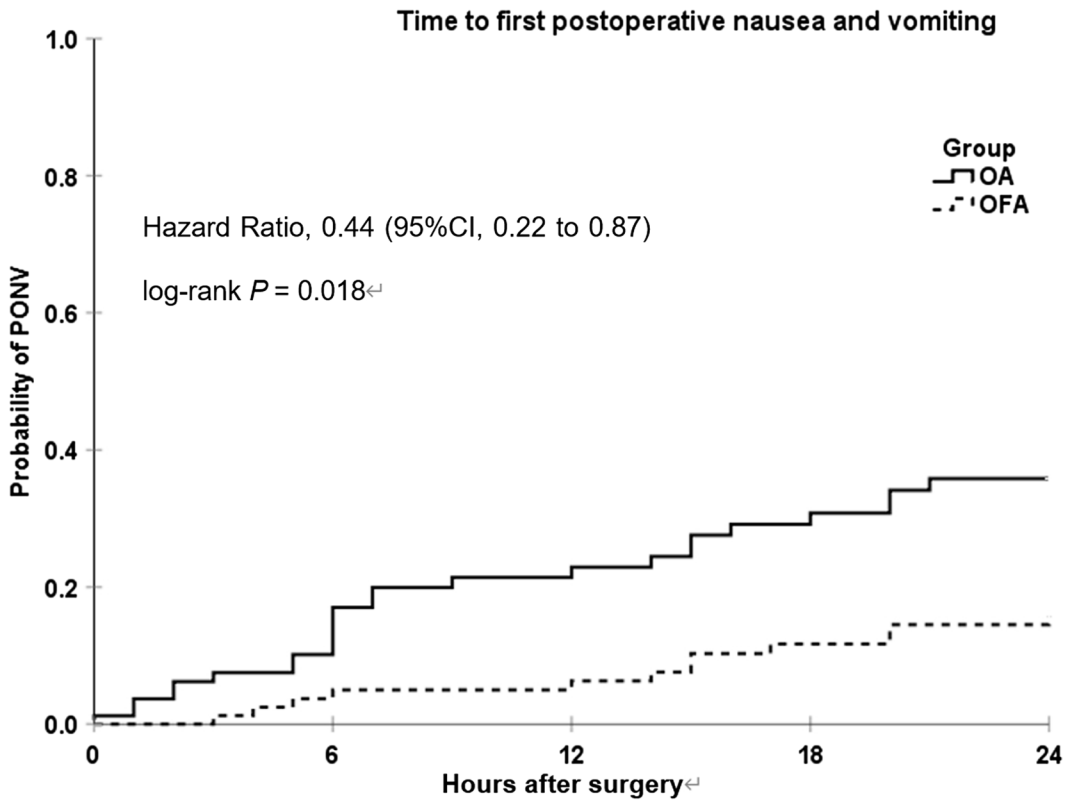

Fig. 3 The Kaplan-Meier curve of time to first postoperative nausea and vomiting. OBA, opioid-based anesthesia; OFA, opioid-free anesthesia

Discussion

In this prospective randomized controlled trial, we examined the effect of OFA on the PONV with 24 h after video-assisted thoracic surgery. Compared to opioid-based analgesia, the OFA reduced the overall incidence of postoperative nausea and vomiting, and it also

Table 2 Perioperative data

Variables	OFA group *n* = 82	OBA group *n* = 83	*P*
Intraoperative data			
Length of surgery, min	94[60,134]	101[60,135]	0.582
Surgery type			0.659
Wedge resection	38(46.3%)	36(43.4%)	
Segmentectomy	15(18.3%)	20(24.1%)	
Lobectomy	29(35.4%)	27(32.5%)	
Converted to thoracotomy	3(3.7%)	2(2.4%)	0.682
Length of anesthesia, min	129[87,160]	124[87,163]	0.912
Length of anesthesia ≥ 2 h	45(54.9%)	46(55.4%)	0.944
Intraoperative medication			
Sufentanil, ug	-	20[20,25]	-
Remifentanil, ug	-	1080[800,1600]	-
Propofol, mg	500[400,600]	420[350,500]	0.013
MAC of desflurane	0.5[0.5,0.5]	0.5[0.5,0.5]	0.326
Rocuronium, mg	60[50,70]	50[50,65]	0.012
Dexmedetomidine, ug	68[54,80]	-	-
Use of Norepinephrine	13(15.9%)	20(24.1%)	0.186
Norepinephrine, mg[a]	0.2[0.1,0.2]	0.1[0.1,0.2]	0.740
Reversal of muscle relaxant[b]	11(13.4%)	8(9.6%)	0.447
Lactate Ringer's fluid, ml	1100[1100,1600]	1100[1100,1500]	0.428
Hydroxyethyl starch 130/0.4, ml	0[0,0]	0[0,500]	0.346
Estimated blood loss, ml	20[10,30]	20[10,30]	0.941
Urinary volume, ml	300[300,400]	300[200,500]	0.828
Postoperative medications within 48 h			
Sufentanil consumption, ug	60[50,80]	57[41,75]	0.658
Use of glucocorticoids[c]	0	1(1.2%)	> 0.999
Use of ondansetron[d]	2(2.4%)	2(2.4%)	> 0.999
Use of metoclopramide[e]	2(2.4%)	0	0.245
Use of flurbiprofen axetil[f]	12(14.6%)	17(20.5%)	0.324
Use of tramadol[g]	4(4.9%)	5(6.0%)	0.746

Data are median [inter-quartile range], or n (%). [a]Amongst patients who were given the medications. [b]I.V neostigmine (2 mg). [c]I.V. dexamethasone (5 mg). [d]I.V. ondansetron (8 mg). [e]I.V. metoclopramide (10 mg). [f]I.V. flurbiprofen axetil (50 mg, twice a day). [g]I.V. tramadol (100 mg). *OFA* Opioid-free anesthesia, *OBA* Opioid-based anesthesia.

delayed the time to first PONV occurrence. However, OFA showed no significant benefits in terms of quality of recovery or mobility after video-assisted thoracic surgery.

In this trial, we observed that the overall incidence of PONV was lower in patients received OFA compared to the OBA group. Previous studies on whether opioid-free anesthesia could reduce the incidence of postoperative nausea and vomiting had inconsistent conclusions [18, 19, 29]. A randomized controlled study of the effects of OFA on PONV hadn't found a significant reduction in the incidence of serious PONV events in patients after gynecological laparoscopy (10.5% vs. 8.1%, $P = 0.57$) [28]. However, given the design of the study, which included only female patients, the conclusions are difficult to generalize to patients undergoing video-assisted thoracic surgery. In thoracic surgery patients, a propensity score study observed the incidence of PONV was 9% in the OFA group and 2% in the control group, but no significant statistical difference could be confirmed due to the small sample size [18]. In this study, we used a randomized controlled study design to include a larger sample size to demonstrate the effect of OFA in reducing the incidence of PONV. We further adjusted the feasibility of opioid-free regimens compared to previous studies [14], and compared the overall incidence and time to first occurrence of PONV, which are consistent with the conclusions of a

Table 3 Primary outcomes and secondary outcomes

Variables	OFA group *n* = 82	OBA group *n* = 83	Estimated effect (95%CI)	*P*
Primary outcome				
Incidence of PONV during 24 h after surgery	12(14.6%)	25(30.1%)	RR 0.49 (0.26 to 0.90)	0.017
Secondary outcomes				
Score of PONV severity during 24 h after surgery[a]			-	0.047
0	70(85.4%)	58(69.9%)		
1–2	9(11.0%)	16(19.3%)		
≥ 3	3(3.6%)	9(10.8%)		
QoR-15 at 24 h after surgery	113[107,119]	112[102,117]	MD 1.00 (−3.11 to 5.11)	0.358
Pain scores at 24 h after surgery				
at rest	3[2,4]	3[2,3]	MD 1.00 (−3.11 to 5.11)	0.540
with movement	5[5,6]	6[5,6]	MD −1.00 (−1.43 to −0.57)	0.740
Pain scores at 48 h after surgery				
at rest	1[1,2]	1[1,2]	MD 0.00(−0.43 to 0.43)	0.304
with movement	3[3,4]	4[3,5]	MD −1.00(−1.43 to −0.57)	0.375
Distance of 6-MWT at 48 h after surgery[b]	305[220,372]	298[210,360]	MD 5.00 (−37.65 to 47.65)	0.545
36-Item Short Form Survey at 180 days after surgery[c]				
Physical functioning	95[80,100]	95[85, 95]	MD 0.00(−3.43 to 3.43)	0.821
Role limitations due to physical health	100[100, 100]	100[100, 100]	MD 0.00(−3.43 to 3.43)	0.822
Role limitations due to emotional problems	100[100, 100]	100[100, 100]	MD 5.00(−0.52 to 10.52)	0.593
Energy/fatigue	80[75, 90]	75[70, 85]	MD 5.00(−0.52 to 10.52)	0.082
Emotional well-being	84[80, 88]	84[80, 88]	MD 0.00(−3.46 to 3.46)	0.488
Social functioning	100[100, 100]	100[100, 100]	MD 5.00(−0.52 to 10.52)	0.934
Bodily Pain	100[84, 100]	100[84, 100]	MD 0.00(−6.92 to 6.92)	0.833
General health	67.5[55, 80]	65[50, 75]	MD 0.00(−6.49 to 6.49)	0.150
Exploratory analyses				
Length of hospital stay after surgery, day	3[2,3]	3[2,4]	MD 0.00 (−0.68 to 0.68)	0.281
Length of PACU stay, min	30[25,47]	30[23,49]	MD 0.00 (−8.29 to 8.29)	0.793

Data are median [inter-quartile range], or n (%). [a]Accessed by simplified postoperative nausea and vomiting impact scale. [b]Three patients unable to perform the test. [c]Two patients were lost to follow up at 180 days. *6-MWT* 6-minute walk test, *PONV* Postoperative nausea and vomiting, *Qor-15* Quality of recovery-15 scale, *PACU* Postoperative anesthesia care unit, *OFA* Opioid-free anesthesia, *OBA* Opioid-based anesthesia, *PONV* Postoperative nausea and vomiting, *CI* Confidence interval, *RR* Relative risk

recent randomized controlled study [29]. The results of this study suggested that OFA are useful in the prevention of PONV.

Severity of PONV is significant correlated with the quality of recovery in patients after non-cardiothoracic surgery, reducing the severity of PONV may have potential benefits [21]. However, few studies reported on the effect of OFA on the quality of recovery of patients after pulmonary surgery [3, 19, 29]. So, we predefined quality of recovery at 24 h, mobility at 48 h, and health status at 180 days after surgery as secondary outcomes. These patient-centered outcomes reflect both subjective feeling and objective mobility, and helped clinicians evaluate the quality of recovery [22, 23]. In this study, OFA didn't show a clinically meaningful advantage over OBA in terms of quality of recovery, mobility, and long-term health status. In addition, the median difference of estimated effect sizes for secondary outcomes between groups did not reach the minimum clinically important difference as we predefined. Therefore, our result is insufficient to support the use of OFA to improve the quality of recovery in patients undergoing video-assisted thoracic surgery. In another small randomized controlled trial, OFA also did not show significant improvement in postoperative recovery quality compared to the OBA group [17]. As we have observed, the occurrence of PONV is mostly concentrated within 24 h, and with the popularization of PONV prevention, the median difference in the quality of recovery at 24 h after surgery is only 1 ponits, which is much lower than the clinically meaningful 6 points. Similarly, a similar conclusion was reached in another multicenter study in patients undergoing major noncardiac surgery [30].

Opioids are the common choice for intraoperative pain control, but withdraw-induced hyperalgesia of opioids has been observed in certain clinical scenarios [31]. In our results, the median differences in pain scores between groups did not meet our pre-defined clinically meaningful minimum difference for both at rest and with movement at 24 and 48 h, suggesting that the use of OFA could not result in a significant difference in the management of early postoperative pain among patients after video-assisted thoracic surgery. The effect of opioid-free regimens on postoperative pain had been conclusively concluded in different studies. Devine et, al., observed that OFA resulted in similar postoperative pain scores and morphine consumption compared with opioid-based anesthesia at 0, 1 and 24 h after lung cancer resection [32]. Jean et, al., found that patients who received OFA not only reduced the median of cumulative morphine consumption at 24 h (−28.50 mg) and 48 h (−27.67 mg), but also had lower pain scores at the same time points (−1.40 and −1.87 of 10-point scales) [18]. On the contrary, Yan et, al., demonstrated that compared with opioid-based anesthesia, the OFA group had higher rates of acute pain at 24 h after video-assisted thoracic surgery, but lower rates of mild chronic pain at 3 and 6 month [3]. In general, the multimodal analgesic regimen has met the analgesic needs of most patients after thoracoscopy surgery, and the minimization of opioid dosage has become a trend.

Since the largest trial of OFA (The POFA trial) to date was terminated prematurely for safety reasons, the optimal protocol for implementing OFA remains unclear [14]. Previous trials applied a diverse range of non-opioids analgesics, including dexmedetomidine, ketamine, nonsteroidal anti-inflammatory drugs, lidocaine, and regional blocks.[14 32 33] We applied OFA protocol comprised intraoperative IV flurbiprofen, dexmedetomidine, lidocaine, and a single injection video-assisted thoracic paravertebral nerve block before incision. No serious adverse events occurred during the operation, and the type of intraoperative complications of interest was comparable between groups. Our study offers evidence into the feasibility and versatility of our OFA regimen.

There are some limitations of our study. First, the attending anesthesiologists in the operating room were not blinded to the treatment allocation. Blinding the sedative and analgesic drugs used during anesthesia could pose challenges for anesthesiologists and potentially compromise patient safety [14]. To minimize information bias in the study, they were not involved in the following procedures, and both the subjects and the follow-up investigators responsible for collecting endpoint events were unaware of the group allocation. Second, the optimal protocol for OFA in video-assisted thoracic surgery remains unclear [13], and our protocol was based on a combination of previous literature and the experience of clinical practice [2, 32]. No serious adverse events were observed with this protocol, providing valuable insights for the practice of OFA. Third, we only enrolled adult participants aged between 18 and 65 years in the present trial. The generalizability of our results to elderly patients may be limited.

Conclusions

The OFA regimen reduced the overall incidence of PONV and reduced the risk of developing first postoperative PONV compared to standard opioid-based general anesthesia. Meanwhile, this opioid-free procedure was not only safe and feasible in video-assisted thoracic surgery, but also did not observe an increase in pain scores in patients at rest or with movement after surgery. Opioid-free anesthesia regimens can help reduce the risk of postoperative PONV and is a potential way to prevent postoperative PONV.

Abbreviations

6-MWT	6-minute walk test
ASA	American Society of Anesthesiologist
BMI	Body mass index
IQR	Inter-quartile range
MD	Median differences
NRS	Numerical Rating Scale
OBA	Opioid-based anesthesia
OFA	Opioid-free anesthesia
PONV	Postoperative nausea and vomiting
QoR-15	Quality of Recovery 15-item scale
RR	Relative risk
SD	Standard deviation
SF-36	36-item short form survey
WLi	Wavelet index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-02938-x.

Supplementary Material 1

Acknowledgements

The authors thank all colleagues in the Department of Thoracic Surgery, Beijing Institute of Respiratory Medicine, and Beijing Chao-Yang Hospital, Capital Medical University for their substantial contributions to the study.

Authors' contributions

Development of hypothesis: XY, A-SW, C-WWStudy planning: XY, CL, A-SWExecution of study protocol: XY, JJ, JY, C-WWData acquisition: XY, CLAnalysis and interpretation of results: XY, CL, JJ, A-SW, C-WWDrafting of manuscript: XY, CL, JJ, C-WWContributed to, approved, and take accountability for the final manuscript: all authors.

Funding

Capital's Funds for Health Improvement and Research (2022-2Z-2039) from Beijing Municipal Administration of Hospitals.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was reviewed by the institutional ethics committee. IRB number: 2022-ke-19, Date of approval: Feb 7, 2022. All included subjects in this study signed written informed consent before study inclusion.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Anesthesiology, Beijing Chao-Yang Hospital, Capital Medical University, No. 8 Gongren Tiyuchang Nanlu, Chaoyang District, Beijing 100020, China. [2]Department of Medical Statistics, Medieco Group Co., Ltd, Beijing, China. [3]Department of Thoracic Surgery, Beijing Institute of Respiratory Medicine and Beijing Chao- Yang Hospital, Capital Medical University, Beijing, China.

Received: 20 October 2024 Accepted: 30 January 2025
Published online: 08 February 2025

References

1. Gao X, Zhao T, Xu G, et al. The efficacy and safety of ultrasound-guided, bi-level, erector spinae plane block with different doses of dexmedetomidine for patients undergoing video-assisted thoracic surgery: a randomized controlled trial. Front Med (Lausanne). 2021;8:577885.
2. Dhawan R, Daubenspeck D, Wroblewski KE, et al. Intrathecal morphine for analgesia in minimally invasive cardiac surgery: a randomized, placebo-controlled, double-blinded clinical trial. Anesthesiology. 2021;135(5):864–76.
3. Yan H, Chen W, Chen Y, et al. Opioid-free versus opioid-based anesthesia on postoperative pain after thoracoscopic surgery: the use of intravenous and epidural esketamine. Anesth Analg. 2023;137(2):399–408.
4. Goldson KV, Brennan E, Burton BN, et al. Does management of postoperative nausea and vomiting differ by patient demographics? An evaluation of perioperative anesthetic management - An observational study. Anesthesiology. 2025. https://doi.org/10.1097/ALN.0000000000005367. Published online January 9, 2025.
5. Apfel CC, Laara E, Koivuranta M, et al. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology. 1999;91(3):693–700.
6. Gan TJ, Belani KG, Bergese S, et al. Fourth Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2020;131(2):411–48.
7. Gress K, Urits I, Viswanath O, et al. Clinical and economic burden of postoperative nausea and vomiting: analysis of existing cost data. Best Pract Res Clin Anaesthesiol. 2020;34(4):681–6.
8. Apfel CC, Heidrich FM, Jukar-Rao S, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting. Br J Anaesth. 2012;109(5):742–53.
9. Imam MZ, Kuo A, Ghassabian S, et al. Progress in understanding mechanisms of opioid-induced gastrointestinal adverse effects and respiratory depression. Neuropharmacology. 2018;131:238–55.
10. Levy N, Quinlan J, El-Boghdadly K, et al. An international multidisciplinary consensus statement on the prevention of opioid-related harm in adult surgical patients. Anaesthesia. 2021;76(4):520–36.
11. Wu CL, King AB, Geiger TM, et al. American Society for enhanced recovery and perioperative quality initiative joint consensus statement on perioperative opioid minimization in opioid-naive patients. Anesth Analg. 2019;129(2):567–77.
12. Shanthanna H, Ladha KS, Kehlet H, et al. Perioperative opioid administration. Anesthesiology. 2021;134(4):645–59.
13. Shanthanna H, Beloeil H, Joshi GP. Opioid-free anesthesia in research and practice: so near yet so far! Can J Anaesth. 2024;71(11):1447–52.
14. Beloeil H, Garot M, Lebuffe G, et al. Balanced opioid-free anesthesia with dexmedetomidine versus balanced anesthesia with remifentanil for major or intermediate noncardiac surgery. Anesthesiology. 2021;134(4):541–51.
15. Forget P. Opioid-free anaesthesia. Why and how? A contextual analysis. Anaesth Crit Care Pain Med. 2019;38(2):169–72.
16. Ziemann-Gimmel P, Goldfarb AA, Koppman J, et al. Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. Br J Anaesth. 2014;112(5):906–11.
17. Choi H, Huh J, Kim M et al. Opioid-free using ketamine versus opioid-sparing anesthesia during the intraoperative period in video-assisted thoracoscopic surgery: a randomized controlled trial. J Pers Med. 2024;14(8):881. https://doi.org/10.3390/jpm14080881.
18. Selim J, Jarlier X, Clavier T, et al. Impact of opioid-free Anesthesia after Video-assisted thoracic surgery: a propensity score study. Ann Thorac Surg. 2022;114(1):218–24.
19. An G, Zhang Y, Chen N, et al. Opioid-free anesthesia compared to opioid anesthesia for lung cancer patients undergoing video-assisted thoracoscopic surgery: a randomized controlled study. PLoS ONE. 2021;16(9):e0257279.
20. Yan X, Liang C, Jiang J, et al. Effects of opioid-free anaesthesia on postoperative nausea and vomiting in patients undergoing video-assisted thoracoscopic surgery (OFA-PONV trial): study protocol for a randomised controlled trial. Trials. 2023;24(1):819.
21. Myles PS, Wengritzky R. Simplified postoperative nausea and vomiting impact scale for audit and post-discharge review. Br J Anaesth. 2012;108(3):423–9.
22. Kleif J, Waage J, Christensen KB, et al. Systematic review of the QoR-15 score, a patient- reported outcome measure measuring quality of recovery after surgery and anaesthesia. Br J Anaesth. 2018;120(1):28–36.
23. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111–7.
24. Dell-Kuster S, Gomes NV, Gawria L, et al. Prospective validation of classification of intraoperative adverse events (ClassIntra): international, multicentre cohort study. BMJ. 2020;370:m2917.
25. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13.
26. Yang J, Huang L, Liu S, et al. Effect of electroacupuncture on postoperative gastrointestinal recovery in patients undergoing thoracoscopic surgery: a feasibility study. Med Sci Monit. 2020;26:e920648.
27. Termpornlert S, Vijitpavan A, Ngodngamthaweesuk M, et al. Analgesic efficacy of intravenous dexamethasone as an adjunct to ultrasound-guided paravertebral block with bupivacaine in video-assisted thoracoscopic surgery. J Pain Res. 2022;15:2351–61.
28. Massoth C, Schwellenbach J, Saadat-Gilani K, et al. Impact of opioid-free anaesthesia on postoperative nausea, vomiting and pain after gynaecological laparoscopy - A randomised controlled trial. J Clin Anesth. 2021;75:110437.
29. Feng CD, Xu Y, Chen S, et al. Opioid-free anaesthesia reduces postoperative nausea and vomiting after thoracoscopic lung resection: a randomised controlled trial. Br J Anaesth. 2024;132(2):267–76.
30. Leger M, Perrault T, Pessiot-Royer S, et al. Opioid-free Anesthesia Protocol on the early quality of recovery after major surgery (SOFA trial): a Randomized Clinical Trial. Anesthesiology. 2024;140(4):679–89.
31. Comelon M, Raeder J, Stubhaug A, et al. Gradual withdrawal of remifentanil infusion may prevent opioid-induced hyperalgesia. Br J Anaesth. 2016;116(4):524–30.
32. Devine G, Cheng M, Martinez G, et al. Opioid-free anesthesia for lung cancer resection: a case-control study. J Cardiothorac Vasc Anesth. 2020;34(11):3036–40.

Publisher's note